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Investigating the Relationship Between Vascular Health, Gait, and Cognition in Community-Dwelling Older Adults Without Dementia

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Abstract

Cardiovascular disease (CVD) risk factors contribute to neuropathological changes within regions of the brain that are involved with both cognitive and motor control processes, and have been identified as potentially modifiable dementia and gait dysfunction risk factors. Exercise training is a corner-stone treatment for vascular risk factor control, and evidence suggests that physical and cognitive training can benefit cognition and gait; however, the exercise training modality that can provide the greatest cognitive benefit remains elusive. Therefore, the purpose of this thesis was three-fold: (i) to determine whether CVD risk factors and gait were associated with cognitive functioning, (ii) to determine whether blood pressure dipping status was associated with cognitive and gait impairments in community-dwelling older adults, and iii) to examine the impact of a dual-task gait training and aerobic exercise (DAE) on cognition, gait, and vascular health. Cumulative CVD risk was an independent predictor of executive functioning. Cross-sectional differences in cognition and usual and dual-task gait were observed between older adults with preserved blood pressure dipping and non-dippers. Last, 26-weeks of DAE training improved cognition and usual and dual-task gait, and the improvements in cognition were maintained for at least 6 months after the exercise program. The management of traditional and novel CVD risk factors should be a primary aim of prevention strategies aimed at mitigating cognitive decline. Although DAE training can benefit cognition and gait, further work is required to unequivocally determine the efficacy of DAE training as a method to improve brain health in older adults without dementia.

Keywords: cognition, dual-task exercise, vascular health, gait, QRISK2, blood pressure dipping

Co-Authorship Statement

Co-authors (Chapter 1): Dr. Gill and Petrella provided assistance with the design and format of the revisions to the document. Dr. Gill and Petrella also provided critical expertise and diligent reviews of the manuscripts prior to final submission for publication. Co-authors (Chapter 2): Dr. Gill, McGowan, and Petrella provided critical expertise and diligent reviews of the manuscript prior to final submission for publication. Dr. Gill was also consulted when designing the statistical analyses for this study. Dr. Liu-Ambrose, Hachinski, and Shoemaker contributed to the development of a research proposal that was funded as an Operating Grant by Canadian Institute of Health Research. Dr. Gill, McGowan, Shoemaker, Holmes, and Petrella also served as members of the thesis advisory committee, and helped to direct the design of the study and the analyses used therein.

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Abbreviations

1MWT	One mile walk test
6MWT	Six minute walk test
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale – Cognitive Battery
AE	Aerobic exercise
aMCI	Amnestic mild cognitive impairment
AMNART	American National Adult Reading Test
AVLT	Auditory Verbal Learning Test
BAT	Balance and toning
BDNF	Brain-derived neurotropic factor
BP	Blood pressure
BTACT	Brief Test of Adult Cognition by Telephone
CAC	Carotid arterial compliance
CERAD	Consortium to Establish a Registry for Alzheimer`s Disease
cIMT	Carotid intima-media thickness
CIND	Cognitive impairment, but not dementia
CT	Cognitive training
CVD	Cardiovascular disease
CWT	Colour-Word Test
DAE	Dual-task gait training and aerobic exercise
DS	Normal dipping status
DSC	Digit-Symbol Coding
DSST	Digit Symbol Substitution Test
DT	Dual-task
EEG	Electroencephalography
fMRI	Functional magnetic resonance imaging
GH	Growth hormone
HbA1c	Glycated hemoglobin
Hcy	Homocysteine

HDL-C	High-density lipoprotein-C
HRR	Heart rate reserve
IALD	Instrumental activities of daily living
IGF-1	Insulin-like growth factor 1
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
IQR	Interquartile range
MCI	Mild cognitive impairment
min	Minute
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
N-DS	Non-dipping status
SPPB	Short Physical Performance Battery
RM	Repetition maximum
RT	Resistance training
SD	Standard deviation
STEP	Step Test for Exercise Prescription
TC	Total cholesterol
TICS	Telephone Interview for Cognitive Status
TMT	Trail Making Test
UG	Usual gait
VLMT	Verbal Learning and Memory Test
WAIS	Wechsler Adult Intelligence Scale
WMS-R	Weschler Memory Scale-Revised

Chapter 1: Exercise to Benefit Cognition and Brain Health in Older Adults – an Updated Review

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The Burden of Cognitive Impairment and Dementia

With the global population aging, there is a growing urgency to identify the most effective strategies to prevent cognitive decline. In 2015, approximately 46 million older adults worldwide were diagnosed with dementia, and by 2050 this number is expected to reach 131.5 million (Prince et al., 2015). This projected increase in dementia cases imposes an economic burden that is expected to reach a trillion dollars as early as 2018 (Prince et al., 2015). Moreover, the incidence of individuals exhibiting some form of cognitive impairment, but not having met the diagnostic criteria for dementia (i.e., mild cognitive impairment, MCI; or cognitive impairment – not dementia, CIND), is two-fold greater than that for Alzheimer's disease (AD) and related dementias (Plassman et al., 2011). Prior to the establishment of identifiable objective cognitive impairment, some individuals are able to perceive recognizable changes/reductions in their cognitive functioning and are able to identify and communicate these difficulties through the report of subjective cognitive complaints. Due to the associated stigma and widespread under-reporting of cognitive difficulties to general practitioners (Waldorff, Siersma, Vogel, & Waldemar, 2012), the estimated prevalence of cognitive complaints in older adults ranges between 11% and 56% (Jonker, Geerlings, & Schmand, 2000; Jorm, Christensen, Korten, Jacomb, & Henderson, 2001; Waldorff et al., 2012). Cognitive complaints have been associated with poorer scores on objective cognitive assessments (i.e., executive functioning; EF; Amariglio, Townsend, Grodstein, Sperling, & Rentz, 2011; Benito-Leon, Mitchell, Vega, & Bermejo-Pareja, 2010; Clarenette, Almeida, Forstl, Paton, & Martins, 2001; Genziani et al., 2013), as well as cortical and hippocampal atrophy (Saykin et al., 2006), and each identified cognitive complaint increases the likelihood of

developing cognitive impairment by approximately 20% (Amariglio et al., 2011). Hence, it is of interest to examine older adults who demonstrate a wide range of cognitive abilities (i.e., those with healthy cognition, and subjective or objective cognitive difficulties) in order to understand the progression of the disease, and identify which populations are best suited for intervention efforts (Jessen et al., 2010; Jessen et al., 2014).

Vascular Disease and the Establishment of Geriatric Conditions

The term vascular cognitive disorders has been established to identify older adults who exhibit cognitive impairments that primarily occur as a result of the accumulation of vascular-related brain pathology (i.e., white matter hyperintensities, subcortical microangiopathy, lacunar infarcts) in addition to other AD biomarkers (i.e., beta amyloid, phosphorylated-tau, impaired glucose metabolism; Jellinger, 2013; Sachdev et al., 2014). Individuals with vascular cognitive disorder are identified according to two core criterion: i) the presence of a subjective cognitive complaint and objective cognitive deficits, and ii) vascular disease is the dominant, if not exclusive cause of the cognitive impairment (Sachdev et al., 2014). Vascular dementia is the second leading form of dementia in Western nations, and the leading cause of dementia in the Orient (Fratiglioni, De Ronchi, & Agüero-Torres, 1999). Indeed, vascular-related brain pathology is common; the prevalence of unsuspected infarction of the cerebral deep small vessels ranges from 15% (Bryan et al., 1999) to 28% (Price et al., 1997), and lesions within the deep subcortical and periventricular white matter were present in 95% of the participants from the neuroimaging extension of the Rotterdam study (de Leeuw et al., 2001). The accumulation of vascular brain injury and the development of white matter lesions within

the frontal-subcortical regions of the brain impact the functional integrity of the neurocircuitry within and between these regions (Pugh & Lipsitz, 2002). The frontal-subcortical circuits that control both cognitive and motor processes are located in close proximity; thus, small vascular lesions that accumulate within this region may simultaneously cause dysfunction in both systems (Pugh & Lipsitz, 2002).

Vascular Disease and Cognitive Impairments in Aging

Cardiovascular disease (CVD) risk factors negatively influence brain health and functioning in aging (Pugh & Lipsitz, 2002). Specifically, atherosclerosis and poor blood pressure (BP) control are strongly associated with long-term risks of cognitive impairment (Brickman et al., 2012; Launer, Masaki, Petrovich, Foley, & Havlik, 1995; Moon et al., 2015). Elevations in BP and the associated arterial stiffening reduce cerebrovascular reactivity and cerebral blood flow (Akinyemi, Mukaetova-Ladinska, Attems, Ihara, & Kalaria, 2013; Brickman et al., 2010), predisposing older adults to greater risk of cortical hypoperfusion (Akinyemi et al., 2013; Cohen, 2007; Dai et al., 2008). These CVD risk factors also contribute to the establishment and presence of cerebrovascular disease (Knopman et al., 2001), and have also been implicated as potential risk factors for white matter lesions (Dufouil et al., 2001; Knopman et al., 2001). Furthermore, sustained hypertension is the primary risk factor for stroke (O'Donnell et al., 2010), and has been associated with hippocampal atrophy (Korf, White, Schelten, & Launer, 2004; Brickman et al., 2015), the presence of neurotropic markers of AD (Petrovitch et al., 2000; Langbaum et al., 2012; Rodrigue et al., 2013) and clinical dementia (Launer et al., 2000; Xu et al., 2015). Arterial stiffness has also been independently associated with presence of brain lesions (i.e., white matter hyperintensities, lacunar infarcts, amyloid plaques, etc.; O'Rourke & Safar, 2005; Tsao et

al., 2013; Hughes et al., 2014; King, 2014; Nation et al., 2013; Singer, Trollor, Baune, Sachdev, & Smith, 2014), and has been implicated as a risk factor for AD and dementia (Vernooij et al., 2008; Tsao et al., 2013; Xu et al., 2015). Associations between CVD risk factors and objective cognitive functioning have also been observed. Lower scores on the Montreal Cognitive Assessment (MoCA) have been associated with increasing age, lower levels of formal education, and the presence of a greater number of CVD risk factors. For instance, the mean MoCA score among CVD populations has been reported as low as 22.8 +/- 2.3, with 72.1% of the population under investigation having scored below the cut-off for cognitive impairment (< 26) (McLennan, Mathias, Brennan, & Stewart, 2011). Aggregate CVD risk has also been associated with EF; a recently published study observed a significant association between higher Framingham Cardiovascular Risk scores and greater task-related activation within the left inferior parietal lobe and poorer Flanker-task performance in community-dwelling older adults (Chuang et al., 2014). These observations suggest that cardiovascular health and the presence of CVD risk factors appear to be intimately linked with brain health in aging.

Vascular Disease and Mobility Impairments in Aging

Vascular brain injury (i.e., stroke) and vascular risk factors (i.e., hypertension) have been associated with mobility and balance impairments in older adults. Gait disorders are prevalent among those with pre-existing CVD (i.e., stroke) (Hajjar et al., 2009) and CVD risk factors (i.e., hypertension) (Annweiler & Montero-Odasso, 2012), and this relationship appears to be mediated by the presence of subclinical cerebrovascular abnormalities (Rosano, Brach, Studenski, Longstreth, & Newman, 2007). For instance, a recent review has revealed a persistent association between periventricular

white matter lesions and gait dysfunction in the elderly, where gait speed, stride length, and stride time were consistently associated with white matter hyperintensity burden (Annweiler & Montero-Odasso, 2012). Furthermore, a higher white matter lesion burden has also been associated with increased gait variability (i.e., the stride-to-stride fluctuations in spatiotemporal gait parameters) in community-dwelling older adults (Rosano et al., 2007), a gait parameter that is considered a significant falls risk factor and index of incident mobility (Brach, Berlin, VanSwearingen, Newman, & Studenski, 2005; Hausdorff, Rios, & Edelberg, 2001).

Taken together, it appears that aging and the accumulation of cardiovascular disease risk factors negatively impact brain health and function, and contribute to the establishment of vascular-related brain injuries within regions of the brain that are essential for healthy cognitive and motor control (Pugh & Lipsitz, 2002). However, as CVD risk factors appear to contribute to the development of white matter lesions, frontal-subcortical dysfunction, and the presence of cognitive and mobility impairments, these significant geriatric conditions are potentially preventable. Although there is an increasing consensus on the role of CVD risk factors in the development of vascular brain injury and cognitive and mobility impairments, few studies have investigated the cognitive and mobility benefits associated with interventions that hold the potential to modify vascular risk in either healthy older adults, or those with cognitive impairments (Naqvi, Liberman, Rosenberg, Alston, & Straus, 2013). Despite the paucity of available research, interventions aimed at mitigating CVD risk factors burden and their impact on the development of cerebrovascular disease may substantially contribute to the prevention of cognitive and mobility impairments in aging (Pugh & Lipsitz, 2002). Indeed, this theory has begun to gain traction; recent observations implicate the successful treatment

of CVD risk factors as a primary mechanism responsible for recent reductions in the global incidence of dementia (Langa, 2015), while the pharmacological management of hypertension has led to a reduced risk for MCI (Gelber et al., 2013; Yasar et al., 2013) and AD (Yasar et al., 2013). Despite these promising initial observations, there is a necessity to further investigate the effect of interventions that are aimed at concurrently reducing CVD risk and improving cognition and mobility in older adults.

The Prevention of Cognitive Impairment in Aging

The trajectory of pathological cognitive decline in aging suggests that there are many forms in which cognitive impairment can manifest, and there is a natural progression from normal or "healthy" cognitive aging through to the development of cognitive impairment and dementia (Sperling et al., 2011). Currently, there is no known cure for AD or other dementias; thus, identifying tolerable, feasible, effective, and scalable interventions that are aimed at mitigating the burden of age-related chronic disease risk and cognitive decline is imperative. Developing interventions that could produce modest delays in the onset of cognitive decline could significantly reduce this economic and societal burden; specifically, a 5-year delay in the onset of cognitive decline could translate to a 50% reduction in the incidence of dementia after several decades (Brookmeyer, Johnson, Ziegler-Graham, & Arrighi, 2007; Camelli, Swan, LaRue, & Eslinger, 1997). Thus, developing early prevention strategies for cognitive and functional decline may provide the greatest impact on the incidence of cognitive impairment in aging (Sperling et al., 2011; Jessen et al., 2010; National Institute of Aging & National Institutes of Health, 2014; Stewart, 2012).

Vascular Risk Factor Control to Prevent Cognitive Impairment in Aging

A recent population-based study reported reductions in the incidence of dementia among high-income nations (Langa, 2015), and these findings have been attributed to advances in the treatment of vascular risk factors and an increased awareness of the importance of preserving vascular health for the prevention of chronic conditions in aging. Despite this promising trend, chronic CVD remains the leading cause of global mortality (World Health Organization, 2012) and continues to contribute to cognitive decline and the development of AD and related dementias. Cognitive and functional impairments are common among individuals with established CVD risk; in fact, it is estimated that 3% and 5% of worldwide AD cases are due to diabetes and hypertension, respectively, while an additional 13% of AD cases can be attributed to physical inactivity (Norton, Matthews, Barnes, Yaffe, & Brayne, 2014). Thus, developing interventions that are specifically designed to mitigate CVD risk while providing a simultaneous benefit to the health and functioning of the brain may provide an opportunity to halt the development of significant vascular-related neuropathological changes to the brain. Exercise training benefits cardiovascular fitness and can help to mitigate CVD risk factor burden (Pescatello et al., 2004; Seals, Desouza, Donato, & Tanaka, 2008), and surmounting evidence implicates exercise training as a method to benefit brain health and functioning. These observations suggest that exercise-based interventions may be one of the most effective strategies to reduce the risk of cognitive impairment by providing a stimulus that can synchronously improve cardiovascular and cognitive health. However, there is currently a paucity of data related to the impact of exercise-related changes vascular health on brain structure and function (Tarumi & Zhang, 2014), and the

association between vascular health and functioning, cognition, and the risk for dementia in aging remains equivocal (Barnes, 2015).

Exercise Training and Cognition in Older Adults – the Current State of the Evidence

With the suggestion that lifestyle modifications may be the best method to prevent cognitive decline (Daviglus et al., 2011; Lehert, Villaseca, Hogervorst, Maki, & Henderson, 2015; Norton et al., 2014), the examination of the effect of exercise on brain health and functioning has received considerable attention. Previously, our group presented a review of the state of the evidence regarding the effect of exercise on brain health and functioning among older adults with and without objective cognitive impairment (Gregory, Gill, & Petrella, 2013). In the current review, the previous findings will be expanded using recently published literature that has further described the effect of exercise on brain health and functioning in older adults (Table 1.1). The relationship between traditional exercise training programs (i.e., aerobic, resistance, and cognitive training, combined and dual-task program) and cognition in community-dwelling older adults is discussed. Lastly, the current state of the evidence is critically reviewed, limitations within the current literature base are highlighted, and suggestions regarding future directions for research are described (Table 1.2).

Aerobic Exercise and Brain Health in Aging

Leading a physically active lifestyle that involves the participation in aerobically-based exercise training has been suggested as a method to prevent cognitive impairment and dementia (Daviglus et al., 2011; Lehert et al., 2015; Naqvi et al., 2013). Although these suggestions are promising, a recent Cochrane review concluded that there is a

paucity of evidence concerning the ability of aerobic exercise to benefit or improve cognition in older adults, even in instances when the intervention lead to improvements in cardiorespiratory fitness (Young, Angevaren, Rusted, & Tabet, 2015). This is despite an exhaustive amount of literature that supports the notion that aerobic exercise (AE) training can improve vascular function and reduce CVD risk, and also benefit the health and functioning of the aging brain.

Observational studies have demonstrated that compared to sedentary age-matched peers, individuals who are more physically active demonstrate greater cognitive performance and are less likely to experience cognitive decline and dementia in later life (Barnes, Yaffe, Satariano, & Tager, 2003; Johnson et al., 2016; Rovio et al., 2005; Tierney, Moineddin, Morra, Manson, & Blake, 2010; Weuve et al., 2004; Wilbur et al., 2012). Others have identified a link between higher cardiorespiratory fitness (i.e., VO2 max) and preserved brain structure (i.e., gray matter and hippocampal volume) and function (i.e., white matter integrity) in aging (Colcombe et al., 2004; Teixeira et al., 2016; Varma, Tang, & Carlson, 2016). Recent observations further this notion, as a greater frequency, cumulative duration, and total amount of low-intensity daily walking exercise have each been independently associated with increased total hippocampal volume (Varma, Chuang, Harris, Tan, & Carlson, 2015), and navigation-based daily walking exercise has been associated with increased volume within the subiculum of the hippocampus (Varma et al., 2016) in cognitively healthy community-dwelling older adults. The high accessibility and relatively low-cost and skill requirements of AE (e.g., walking, jogging, running, cycling, and swimming) are key components that have made this exercise modality the primary focus of research and has thus, resulted in the collection of the most robust evidence related to the effects of exercise on the aging brain.

Previous meta-analyses have concluded that AE training can indeed benefit cognition, specifically EF (Colcombe & Kramer, 2003; Hindin & Zelinski, 2012), information processing speed (Colcombe & Kramer, 2003; Smith et al., 2010), attention and memory (Smith et al., 2010) in cognitively healthy older adults, and can benefit verbal fluency (Gates, Fiatrone Singh, Sachdev, & Valenzuela, 2013) and general cognitive functioning (Heyn, Abreu, & Ottenbacher, 2004) in older adults with objective cognitive impairment. Several more recent reviews have led to some speculation around the results and conclusions of these previous studies, as Kelly and colleagues (2014b) and the above-noted recent Cochrane review (Young et al., 2015) failed to identify a significant effect for AE training on any cognitive outcome. The inconsistencies in the reported effect of AE on cognition can be attributed to an increase in the number and the quality of the studies available for inclusion, the heterogeneity in the design of the studies (i.e., the specific neuropsychological outcomes used, the intensity, frequency, and total duration of the interventions, etc.) and the low statistical power of the interventions included in these meta analyses. Although these studies span over a decade, the recommendations that conclude each of these meta-analyses have followed a consistent theme: i) the need for higher-quality interventions, ii) examine the cognitive effect of AE interventions of various intensity and duration, iii) the identification and incorporation of appropriate control groups, and iv) the examination of the maintenance of the effects (i.e., inclusion of follow-up periods). Thus, it appears that the effect of AE training on cognitive functioning in older adults with and without objective cognitive impairment will remain equivocal until a sufficient quantity of high quality interventions are developed and evaluated.

Table 1.1

Key Features of the Reviewed Studies Examining the Effect of Exercise on Cognition In Older Adults.

Aerobic training and cognitive health					
Study	Design	Sample	Treatments	Outcome(s) & Measure Used	Main Findings
Colcombe *et al.*, (2004)	6 month RCT	29 high-functioning community-dwelling adults 65.6 ± 5.66 years 62% female	Intervention: Progressive walking 40-70% HRR Control: Stretching & toning 40-45 min/day, 3 days/week	Brain structure & activation: fMRI EF: Flanker Task	• Improved EF • Increased recruitment of parietal and frontal cortical regions necessary for successful task completion • Reduced activity in behavioural conflict and attentional control processing areas • The neurocognitive benefits of exercise can manifest in a relatively short time period (6 months) in aging humans
Colcombe *et al.*, (2006)	6 months RCT	59 Sedentary community-dwelling older adults 65.5 years 53% female	Intervention: Progressive walking 40-70% HRR Control: Stretching & toning 60 min/day, 3 days/week	Brain structure: MRI	• Elevated prefrontal and parietal cortical volume following aerobic training • The AE group had 27-42% less risk for brain volume loss compared to the control
Lautenschlager *et al.*, (2008)	6 month RCT	138 older adults with subjective memory complaints, or MCI 68.6 ± 8.7 years 50.5% female	Intervention: Individualized progressive walking & aerobics Control: Education & usual care 50 min/day, 3 days/week, accumulating 150 min/week	Dementia: ADAS-Cog	• Improved scores on ADAS-Cog scale occurred in older adults with subjective and objective MCI • The cognitive benefits present following 6 months of exercise can be maintained for ≥ 12 months in older adults with MCI
Williamson *et al.*, (2009)	12 month RCT	102 cognitively healthy sedentary older adults MMSE ≥ 21 76.8 ± 4.37 years 72% female	Intervention: Comprehensive fitness program that emphasised AE & walking Control: Health education	Global cognitive health: MMSE Cognitive flexibility, processing speed, & inhibition or disinhibition: Modified Stroop task Psychomotor speed & working	• Improvements in psychomotor speed and information processing were correlated with improved physical fitness

			2-3 days/week, achieving ≥150 min/week	memory: DSST Short- & long-term verbal memory: Rey's AVLT	
Baker *et al.*, (2010)	6 months RCT	33 older adults with aMCI 70.4 ± 8.33 years 52% female	Intervention: High-intensity AE using a treadmill, stationary bicycle, or elliptical trainer 85% HRR Control: Stretching 45-60 min/day, 4 days/week	EF: TMT B, Task Switching, Verbal Fluency, & Symbol-Digit modalities Memory: List learning Declarative memory: Story recall Visual memory: Delayed-Match-To-Sample Attention & response inhibition: Stroop CWT	• Women experienced significant improvements in multiple measures of EF • Males experienced improvements in EF, specific for TMT B • High-intensity AE-based exercise can improve EF in individuals with aMCI
Voelcker-Rehage *et al.*, (2011)	12 month RCT	44 cognitively healthy community-dwelling older adults MMSE ≥ 27 69.64 ± 3.84 years	Intervention: Progressive walking at spiroergometry exercise testing-based gas exchange threshold Control: Coordination training using exercise balls, twist boards, fitness balls, jump ropes, exercise bands, and stability boards 60 min/day, 3 days/week	Brain structure & activation: fMRI EF: Modified Flanker task Perceptual Speed: Visual Search Task	• Aerobic and coordination training differentially improve EF, performance accuracy, and speed in older adults • Reduced brain activation was associated with increased O_2 supply following 12 months of AE training • Improvements in brain activation were linear and did not plateau during the 12 month intervention
Erickson *et al.*, (2011)	12 month RCT	120 community-dwelling older adults 66.5 ± 5.63 years 67% female	Intervention: Progressive walking 60-75% HRR Control: Stretching & toning 40 min/day, 3 day/week	Brain structure: MRI Neural health: circulating BDNF Memory: Computerized spatial memory task	• 1 year of progressive walking can improve or reverse age-related reductions in anterior hippocampus volume • Increases in hippocampal volume are associated with elevated circulating BDNF and improved spatial memory in late adulthood

Uemura *et al.*, (2012)	12 month RCT	100 older adults with MCI 75.3 ± 6.8 years 51% female	Intervention: Moderate-intensity (60% HR_{max}) AE with strength and stretching 90 min/day, 2 days/week Control: Educational control, involving participation in 3 classes about health promotion over the course of the intervention	Blood markers and Blood Pressure: TC, HDL-C, TG, HbA1c, seated resting BP Physical fitness: 6MWT	• Improvements in physical fitness and reductions in TC and TC-HDL-C risk ratio were observed following the intervention • Exercise training can benefit vascular risk factor profiles in older adult with MCI
Nagamatsu *et al.*, (2013)	6 month RCT	86 older women with subjective memory complaints 74.9 ± 3.5 years	Interventions: Progressive AE involving walking 40% HRR at baseline, progressed to 70-80% HRR at 12 weeks Free weight and machine based RT of 7 muscle groups, progressed using the 7RM method 2 sets, 6-8 reps Control: Balance & toning 60 min/day, 2 days/week	Verbal learning & memory: Rey's AVLT total acquisition, recall after interference, loss after interference, and delayed recall Spatial memory: Customized, computer-based task, requiring participants to recall the spatial location of objects; reaction time and accuracy Physical performance: (SPPB Cardiovascular capacity: 6MWT	• There were no between group differences in total acquisition, recall after interference, delayed recall, or spatial memory task accuracy following the intervention • Loss after interference was reduced by 43.4% and 32.5% following AE and RT, respectively, but only the reduction following AE was significantly different than the BAT control • Reductions in loss after interference were not apparent at 3 months • Compared to BAT, improved reaction time to the spatial memory task were observed following AE and RT • Spatial memory task reaction times were positively associated with SBBP performance following AE
Ten Brinke *et al.*, (2014)	6 month RCT	86 older women with MCI MMSE > 24 MoCA < 26 74.9 ± 3.5 years	Interventions: Progressive AE involving walking 40% HRR at baseline, progressed to 70-80% HRR at 12 weeks	Hippocampal volume: MRI Verbal learning & memory: Rey's AVLT	• Compared to the balance and toning control, AE was associated with increased left, right and total hippocampal volume • Increased left hippocampal volume was correlated with

			Free weight and machine based RT of 7 muscle groups, progressed using the 7RM method 2 sets, 6-8 reps Control: Balance & toning 60 min/day, 2 days/week		poorer performance on verbal learning and memory tasks • The influence of exercise-induced changes in hippocampal volume on memory performance in older adults with MCI remains equivocal
Maass *et al.*, (2015)	3 months non-randomized controlled trial	40 previously sedentary older adults 68.4 ± 4.3 years 55% female	Intervention: Progressive treadmill-based AE 65% target HR, increased by 5% every week for 4 weeks 30 min/day, 3 days/week Control: Relaxation & stretching 45 min/day, 2 days/week	Global cognitive health: MMSE Memory: VLMT, Complex Figure Test Brain structure & function: Perfusion imaging, MRI	• 3 months of progressive, treadmill-based AE increased hippocampal perfusion and volume • Structural and functional changes within the hippocampus are correlated with improvements in cardiorespiratory fitness and memory
Varma *et al.*, (2015) Varma *et al.*, (2016)	Cross-sectional	92 cognitively healthy community-dwelling older adults 67.3 ± 6.1 years 70% female 89% African American 90 cognitively healthy community-dwelling older adults 67.3 ± 6.0 years 70% female 89% African American (MMSE >26)	Assessed the association between objectively measured low-intensity daily walking activity and hippocampal volume	Daily walking activity: Total amount, duration, and frequency collected using Accelerometry for 3-7 days Hippocampal volume: MRI	• A higher frequency, duration, and total volume of low-intensity daily walking activity were each independently associated with increased total hippocampal volume and increased subiculum surface area among older women, but not men • Navigation-based low-intensity daily walking may provide specific benefits to sub-regions of the hippocampus • Low-intensity, non-exercise based lifestyle activities can benefit the structure of regions of the brain that are susceptible of Alzheimer's disease pathology

Resistance training and cognitive health					
Study	Design	Sample	Treatments	Outcome(s) & Measure Used	Main Findings
Perrig-Chiello *et al.*, (1997)	2 month RCT	46 older adults from the Interdisciplinary Aging Study 73.2 years 39% female	Intervention: 10 min warm-up 8 machine-based resistance exercises that focus on the major muscle groups Control: Unspecified 1 day/week	Memory: Immediate and delayed recall (8, two-syllable words) & recognition (original list + 8 distractor words) Cognitive speed: WAIS-revised digit-symbol subtest	• Improvements in delayed recall and immediate recognition following 2 months of RT • Improvements in free recall persisted up to 1 years post-intervention mechanisms influencing cognitive health following RT remain equivocal
Lachman *et al.*, (2006)	6 month RCT	210 community-dwelling older adults with ≥1 disability from the Short Form Health Survey physical-function scale 75.32 ± 7.37 years 77.6% female	Intervention: Home-based video-taped RT program consisting of 10 band exercises that focusing on movements used for functional activities Control: Wait-list control 35 min/day, 3 days/week	Memory: WAIS backwards digit span	• Changes in resistance level throughout the intervention was a significant predictor of memory change in the RT group • Strength training can benefit memory among older adults, especially when using higher resistance levels
Cassilhas *et al.*, (2007)	6 month RCT	63 cognitively healthy, sedentary older males (MMSE ≥ 24) 68.71 ± 0.84 years sex undisclosed	Interventions: *2 groups* ACSM guidelines for RT in seniors at *one of two* intensities: I) *Moderate intensity* 50% 1RM II) *High Intensity* 80% 1RM 2 sets, 8 reps each set Control: Stretching & toning 60 min/day, 3 days/week	Central EF: WAIS-III similarities Short-term Memory: WAIS-III digit span forwards & backwards Visual modality of short-term memory: Corsi's block-tapping task forward and backward Long-term, episodic memory: Rey-Osterrieth complex figure test Attention: Toulouse-Pieron's concentration attention test	• Both RT groups outperformed the controls on measures of short and long term memory • High intensity RT, but not moderate intensity RT, was also associated with better performance on measures of central EF and attention compared to the controls • Significant correlations were observed between elevations in circulating IGF-1 and improved cognitive performance following the intervention • Moderate- and high-intensity RT can impart beneficial effects on cognitive functioning in previously sedentary older adults • High intensity RT may be required to produce a greater IGF-1 response and stimulate

					changes in EF
Liu-Ambrose *et al.*, (2010)	12 month RCT	155 community-dwelling women 69.6 ± 2.9 years	Intervention: *2 RT groups* Machine-based and free weight RT (7 exercises focusing on major muscle groups) 2 sets, 8-10 reps each *I) 60 min/day, 1 day/week* *II) 60 min/day, 2 days/week* Control: Balance & toning 60 min/day, 2 days/week	Brain structure: MRI *Executive functions* Attention and conflict resolution: Stroop task Set-shifting: TMT A & B Working memory: WAIS-revised verbal digit span forwards & backwards	• 12 months of progressive RT once or twice-weekly can impart beneficial effects executive cognitive function, selective attention, and conflict resolution in comparison to a twice-weekly balance and toning group • However, reductions in brain volume were observed in both training groups • More research is needed to discern the effects of RT on cognitive health in older women
Anderson-Hanley *et al.*, (2010)	1 month Quasi-experimental design	16 community-dwelling older adults 72.1 ± 10 years 19% female	Intervention: Community-based exercise class focusing on chair and standing exercises using small free weights ("Strong Bones" Program, Tufts University) Control: Wait-list control 45 min/day 2-3 days/week	EF: WMS-III digit span backwards subtest, Stroop tasks C, & Colour Trails 2 Processing speed: WMS-III digit span forward, Stroop tasks A & B, colour trails 1, & letter-digit substitution test	• RT can benefit EF in community-dwelling older adults • Benefits of training were specific for measures of verbal fluency rather than global EF suggesting that specific aspects EF may be differentially affected by a specific exercise modality
Yerokhin *et al.*, (2012)	2.5 month Non-randomized clinical trial	13 older adults with early dementia (physician identified) 79.3 ± 11 years 9 cognitively healthy controls 62.8 ± 7.2 years	Intervention: Community-based exercise class focusing on chair and standing exercises using small free weights ("Strong Bones" Program, Tufts University 45 min/day, 3-5 days/week	Brain activity: EEG *Executive functions* Selective Attention & cognitive flexibility: Stroop task C, Colour Trails 2, WAIS-III digit span backwards *Memory* Immediate & delayed recall: Fuld Object Memory Evaluation Visuospatial skill & memory: Rey-Osterrieth and Taylor complex	• Improvements in verbal memory coincided with frontal beta and delta power asymmetries, and N200 amplitude asymmetry following RT • Improvements in cognitive efficiency were observed following 6 weeks of RT in older adults with early dementia • Changes in neurophysiology may occur more quickly than changes in neuropsychological performance following RT

				figure recall	
Xu *et al.*, (2014)	Cross-sectional	59 community-dwelling older adults MMSE ≥ 26 66.7 ± 9.6 years 57.6% female	Assessed the association between self-reported levels of RT and cerebral perfusion	Resting cortical blood flow: MRI Physical activity: Rapid Assessment of Physical Activity Questionnaire	• Compared to men, women demonstrated greater cerebral perfusion • Women who engaged in strength training ≥ 1 day/week had greater resting cerebral perfusion than those who did not • There was no relationship between physical activity and resting cerebral perfusion among men • There was no relationship between AE and resting cerebral perfusion
Iuliano *et al.*, (2015)	3 month RCT	80 community-dwelling older adults 67.0 ± 11.7 years 60% female	Interventions: I) Machine-based RT (exercises focused on 6 major muscle groups), progressed from 60-70% 1RM (weeks 1-4, 3 sets with 12 reps) to 80-85% 1RM (weeks 9-12, 3 sets with 6 reps) II) Treadmill- or ergometer-based AE, progressed from 50-60% HRR (weeks 1-2) to 70-80% HRR (weeks 11-12) III) Postural training, focused on flexibility, balance and relaxation 30 min/day, 3 days/week Control: Passive (maintained regular lifestyle routine throughout the intervention)	*Attention:* Attentive Matrices Test, Alternate version *Abstract reasoning:* Raven's Progressive Matrices Test *Inhibitory control:* Stroop Colour Word Test *Mental flexibility & set-shifting:* TMT A & B *Praxis:* Drawing Copy Test Strength: 1RM test Cardiovascular fitness: 1MWT Balance: Stork Balance Stand Test	• Praxis was the only cognitive outcome that significantly changed following RT • Improvements in attention and abstract reasoning, but not inhibitory control, mental flexibility, or praxis were observed following AE training • The cognitive benefits of exercise are moderated by the specific exercise modality being performed, • Combined, multiple modality exercise training programs may provide additive cognitive benefits
Best *et al.*, (2015)	12 month RCT	155 community-dwelling older women	Intervention: *2 RT groups* Machine-based and free weight RT (7 exercises	Brain volume: MRI	• Compared to BAT, improvements in EF were observed immediately following

	Follow-up at 24 months	MMSE >26 69.4 4 ± 2.8 years	focusing on major muscle groups) 2 sets, 8-10 reps each *I) 60 min/day, 1 day/week* *II) 60 min/day, 2 days/week* Control: BAT 60 min/day, 2 days/week	Cognition *EF:* Stroop Colour Word Test TMT A & B Digit Span backwards DSST *Verbal memory:* Rey's AVLT immediate recall, delayed recall, and recognition	the intervention and after 12 months of follow-up for those who performed RT once per week • Compared to BAT, improvements in memory were observed immediately following the intervention, and improvements in EF and reductions in cortical atrophy (BAT: 2.0% reduction vs. 2x RT: 0.8%) were observed after 12 months of follow-up for those who performed RT twice per week • Progressive RT can impart long-term benefits to cognition and brain volume in older women
Bolandzadeh *et al.,* (2015)	12 month RCT	155 community-dwelling older women MMSE >26 69.4 4 ± 2.8 years	Intervention: *2 RT groups* Machine-based and free weight RT (7 exercises focusing on major muscle groups) 2 sets, 8-10 reps each *I) 60 min/day, 1 day/week* *II) 60 min/day, 2 days/week* Control: BAT 60 min/day, 2 days/week	White matter lesion volume: MRI *EF:* Stroop Colour Word Test Mobility: Usual gait speed	• Compared to BAT, reductions in white matter lesion volume were only observed among those who performed RT twice per week • Reduced white matter lesion progression following once- or twice-weekly RT was associated with maintained usual gait speed, but not EF
Tsai *et al.,* (2015)	12 month RCT	48 cognitively healthy older men MMSE > 26 71.4 ± 3.8 years	Interventions: Progressive, high-intensity (75-80% 1RM) RT of the major muscle groups using machines and free weights 3 sets of 10 reps each 60 min/day, 3 days/week Control: Passive (maintained regular	*EF:* Oddball task reaction time Brain function: EEG Growth factors & blood markers: IGF-1, GH, Hcy	• 12 months of progressive RT stimulated improvements in reaction time to the oddball task, sustained P3a and P3b amplitudes during the oddball task, elevations in circulating IGF-1, and reductions in circulating Hcy • Elevations in serum IGF-1 were associated with improved

			lifestyle routine throughout the intervention)		reaction time and sustained P3b amplitudes during the oddball condition • Attenuations in cognitive aging after RT are, in part, mediated by IGF-1
Fiatrone-Singh *et al.*, (2014) Suo *et al.*, (2016)	SMART Study 6 month RCT Follow-up at 18 months	100 older adults with MCI MMSE ≥ 26 70.1 ± 6.7 years	Interventions: Participants randomized to progressive RT, CT, combined progressive RT + CT, or sham control Resistance training: Machine-based group training of major muscle groups 3 sets, 8 reps each 45 min/day, 3 days/week Cognitive training: GOPACK computer-based Neurorehabilitation program 45 min/day, 3 days/week Combined RT + CT: Both interventions delivered each training day Control: Educational and stretching/seated calisthenics control 90 min/day, 3 days/week	Global Cognition: ADAS-Cog MMSE *Executive functions:* WAIS-III Matrices and Similarities subtests, verbal fluency *Memory:* WAIS-III Auditory Logical Memory immediate and delayed recall subtest, ADAS-Cog List learning subsection, Benton Visual Retention test-Revised, 5th Ed. *Attention:* Symbol Digit Modalities test *Global Function Domain:* Domain-specific and global cognitive functioning outcomes calculated using z-scores from tasks within each assessed cognitive domain Brain structure & function: Multimodal MRI	• RT (with or without CT) was associated with significant improvements in global cognitive functioning that were correlated with increased gray matter volume within the posterior cingulate cortex, improvements in EF and an attenuation in the decline of visual/constructional memory, but also worse performance on the delayed auditory memory task a reversion in the progression of white matter hyperintensities, • CT (with or without RT) demonstrated maintained memory-domain z-scores, which were associated with enhanced functional connectivity between the hippocampus and superior frontal cortex, but did not effect global cognitive functioning • Although improvements in attention and global cognitive function z-scores were observed following each intervention, the RT group displayed a 48% greater benefit than the combined RT+CT group at 18 months • Combined RT+CT was associated with worse performance on EF tasks and global cognitive functioning post-training • Future work is required to elucidate the neurophysiological

					and cognitive effects of combined training interventions
Cognitive training and cognitive health					
Study	Design	Sample	Treatments	Outcome(s) & Measure Used	Main Findings
Plassman *et al.*, (2007)	Population-based cross sectional study	856 older adults from the Aging, Demographics, and Memory Study 355: 71-79 years 366: 80-89 years 135: ≥ 90 years	Assessed prevalence of AD and other dementias, while attempting to identify predictors of cognitive health	Diagnosis of Alzheimer's, dementia, or vascular dementia: Abbreviated version of the TICS & the IQCODE	• Prevalence of dementia increases with age • Presence apolipotrotein ε4 significantly associated with increased risk of dementia • Higher education was associated with lower dementia risk
Lachman *et al.*, (2010)	Population-based cross-sectional study	3343 non-institutionalized adults from the second wave of the MIDUS study	Average of self-reported frequencies of cognitive activity on a 6-point scale Where: 1 = never 2 = once a month 3 = several times a month 4 = once a week 5 = several times a week 6 = daily	Global cognitive health: BTACT *Executive functions* Working memory: digit-span backwards, verbal fluency, inductive reasoning, processing speed Episodic memory: Immediate & delayed verbal recall (15 words) Attention switching and inhibitory control: Stop & Go Switch Task	• Higher education and frequent participation in cognitive activities were associated with higher episodic memory and EF • The disadvantages of lower education on episodic memory, but not EF, are attenuated by frequent cognitive activity across adulthood and older age
Klussman *et al.*, (2010)	6 month RCT	76 cognitively healthy older women MMSE ≥ 26 73.6 ± 4.2 years	Randomized to *1 of 3 groups*: I) *Mental exercise:* Computer-based exercises focused on creativity, coordination and memory e.g., learning how to operate common software and hardware, writing, playing game, calculating, surfing the Internet, emailing, drawing, image editing, and video taping II) *Physical exercise:* 30 min AE, with resistance and	General cognitive status: CERAD Fluid intelligence: Leistungs-Prüf-System-3/50+ *Executive functions* EF & working memory: TMT A & B Executive attention: Stroop task Episodic memory: Rivermead Behavioural Memory Test: story recall subtest & Free &	• Improvements and maintenance of episodic memory, working memory, and EF were observed at similar degrees following either mental or physical exercise training in older women • Mental exercise training has the potential to impact cognitive health to a similar degree as AE in older women

			flexibility training III) *Non-exercising control* 90 min/day, 3 days/week	Cued Selective Reminding Test	
Rahe *et al.*, (2015)	1.5 month clinical trial	32 older adults with MCI 75.0 ± 5.2 years 50% female	Intervention: NEURO*vitalis* cognitive training program; targets attention, memory, and EF 90 min/day, 2 days/week, plus cognitive home work 10 min/day, 7 days/week	Global cognitive function: MMSE DemTect MCI screening tool *Memory* Verbal episodic memory: Memo Test Figural memory: Complex Figure Test delayed recall *Executive functions* Working memory: DemTec digit span backwards subtest Verbal fluency: semantic and phonemic fluency Executive control: TMT A & B *Visuo-construction abilities* Complex Figure Test *Number processing* DemTec number transcoding subtest	• There were no sex-specific baseline differences in cognitive performance • Women performed better than men on measures of immediate and delayed verbal episodic memory and working memory following 6 weeks of CT • CT produces more pronounced cognitive benefit among women when compared to men • There were no observable training effects when sex was omitted as a covariate within the analyses • Future research is required to elucidate the mechanisms of the observed sex-specific response to CT in MCI
Dual-task exercise training and cognitive health					
Study	Design	Sample	Treatments	Outcome(s) & Measure Used	Main Findings
Erickson *et al.*, (2007)	2-3 week RCT	31 younger adults 23.74 years 61.2% female	Intervention: Single- and dual-task training with continuous and adaptive performance feed-back Control: Non-exercising control	Brain activity: fMRI during single- and dual-task performance	• Dual-task training produced a shift in the location of dual-task-related brain activity • The shift may represent a training-induced reorganization of the cortical areas involved while dual-tasking, resulting in more efficient task performance

			60 min/session, 5 sessions		
You *et al.*, (2009)	1.5 month RCT	13 older adults with a history of falls MMSE ≥ 24 68.3 ± 6.5 years 84.6% female	Intervention: Dual-task cognitive-motor intervention (walking + memory recall) Control: Dual-task placebo (walking + music) 30 min/day, 5 days/week	Memory: Correct number of items recalled while performing dual-task Dual-task gait analysis: Mean velocity & deviation	• Improvements in memory recall were observed after 6 weeks among those randomized to the intervention group • No significant improvements in gait performance were observed in the intervention group following the training period
Silsupado *et al.*, (2009*a*)	1 month RCT	23 cognitively healthy older adults with balance impairment MMSE ≥ 24 75.03 ± 6.2 years 80.9% female	Intervention: *1 of 3 groups:* I) *Single-task* balance training: focused on balance exercises II) *Fixed-priority dual-task* balance training III) *Variable-priority dual-task* balance training 45 min/day, 3 days/week	*Executive functions:* Single- & dual-task gait analysis <u>Single-tasks:</u> Narrow walking & Obstacle crossing <u>Dual-tasks:</u> Narrow walking + counting backwards by 3's, Obstacle crossing + auditory Stroop task	• Single- and dual-task training improves gait speed during single-task conditions • Individuals in either dual-task training group experienced greater improvements in dual-task gait speed compared to those training under single-task conditions • Dual-task training with variable-priority instructions produced improved dual-task gait speed after 2 weeks of training, which were maintained for 3 months following the intervention
Silsupado *et al.*, (2009b)	1 month RCT	23 cognitively healthy older adults with balance impairment MMSE ≥ 24 75.03 ± 6.2 years 80.9% female	Intervention: *1 of 3 groups:* I) *Single-task* balance training: focused on balance exercises II) *Fixed-priority dual-task* balance training III) *Variable-priority dual-task* balance training 45 min/day, 3 days/week	*Executive functions*: Single- & dual-task gait analysis <u>Single-tasks:</u> Narrow walking Obstacle crossing <u>Dual-tasks:</u> Narrow walking + counting backwards by 3's, Obstacle crossing + auditory Stroop task	• Variable priority dual-task balance training produced significant improvements in cognitive performance under dual-task conditions • Variable priority dual-task balance training is more effective in improving both balance and cognitive performance under a dual-task condition than either fixed-priority dual-task or single-task training strategies • Dual-task processing skills acquired during training did not transfer to a novel dual-task • Functional differences between the requirements of the practiced

					and novel dual-tasks may explain these discrepancies
Schwenk *et al.*, (2010)	3 month RCT	61 older adults with mild-to-moderate dementia MMSE: 21.4 ± 2.9 81.9 ± 7.5 years 63.9% female	Intervention: Dual-task training (walking while catching a ball, serial subtractions), with additional progressive resistance-balance and functional-balance training. 15 min/day dual-tasking, 120 min/day total, 2 days/week Control: Low-intensity AE focusing on flexibility, calisthenics, and seated ball games 60 min/day, 2 days/week	Cognitive health and dementia: CERAD Cognitive function: TMT A & B *Executive functions* Dual-task gait analysis (serial subtraction using 2's or 3's)	• No changes in cognitive health or function were observed • Significant improvements in dual-task motor performance were observed in the intervention group • Older adults with mild-to-moderate dementia can modify attentional control and improve performance during dual-task conditions to levels comparable to age-matched, cognitively healthy adults
Forte *et al.*, (2013)	3 month RCT	42 sedentary, community-dwelling older adults 69.8 ± 3.4 years 62% female	Interventions: *Randomized to 1 of 2 groups* I) Multicomponent training, involving group-based coordination, balance, strengthening, agility, stretching and relaxation exercises. Cognitive challenges were incorporated into the physical training components. II) Progressive (60 % 1RM to 80% 1RM) RT, involving a circuit of 12 exercises of the major muscle groups using machines and free weights 3 sets, 8 reps 60 min/day, 2 days/week	*Executive functions* *Inhibition* Random number generation task *Mental flexibility* TMT A & B Cardiorespiratory fitness VO_2max Muscular strength Isokinetic maximal knee extension & flexion Walking speed Max Walking Speed test	• Multicomponent and progressive RT can benefit inhibitory control and functional mobility • Mediation analyses suggest that each modality imparted benefits on inhibitory control along different pathways; multicomponent training directly effected inhibitory control, whereas gains were mediated by elevations in muscular strength following RT • Physical exercise training benefits executive control processes in older adults
Dorfman *et al.*,	1.5 month	10 older adults with	Intervention:	*Executive functions*	• Improvements in usual and dual-

(2014)	open label pilot study 1 month follow-up	a history of falls 78.1 ± 5.8 years 70% female	Progressive, treadmill-based AE with simultaneous verbal fluency and arithmetic tasks 15, progressed to 45 min/day, 3 days/week	Frontal Assessment Battery Verbal fluency TMT B *Scanning abilities* TMT A Mobility & Balance Usual and dual-task (serial 3's) gait speed, step length, and stride time variability	task gait speed and step length, and a reduction in usual stride time variability were observed following training; these were not maintained at follow-up • Improvements in EF (i.e., TMT B and serial subtractions while walking) were observed following training • Changes in performance on the other cognitive tasks did not reach significance • Dual-task treadmill training can benefit cognition and mobility in elderly fallers • Longer duration interventions may be required to impart the greatest cognitive benefit
Eggenberger *et al.*, (2015)	6 month RCT 12 month follow-up	71 cognitively healthy older adults MMSE ≥ 22 78.9 ± 5.4 years 65% female	Interventions: *Randomized to 1 of 3 groups* I) Combined cognitive + physical training 1; Impact Dance Platforms and StepMania Software, participants replicate stepping patterns in response to real-time visual cues II) Combined cognitive + physical training 2; dual-task treadmill walking with verbal memory tasks III) Physical training; moderate intensity (7 RPE) treadmill-based AE 60 min/day, 2 days/week	*EF* TMT B *Working memory* Executive Control Task *Short- and long-term verbal memory* WMS-R Digit Forward & backward, WMS-R Logical Memory subtest *Attention* Age Concentration Tests A & B *Information Processing speed* TMT A, WAIS-R DSST	• Improvements on all of the cognitive tasks, aside from Digit Forward, were observed following each on the 3 interventions • Changes in EF were apparent after 3 months of dual-task treadmill walking, but regressed back to baseline by intervention endpoint • Improvements in EF were apparent following 3 months and 6 months of virtual dance training • Improvements in cognition following the interventions were maintained at follow-up • The combined training interventions provided a subtle advantage to performance on measures of EF (switching attention and working memory) when compared to physical training alone • Longer duration, combined cognitive and physical training

					interventions may be most efficacious at improving cognition in older adults

Abbreviations: 1RM, 1 rep max; 1MWT, one mile walk test; 6MWT, six minute walk test; ACSM, American College of Sports Medicine; ADAS-Cog, Alzheimer's Disease Assessment Scale Cognitive Subsection; AE, aerobic exercise; AMNART, American National Adult Reading Test; aMCI, amnestic mild cognitive impairment; AVLT = Auditory Verbal Learning Test; BDNF = brain-derived neurotropic factor; BP = blood pressure; BTACT = Brief Test of Adult Cognition by Telephone; CERAD = Consortium to Establish a Registry for Alzheimer`s Disease; CT = cognitive training; CWT = Colour & Word test; DSST = Digit Symbol Substitution Test; EEG = electroencephalography; fMRI = functional magnetic resonance imaging; GH = growth hormone; HbA1c = glycated haemoglobin; Hcy = homocysteine; HDL-C = high density lipoprotein C; HRmax = maximum heart rate; HRR = heart rate reserve; IGF-1 = insulin-like growth factor-1; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; MCI = mild cognitive impairment; MMSE = Mini Mental State Examination; MoCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; RCT = randomized controlled trial; RT = resistance training; SPPB = Short Physical Performance Bettery; TC = total cholesterol; TG = triglycerides; TICS = Telephone Interview for Cognitive Status; TMT = Trail-Making test; WAIS-III = Weschler Adult Intelligence Scale, 3rd Edition; WMS-III = Weschler Memory Scale, 3rd Edition; WMS-R, Weschler Memory Scale-Revised

Results from several randomized controlled trials (RCT) do suggest that the cognitive functioning of older adults can benefit from AE training. Relatively short duration (i.e., ≤3 months), moderate intensity (i.e., 40-70% heart rate reserve; 65-75% maximal heart rate) AE training has stimulated increased hippocampal perfusion and volume, which were both associated with improved cardiorespiratory fitness and improved memory performance among older adults with objective cognitive impairment (Maass et al., 2015).

Longer duration (i.e., ≥ 6 months), moderate intensity (i.e., 40-70% heart rate reserve; 75-85% of their maximum heart rate; 60% of their maximum heart rate; 65-75% maximal heart rate) AE training has also led to improvements in perceptual speed and EF, which were correlated with elevations in cerebral oxygenation (Voelcker-Rehage, Godde, & Staudinger, 2011), greater flanker task-related activation within the attentional networks of the prefrontal and parietal cortices (Colcombe et al., 2004), increased prefrontal and temporal cortical volume, and attenuated brain volume loss by magnitudes of 27 - 42% (Colcombe et al., 2006) among cognitively healthy older adults. The benefits of AE training are not reserved solely for those with intact cognitive functioning. A number of studies have reported cognitive improvements following AE training among those with objective cognitive impairment, including global cognitive functioning (Lautenschlager et al., 2008), psychomotor and information processing speed (Williamson et al., 2009), verbal learning and memory (Nagamatsu et al., 2013), and EF (Baker et al., 2010; Nagamatsu et al., 2013). Furthermore, AE training can also lead to physiological improvements within the brain of those with objective cognitive impairment, including increased hippocampal perfusion (Maass et al., 2015) and volume (Erickson et al., 2011; Maass et al., 2015; Ten Brinke et al., 2014), and a reduction the

number of circulating vascular risk factors associated with the development of AD (i.e., systolic BP, total cholesterol, and total cholesterol/high density lipoprotein C risk ratio; Uemura et al., 2012).

Several observations from these studies are of particular interest. First, the exercise-induced changes in hippocampal volume were associated with a number of physiological phenomenon, including elevated concentrations of circulating brain-derived neurotropic factor (Erickson et al., 2011), improved cardiorespiratory fitness (Maass et al., 2015) and improved memory performance in some studies (Erickson et al., 2011; Maass et al., 2015), but also reduced verbal learning and memory performance in others (Ten Brinke et al., 2014). Although exercise-induced changes in brain structure and function can be rationalized as beneficial, the discrepancies in the observed association between exercise-induced changes in hippocampal volume and memory performance suggest that the nature of the relationship between AE, memory-related cortical structural changes, and memory performance remains equivocal. Second, although AE and resistance training (RT) appeared to benefit EF (i.e., reaction time to a complex spatial memory task) to a similar extent in the RCT conducted by Nagamatsu and colleagues (2013), the improvements in verbal learning and memory (i.e., loss after interference on the auditory verbal learning test) were greater following AE compared to RT (43.4% vs. 32.5%, respectively). This comparison suggests that although some aspects of cognition appear to be responsive to a number of different types of exercise training, certain cognitive domains (i.e., EF) may be more sensitive to change following the practice of specific exercise training modalities (i.e., AE). Last, the majority of the AE intervention trials have utilized a progressive exercise training paradigm (Colcombe et al., 2004; Colcombe et al., 2006; Erickson et al., 2011; Nagamatsu et al., 2013; Ten Brinke et al.,

2014; Voelcker-Rehage et al., 2011; Williamson et al., 2009), which suggests that monitoring progression in fitness and modifying the exercise training intensity to reflect this progression may contribute to sustained elevations in the physiological stimuli [(i.e., increased cerebrovascular perfusion; (Colcombe et al., 2004)] that are required to benefit the health and functioning of the brain.

Nevertheless, it would appear that AE training can benefit brain health and functioning in older adults with or without cognitive impairment. The preserving effects of AE on cognition are likely related to some combination of an exercise-induced reduction in CVD risk-factor profiles (Uemura et al., 2012), increased cerebral perfusion (Ribeiro, Alves, Duarte, & Oliviera, 2010; Voelcker-Rehage et al., 2011) or hippocampal perfusion and volume (Maass et al., 2015; Ten Brinke et al., 2014), elevations in circulating neural and vascular growth factors (Lista & Sorrentino, 2010), or improved neurotransmission or the maintenance of prefrontal and subcortical structural or functional integrity (Colcombe et al., 2004; Colcombe et al., 2006); however, the specific mechanisms responsible remain equivocal. Although there is a large evidence base supporting the association between previous or current AE training and maintained or improved cognitive functioning in later life, issues related to differences in exercise program prescription, small sample sizes, lack of control groups, short study durations without follow-up assessments, lack of participant adherence reports, a lack of consensus on which standardized measures represent clinically meaningful outcomes, and which outcomes should be used to monitor the effectiveness of an intervention remain {Gregory et al., 2013, #3710}. The majority of studies investigating the effect of exercise training on brain health have primarily focused on AE training; however, evidence suggests that other forms of exercise training can also benefit the brain.

Resistance Exercise Training and Brain Health in Aging

For older adults who may not be functionally capable of participating in AE, there is a possibility to obtain cognitive benefits from resistance training (RT) as well. However, due to the relatively recent nature of scientific inquiry into the matter, the available literature is sparse but nevertheless promising.

Previous meta-analyses have identified a significant effect of RT on broad cognitive functioning (Heyn et al., 2004), reasoning but not attention or memory (Kelly et al., 2014b), and memory but not EF (Gates et al., 2013) among older adults with objective cognitive impairment. These observations should be considered preliminary, however, as the reviews were limited by the low number of studies that were available for inclusion in the meta-analyses. Increased attention has been recently directed towards the investigation of the effects of RT on cognition in older adults. Short-duration (i.e., ≤ 3 months) moderate intensity RT has led to improvements in memory (Lachman, Neupert, Bertrand, & Jette, 2006; Perrig-Chiello, Perrig, Ehrsam, Staehelin, & Krings, 1998) and EF (Anderson-Hanley, Nimon, & Westen, 2010) among cognitively healthy older adults, and has been found to benefit global cognition (Lü et al., 2016) and stimulate improvements in verbal memory that were associated with improved resting frontal lobe neurophysiology (Yerokhin et al., 2012) among those with objective cognitive impairment. Of particular interest, the improvements in memory performance following RT among cognitively healthy older adults were associated with progressive RT (Lachman et al., 2006) and preliminary evidence suggests that the benefits of short duration RT can persist for up to 1 year post-training (Perrig-Chiello et al., 1998).

Longer duration (i.e., ≥ 6 months) RT programs have also been associated with improved cognition. Specifically, improvements in praxis (Iuliano et al., 2015), memory

(Best, Chiu, Liang Hsu, Nagamatsu, & Liu-Ambrose, 2015; Cassilhas et al., 2007), verbal concept formation (Cassilhas et al., 2007), and EF (Liu-Ambrose et al., 2010; Tsai, Wang, Pan, & Chen, 2015) have been observed following 6 months of RT. RT can also benefit the function of the brain, as RT has been associated with sustained event-related potential (i.e., P3a and P3b amplitudes) during executive tasks over 1-year (Tsai et al., 2015), a reduction in the progression of white matter lesions (Bolandzadeh et al., 2015), a attenuation in cortical white matter atrophy (Best et al., 2015), and elevations in circulating growth factors [i.e., insulin-like growth factor 1 (IGF-1; Cassilhas et al., 2007; Tsai et al., 2015)] among cognitively healthy older adults. Of particular interest, the improvements in EF (i.e., oddball task reaction time) and sustained EEG activity following RT have been associated with elevations in circulating concentrations of IGF-1 (Tsai et al., 2015). IGF-1 mediates exercise-induced neurogenesis within the hippocampus (Lista & Sorrentino, 2010), a region of the brain that is intimately involved with memory processes. Taken together, these observations suggest that the cognitive benefits of RT among cognitively healthy older adults are at least, in part, mediated by elevations in circulating growth factors, specifically IGF-1. Longer duration RT can also benefit the brain health and functioning of older adults with objective cognitive impairment, and has been associated with elevations in global cognition, increased gray matter volume within the posterior cingulate cortex, and revert the progression of white matter hyperintensities (Fiatarone Singh et al., 2014; Suo et al., 2016) in these individuals.

Collectively, these studies demonstrate that the beneficial cognitive effects of RT are possible following progressive, moderate to high intensity (50-80% 1RM) RT , performed at least at least once per week for 3- to 6-months. Furthermore, these

observations suggest that RT can provide the appropriate physiological stimulus, by means of modifications in resting cerebral perfusion (Xu et al., 2014) and elevations in circulating growth-factor profiles, specifically IGF-1 (Cassilhas et al., 2007; Tsai et al., 2015), to initiate improvements in cognition. However, it appears that certain aspects of cognitive functioning differ in how they are influenced by RT, depending upon the duration, intensity, and specific modality of RT. Furthermore, the cognitive benefits provided through RT may be selective and sex-specific; specifically, improved memory and verbal concept formation may be more pronounced in males (Cassilhas et al., 2007; Yerokhin et al., 2012), while elevations in cerebral perfusion (Xu et al., 2014), reductions in white matter lesion volume (Bolandzadeh et al., 2015), attenuated cortical atrophy (Best et al., 2015), and improved EF may be more likely to occur in females (Anderson-Hanley et al., 2010; Liu-Ambrose et al., 2010). Specific characteristics of the RT program may help mitigate these sex-specific differences; improvements in EF have been observed in previously sedentary older men who performed 6 months (Cassilhas et al., 2007) and 12 months (Tsai et al., 2015) of high intensity RT. Furthermore, there has been heterogeneity in the effect of RT on EF, where some have observed improvements following RT that were specific for verbal fluency outcomes (Anderson-Hanley et al., 2010), while others have identified an effect of RT on other executive sub domains, including conflict resolution (Liu-Ambrose et al., 2010), reasoning (Fiatarone Singh et al., 2014), reaction time (Tsai et al., 2015), and central (Cassilhas et al., 2007) EF, and still others did not observe any significant effect of RT on EF (Jensen & Rohwer, 1966; Yerokhin et al., 2012). The heterogeneity in the effect of RT on EF can likely be attributed to differences in the design of these studies, including: i) the population under investigation (i.e., cognitively healthy vs. objective cognitive impairment, males vs.

females), ii) the duration of the interventions, and iii) the relative nature of the RT program (i.e., intensity and progression). Nevertheless, these observations suggest that certain aspects of EF may be differentially affected by exercise training modality, and that the effect of RT on certain cognitive domains depends upon the duration, intensity, and specific modality of RT. Further research is needed to elucidate the mechanisms that drive the sex-specific response to RT, and to determine the characteristics of a RT program (i.e., training intensity, frequency of training, duration of the training program) that will impart the greatest cognitive benefits.

Cognitive Training and Brain Health in Aging

Cognitive training (CT) and the performance of cognitively challenging activities requires the organization and direction of a significant number of neurological processes, such as attention, perception, memory, and EF, and has also been found to benefit intellectual wellness in aging (Kramer, Bherer, Colcombe, Dong, & Greenough, 2004). The potential therefore exists for CT to influence the health and functioning of the aging brain.

It is well understood that years of formal education has a direct correlation with cognitive functioning in older age {Plassman et al., 1995, #81937; Brickman et al., 2011, #34955}. Observational studies have demonstrated that the participation in multiple forms of cognitively stimulating activities has the potential to maintain or improve cognitive functioning in late-life (Verghese et al., 2003; Wang et al., 2013), and has been associated with a reduced risk of MCI when combined with physical exercise training (Hughes, Becker, Lee, Chang, & Ganguli, 2015). Furthermore, a recent review by Plassman and colleagues (2007) found that individuals who had at least 12-years of formal education exhibited stronger cognitive functioning and a reduced risk of AD in later life. However,

recent work by Lachman *et al.*, (Lachman, Agrigoroaei, Murphy, & Tun, 2010) suggests that the influence of less education on cognitive functioning, specifically episodic memory, can be compensated for in later life through the participation in cognitively stimulating activities (e.g., reading, solving word games or puzzles, attending educational lectures or courses, writing) at least once per week across adulthood and into old age. Taken together, these observations suggest that although the participation in certain cognitively stimulating activities throughout life can provide considerable protective benefit to the brain, CT can serve as a method to impart additional cognitive benefits.

Cognitive function has also been shown to improve following CT interventions. Previous meta-analyses have reported a positive effect of CT on memory and subjective cognitive function when compared to non-exercising controls, and also EF and global cognitive composite scores when compared to active (i.e., educational training, health-promotion, or unstructured learning) controls (Kelly et al., 2014a). Of particular interest, the discrepancies in the observed cognitive effects of CT when compared to passive and active controls suggests the possibility that the mentally stimulating activities performed by the active control participants (i.e., health and educational programs) may also benefit certain aspects of cognition, specifically memory performance, to a similar extent as CT. Nonetheless, these observations have led to the implication of CT and mental stimulation as potentially powerful methods to improve cognition in aging (Lehert et al., 2015).

Results from several RCTs have also identified a beneficial cognitive effect of CT. Participation in ≤ 3 months of CT has been associated with improvements in episodic and working memory in older women with MCI (Rahe et al., 2015), while participation in longer duration (i.e., ≥ 6 months) CT interventions has led to improvements in composite memory scores (Fiatarone Singh et al., 2014) that were associated with enhanced

functional connectivity between the hippocampus and superior frontal cortex (Suo et al., 2016), as well as episodic memory, working memory, and EF (Klusmann et al., 2010) among older adults with cognitive impairment. Of particular interest, the improvements in episodic memory in the study by Klussman and colleagues (2010) occurred to a similar degree following both the cognitive and physical training interventions, suggesting that a 6-month CT intervention holds the potential to benefit the brain and reduce the risk of developing dementia to a comparable degree as AE in older women. There may also be sex-specific effects to the cognitive response of CT, as improvements in episodic and working memory following computerized CT for older adults with MCI were specific for women (Rahe et al., 2015). Taken together, these observations support the use of CT in older adults to prevent cognitive impairment, and suggest that the effect of CT on cognitive health may be similar to that seen following participation in habitual exercise training. Although CT can benefit cognition, there is currently uncertainty related to whether cognitive improvements following CT are specific to the trained task or if transfer effects are possible (Bherer, 2015). Furthermore, cross-sectional observations suggest that the most pronounced cognitive benefits might be reserved for those who participate in both CT and physical exercise training (Hughes et al., 2015). Therefore, investigating the effects of interventions that combine physical exercise and cognitive training is warranted.

Novel Exercise Modalities and Brain Health in Aging - Dual-task Exercise

Dual-task (DT) training is a multi-dimensional type of intervention that combines simultaneous cognitive and motor-tasks, and evidence implicated DT training as a potential method to improve physical function in older adults (Pichierri, Wolf, Murer, &

de Bruin, 2011). According to task-coordination and management theory, single-task training has fewer processing demands compared with DT training, since single-task training does not require a participant to practice the coordination of two tasks performed concurrently {Pashler, 1994, #40296}. In contrast, DT training allows for the practice and efficient integration of DT coordination (Kramer, Larish, & Strayer, 1995), such as walking while talking. DT training reflects the demands often experienced during daily living and can provide an appropriate platform for training effects to be carried over to daily life (Yogev-Seligmann, Hausdorff, & Giladi, 2008). The cognitive demands of dual-tasking relates to the cognitive demands of the DT exercise and the cognitive capacity of a given individual; if the demands of performing two tasks simultaneously exceeds the cognitive capacity of the individual, performance in either one or both tasks is reduced (Yogev-Seligmann et al., 2008).

DT coordination is controlled by EF (Yogev-Seligmann et al., 2008). This control has been localized to networks within the dorsolateral prefrontal and superior parietal cortices (Szameitat, Schubert, Muller, & Von Cramon, 2002), and research suggests that executive control processes and their underlying brain regions are plastic and can be modified by training. For instance, Erickson and colleagues (2007) demonstrated a DT training-related 'shift' in the location of DT-related brain activity in younger adults, and suggest that this may represent a training-induced reorganization of the cortical areas involved in dual tasking which resulted in more efficient task performance. In lieu of these observations, numerous small-scale studies have attempted to discern the cognitive benefits associated with DT exercise training. Short duration (i.e., < 6-months) DT exercise training programs have been shown to benefit memory (You et al., 2009), EF (Forte et al., 2013), global cognition (Silsupadol et al., 2009a), and DT gait performance

(Pichierri, Coppe, Lorenzetti, Murer, & de Bruin, 2012; Silsupadol et al., 2009a; Silsupadol et al., 2009b) among cognitively healthy older adults. Longer duration (i.e., ≥ 6 months) DT training interventions have also been shown to benefit EF in cognitively healthy older adults (Eggenberger, Schumacher, Angst, Theill, & de Bruin, 2015). Of particular interest, improvements in EF following DT training were significantly larger than that which was observed among those performing treadmill-based AE alone (Eggenberger et al., 2015), suggesting that DT training holds the potential to provide the most pronounced benefits to EF when compared to single-modality exercise training programs. The impact of short duration (i.e., < 3 months) DT exercise has also been investigated in older adults with pre-existing health issues and cognitive impairment. Short-duration DT training has been shown to improve EF, improve gait (i.e., increase usual and DT gait speed and reduce usual gait stride time variability; (Dorfman et al., 2014), and improve DT gait performance (i.e., reduced DT cost on gait speed; Schwenk, Zieschang, Oster, & Hauer, 2010) among older adults with a history of falls (Dorfman et al., 2014) and those with dementia (Schwenk et al., 2010). Collectively, these preliminary findings are indeed promising; however, there are a number of limitations that are specific to DT exercise training programs that must be considered when interpreting these results. First, there is considerable heterogeneity in the design of the DT interventions used, and the majority of studies investigate the effects of a unique DT intervention. Second, each of these DT interventions imposes unique cognitive and motor requirements that are specific to the given DT exercise, which ultimately impact the cognitive and neurophysiological response to the exercise program. Third, although preliminary evidence exists, the effect of longer duration DT interventions remains relatively understudied. Last, diversity of the populations within current available literature (i.e.,

previously sedentary, cognitively healthy, MCI, and dementia) limits the ability to draw firm conclusions regarding the cognitive and physiological benefits associated with DT training in any population of older adults. Nevertheless, these results suggest that DT training can benefit EF and other aspects of cognition, as well as usual and DT gait characteristics in a number of geriatric populations. DT exercise interventions may be of particular importance to those with cognitive impairment, as these individuals can experience post-training improvements in DT performance that allow them to reach levels that are comparable to cognitively intact older adults (Schwenk et al., 2010). Together, these studies have provided an exciting foundation for the inclusion of DT training in cognitive rehabilitation and other exercise programs for older adults, particularly those at increased risk for cognitive impairment and further pathological cognitive decline..

Limitations and Future Directions for Investigating Cognitive Health and Exercise

Although a number of exercise training modalities can benefit the structure and function of the aging brain, a number of limitations to the current literature base must be identified and overcome before definitive recommendations can be made (Daviglus et al., 2011). First, there is considerable heterogeneity in the neuropsychological tests used to evaluate the cognitive effects of exercise training interventions. In order to effectively compare the impact of various exercise-training modalities on cognition and to avoid the potential for practice effects, a comprehensive cognitive battery that includes a diverse set of tests with alternate forms that evaluate cognition across a number of domains should be developed and endorsed for use (Anderson-Hanley et al., 2010; Daviglus et al., 2011; Yerokhin et al., 2012). Second, in order to elucidate the association between exercise-induced improvements in cognition and structural and functional changes to the brain,

interventions that assess cognition should include neurophysiological and neuroimaging outcomes (e.g., EEG, perfusion CT, transcranial Doppler, fMRI) and determine whether structural and functional outcomes mediate improvements in cognition following training. Third, although a number of long duration (i.e., ≥ 6 months) and large (i.e., > 150 participants) intervention trials exist, more large-scale RCTs are required to determine whether physical, cognitive, and particularly DT exercise training can benefit aspects of cognition that have remained undetected due to low statistical power (Daviglus et al., 2011), and to identify the dosage of exercise (i.e., frequency, intensity, time, and type) that is required to benefit cognition. Fourth, although several RCTs have suggested the presence of sex-based differences in the cognitive response to exercise training (Baker et al., 2010; Xu et al., 2014), the presence of sex-specific and other population-specific (i.e., cognitive status, ethnicity) responses to physical and cognitive exercise training has not yet been definitively determined. Fifth, although observations suggest that each specific type of exercise training modality (i.e., AE, RT, CT, DT) can provide unique and potentially complimentary cognitive benefits, the impact of combined exercise training programs remains relatively understudied and equivocal (Fiatarone Singh et al., 2014; Suo et al., 2016). Sixth, due to the relatively high drop-out rate among the oldest participants within exercise-training programs (Oswald, Gunzelmann, Rupprecht, & Hagen, 2006), interventions should include methods to increase adherence and compliance to the exercise program among the oldest-old through higher level of engagement or the use of novel exercise training components (Silveira, van het Reve, Daniel, Casati, & de Bruin, 2013). Seventh, the brain appears to be less responsive to exercise as neuropathological changes accumulate and cognitive impairment progresses. Intervention efforts that are focused on the prevention of cognitive decline through risk

536 factor management earlier in life may be the most effective strategy to protect and benefit
537 the aging brain. If prevention is the goal of the intervention, longitudinal studies
538 incorporating extended follow-up periods may be required to determine the beneficial
539 effects of an exercise program on the basis of when impaired cognitive functioning is
540 identified. Thom and colleagues (Thom & Clare, 2011) suggested that older adults with
541 declining physical function may be able to sustain the associated benefits of a brief
542 exercise intervention (≥ 3-months) for longer durations if booster sessions are performed
543 at regular intervals; however, the nature and frequency of these booster sessions have yet
544 to be defined.
545

Table 1.2

Limitations within the Current Literature and Recommendations for Future Research

Limitations	Recommendations
Non-standardized use of neuropsychological tests • A given test administered by multiple groups is used to assess different domains of cognition • Results in confusion as to what is being measured and what domain of cognition responds to an intervention • Different tests are being used across studies making comparisons difficult	Standardize the use of the neuropsychological batteries employed, and determine which domain of cognition each test most closely represents
Simple neuropsychological batteries often employed • Assessments employing single outcome measures may not capture significant changes across all domains of cognition • Training effects on certain domains of cognition are missed	Identify single assessments that best represent functioning in a given cognitive domain Include comprehensive neuropsychological batteries that assess multiple domains of cognition
Practice effects can be encountered • Repeat testing using the same version of an outcome assessment may promote practice effects • Resulting in skewed/biased results	Use multiple valid versions of neuropsychological tests for pre- and post-assessments
A lack of association between neuropsychological performance and neurophysiological structure and/or functioning • Association between neuropsychological test performance and cerebral functional integrity have not been captured • A definitive association between an intervention and improvements in cognitive health have not been identified	Couple novel imaging techniques with neuropsychological assessment batteries within randomized controlled trials • Perfusion CT scan, transcranial Doppler, fMRI
Vascular health, cognitive functioning, and neurophysiological outcomes are often not incorporated together within intervention studies • Vascular risk factors have been identified as potentially modifiable risk factors for cognitive decline in aging • Whether improvements in vascular health mediate exercise-induced benefits to brain health and function has yet to be determined	Incorporate vascular risk factor outcomes within interventions trials aimed at improving cognitive functioning • Resting and ambulatory BP • Indices of arterial stiffness • Phlebotomy and blood chemistry • Glucose metabolism • Cardiac functioning
Dropout rates for exercise interventions in older adults are high • Older adults have the lowest cognitive functional reserve, and maybe removing themselves from an intervention prior to the realization of any associated benefits	Include novel training modalities • Engaging and stimulating interventions may promote adherence
Longitudinal and follow-up studies are lacking • Long duration interventions are labour intensive and often result in high dropout rates • Unable to determine whether the effects of an intervention persist for prolonged periods of time	Incorporate de-training periods with extended and multiple follow-up assessments to evaluate the prolonged effect of an exercise intervention on cognitive health
Small sample sizes • Studies to date lack statistical power to detect significant effects of an intervention	Large-scale trials employing recruitment strategies aimed towards larger sample sizes should be encouraged and employed
The potential for "booster" training sessions performed to maintain cognitive benefits that are obtained following an intervention remains to be investigated	Develop and incorporate a "booster" training regimen into future randomized controlled trials

Lastly, the majority of studies have focused on examining the cognitive effects of exercise in relatively healthy, predominantly Caucasian older adults. Although several studies have recruited previously sedentary (Cassilhas et al., 2007; Colcombe et al., 2006; Maass et al., 2015; Williamson et al., 2009) and ethnically-diverse populations (Varma et al., 2015; Varma et al., 2016), future works should aim to include these and other clinical and cognitively healthy populations in order to identify those who stand to achieve the greatest benefits, and to determine whether the cognitive response to exercise training differs between populations. If these current limitations are collectively addressed, future studies would have the potential to identify the most effective exercise regiment to improve cognition in aging while shedding light on the possible mechanisms that drive improved brain health and functioning following exercise training.

Conclusions

Leading a physically active and cognitively engaged lifestyle can have a beneficial influence on cognitive health as individuals advance in age. Exercise training is relatively inexpensive, tolerable, safe, and is readily accessible to the majority of older adults. Identifying interventions that could effectively delay the onset cognitive decline would lead to significant reductions in the incidence of dementia after several decades, and the prevention of approximately 1 million fewer cases by 2050 (Brookmeyer et al., 2007; Camelli et al., 1997). Therefore, attempts should continue to be made to further our understanding of the beneficial impact that exercise training (i.e., physical and CT programs) and other simple lifestyle modifications (i.e., nutrition and diet, risk factor reduction, etc.) have on brain health and functioning and the prevention of cognitive impairment in aging.

The cardiovascular benefits of physical exercise and the cognitively demanding requirements of CT have been proposed as the driving factors that influence the underlying mechanisms responsible for the preservation of cognitive functioning and improved cognition. While recent evidence suggests that motor tasks combined with a cognitive stressor (i.e., DT training) can provide additive cognitive benefits, a specific exercise program aimed at preserving cognitive health has yet to be endorsed by the scientific community. Nonetheless, it appears that the AE-induced benefits to memory and EF can be maximized with individualized or progressive, moderate-to-high intensity AE training over a period of 6- to 12-months. Although the evidence supporting the beneficial effect of RT on the aging brain is promising, future research is required to further determine the effectiveness of RT at maintaining and improving brain health and functioning in older adults. Further investigations that are focused on determining the individual and combined cognitive benefits of multiple exercise training modalities (i.e., AE, RT, CT, and DT) that utilize a standardized and comprehensive battery of neuropsychological and neurophysiological outcomes will provide the most robust evidence related to the benefits of exercise in aging, and will help to further define the mechanisms by which cognitive functioning may be preserved in advancing age

Overarching Purpose

The overarching purpose of this thesis was three-fold: (i) to determine whether CVD risk factors and gait are associated with poor cognitive functioning, (ii) to determine whether blood pressure dipping status (a novel CVD risk factor) was associated with cognitive and gait impairments (iii) to examine the impact of a dual-task gait training and aerobic exercise (DAE) intervention on cognition, gait, and vascular health in

community-dwelling older adults without dementia. Specifically, Chapter 2 sought to retrospectively determine whether cumulative CVD risk (i.e., QRISK2 risk score) and gait performance can contribute to the prediction of global cognition and executive functioning above and beyond age, education, depression, and the presence of uncontrolled hypertension. Chapter 3 sought to retrospectively and cross-sectionally determine whether group differences in cognition, gait, and vascular health exist between older adults with normal BP dipping status and those with reduced BP dipping status. Chapter 4 investigated the longitudinal effect of a novel 26-week dual-task gait training and aerobic exercise (DAE) program on cognition, usual and DT gait, and vascular health in community-dwelling older adults without dementia.

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Chapter 2: Cardiovascular risk contributes to the prediction of executive function but not global cognition in older adults at risk for future cognitive decline

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Vascular Health and the Pathophysiology of Cognitive Function in Aging

Vascular cognitive impairment and vascular dementia (VaD) describe older adults who exhibit impaired cognition that occur as a result of vascular-related brain pathology (Sachdev et al., 2014). VaD is the second leading form of dementia in Western nations and the most prevalent form of dementia in the Orient (Fratiglioni, De Ronchi, & Agüero-Torres, 1999). Subclinical vascular-related brain pathology is common; the prevalence of unsuspected infarction of the cerebral deep small vessels in the elderly ranges from 15% (Bryan et al., 1999) to 28% (Price et al., 1997), and lesions within the deep subcortical and periventricular white matter were present in 95% of the individuals included in the neuroimaging extension of the Rotterdam study (de Leeuw et al., 2001). The frontal-subcortical circuits that control both cognitive and motor processes are located in close proximity; thus, vascular lesions in the frontal cortices may simultaneously cause dysfunction in both systems (Pugh & Lipsitz, 2002). Developing a greater understanding of the link between vascular risk factors and cognitive impairment is imperative, as they are considered the most readily modifiable risk factors for dementia (Smetanin et al., 2009).

Cumulative Cardiovascular Risk and Cardiovascular Disease

Although individual cardiovascular disease (CVD) risk factors have been associated with cognitive impairment and brain pathology in aging (e.g., hypertension, type 2 diabetes) (Langbaum et al., 2012), cumulative CVD risk may aid in the identification of individuals who are at increased risk for future cognitive impairment. Cumulative CVD risk scoring systems, such as the QRISK2 (Hippisley-Cox et al., 2008), utilize predictive algorithms to estimate an individual's 10-year CVD risk, and can

identify populations who may garner the greatest benefit from interventions. The algorithms that are at the core of these scoring systems consider a collection of appropriately weighted clinical characteristics (i.e., age, medical history, smoking status, presence and severity of CVD risk factors) to provide a comprehensive representation of an individual's overall CVD risk when compared to the consideration of a single CVD risk factor in isolation (Hippisley-Cox et al., 2008). The QRISK2 is a well-established, reliable and validated CVD risk calculator (Hippisley-Cox et al., 2008), and recent analyses suggest that the QRISK2 outperforms other established CVD risk scores (i.e., Framingham score and Scottish ASSIGN score) (Collins & Altman, 2012). Although the QRISK2 can provide considerably accurate and reliable prognostic information regarding CVD health, the relationship between QRISK2 scores and cognitive function in aging is currently unknown.

Vascular Health and Pathological Mobility Impairments in Aging

Mobility impairments are characteristic of underlying cognitive impairment (Annweiler & Montero-Odasso, 2012), and vascular brain injury has been implicated as one of the mechanisms that drive age-related changes in gait (Annweiler & Montero-Odasso, 2012; Rosano, Brach, Studenski, Longstreth, & Newman, 2007). Despite these observations, the specific factors that directly contribute to the identification of those with cognitive impairment (i.e., those related to vascular health, mobility, or otherwise) remain equivocal.

Thus, this study sought to determine whether cumulative CVD risk and UG performance independently contribute to the prediction of global cognition and EF, after

controlling for potential confounders (i.e., age, education, depression, uncontrolled hypertension).

Methods

Study Design

This retrospective analysis used pooled baseline data collected from two, 6-month exercise interventions designed to investigate the cognitive, mobility, and vascular responses to exercise among community-dwelling older adults; the inclusion and exclusion criteria for each study were identical.

Eligibility

Following consent, eligibility was determined during a screening visit via a medical history review, resting BP measures, and a sensory and motor function neurological exam. Older adults (55-90 years) without dementia [i.e., no previous dementia diagnosis and a Mini-Mental State Examination (MMSE) score > 24 (Folstein, Folstein, & McHugh, 1975)] and preserved instrumental activities of daily living (IADL) (Lawton & Brody, 1969)] were enrolled. Individuals with significant neurological (Parkinson's) or orthopaedic (severe osteoarthritis) conditions, clinical depression [>16 on the Centre for Epidemiological Studies-Depression Scale (CES-DS) (Radloff, 1977) or based on the clinical judgement of the study physician], BP unsafe for exercise [i.e., > 180/100 mmHg or < 100/60 mmHg (Thompson, Gordon, & Pescatello, 2010)], a recent (< 6 months) severe cardiovascular event (i.e., myocardial infarction, congestive heart disease), and those who were unable to comprehend the questionnaire material were excluded.

Primary Outcomes

Cognition: Global cognition (i.e., MoCA (Nasreddine et al., 2005)) and EF (i.e., Trail Making test Part B; TMT-B (Reitan, 1958)) were considered as the primary outcomes for this study. The MoCA is a valid and reliable (Freitas, Simões, Alves, Vicente, & Santana, 2012) 13-item, 30-point cognitive screening questionnaire that assesses 8 cognitive domains, including attention and concentration, orientation, short-term memory, visuospatial abilities, EF, working memory, and language. The maximum total score is 30, with higher scores indicating better cognition (Nasreddine et al., 2005). The TMT-B is a valid and reliable (Hagen et al., 2014) assessment of EF, and requires participants to draw a line between alternating numbers and letters (e.g., 1, A, 2, B, 3, C, etc.) as quickly and accurately as possible. The time to test completion in seconds represents the outcome score for this test, with higher scores indicating worse performance.

Primary Predictor Variables

Gait: Spatiotemporal gait characteristics were collected using a valid and reliable (Brach, Perera, Studenski, & Newman, 2008) portable electronic walkway system [GAITRite® System and software version 4.7.1, CIR Systems, Peekskill, NY, USA]. Participants completed three standard ("usual") walking trials at preferred speed. The performance from the final two trials were averaged and used for analysis. Start and end points were positioned 1.5 metres from either end of the mat in order to avoid recording the acceleration and deceleration phases of the gait cycle, and footfalls that did not entirely fall on the walkway at the start and the end of each trial were removed prior to analyses. Three gait outcomes, specifically gait velocity (m/sec), step length (cm), and

stride time variability were used to create a UG composite score for analysis. The composite score was derived by converting the parameters to standardized z-scores (i.e., subtracting the baseline group mean from the raw score and dividing by the baseline standard deviation), which were then averaged to create the standardized UG composite score for analysis.

Cardiovascular Risk: CVD risk was quantified using the QRISK®2-2015 cardiovascular risk calculator (available at: www.qrisk.org). QRISK2 uses participant demographics (i.e., age, sex and ethnicity) and clinical information (i.e., smoking status, previous diagnoses of type 2 diabetes, kidney disease, atrial fibrillation, or rheumatoid arthritis, the use of antihypertensive medications, and BP measures) to identify the likelihood of experiencing a significant cardiovascular event (i.e., stroke, transient ischaemic attack, myocardial infarction, or angina pectoris) over the subsequent 10 years (Collins & Altman, 2012). The QRISK2 is a well-established, valid, and reliable (Collins & Altman, 2012; Hippisley-Cox, Coupland, & Brindle, 2014) CVD risk calculator, whose predictive ability has surpassed that of other established CVD risk scores [i.e., National Institutes for Health and Clinical Excellence (NICE) modified Framingham score (Collins & Altman, 2010; Collins & Altman, 2012) and Scottish ASSIGN score (Hippisley-Cox et al., 2007)].

Covariates

Demographic and Clinical Characteristics

Participant demographics and anthropometrics, including age, sex, ethnicity, education, medical history, body mass index, predicted cardiovascular fitness level, and the presence of self-reported cognitive complaints (SCC) were collected. Predicted

cardiovascular fitness was determined using the Step Test for Exercise Prescription (STEP) tool (Stuckey, Knight, & Petrella, 2012), which required participants to ascend and descend a standardized set of two stairs at a self-selected pace; cardiorespiratory fitness was calculated using a prediction algorithm that utilized time to test completion, post-test radial heart rate, age, and sex. The presence of SCC was determined by asking the question "Compared to yourself five years ago, do you think that your memory is: much better (1), better (2), about the same (3), worse (4), or much worse (5)? Responses that were ≥ 4 were coded as a subjective cognitive complaint. Uncontrolled hypertension and was identified using ambulatory BP monitoring. Participants were fitted with an appropriately sized ambulatory BP cuff and monitor (Spacelabs^{TM} 90207 Ambulatory BP Monitor, SpaceLabs Inc), and ambulatory BP was recorded over a 24-hour period: twice per hour during the day (i.e., 06:00 to 22:00), and once per hour during the night (i.e., 22:00 to 06:00). Mean 24-hour systolic BP values > 135mmHg and hypertensive medication status were used together to create a binary variable that identified participants with uncontrolled hypertension (i.e., 0 = controlled hypertension or normotensive; 1 = uncontrolled hypertension). The covariates used for analysis included age, education, CES-DS, and uncontrolled hypertension.

Analysis

Analyses were performed using SPSS version 20 (SAS Institute Inc., Cary, NC, USA). Following the removal of any significant outliers, hierarchical regression models were used to determine the predictive utility of QRISK2 and UG performance on cognition. Specifically, global cognition (i.e., MoCA score) and EF (i.e., TMT-B score) were considered as the dependent variable within their respective models, while QRISK2

score and the UG composite score were considered as the primary predictor variables within each model. Covariates (age, education, CES-DS, uncontrolled hypertension) were entered at the first, second, third, and fourth steps, respectively, to account for the variance in the dependent variables that are attributable to these covariates. QRISK2 score and the UG-composite score were entered into the models at the fifth, and sixth step, respectively, in order to account for the variance in the dependent variables that is uniquely attributable to QRISK2 and UG performance in isolation, after controlling for the influence of the covariates. The increment in explained variance (R^2 change) was obtained and tested for significance at each step of the analysis. Means and standard deviations were determined and two-sided p-values less than 0.05 were claimed as statistically significant.

Results

Participants were enrolled starting on June 26th, 2012, and data collection ended on September 23rd, 2014 (Figure 2.1). A total of 167 individuals were assessed for eligibility, and 48 were excluded from participation (30 did not meet inclusion criteria, 14 declined to participate, 4 were missing baseline data). This left 119 individuals who were enrolled and had complete baseline data.

1

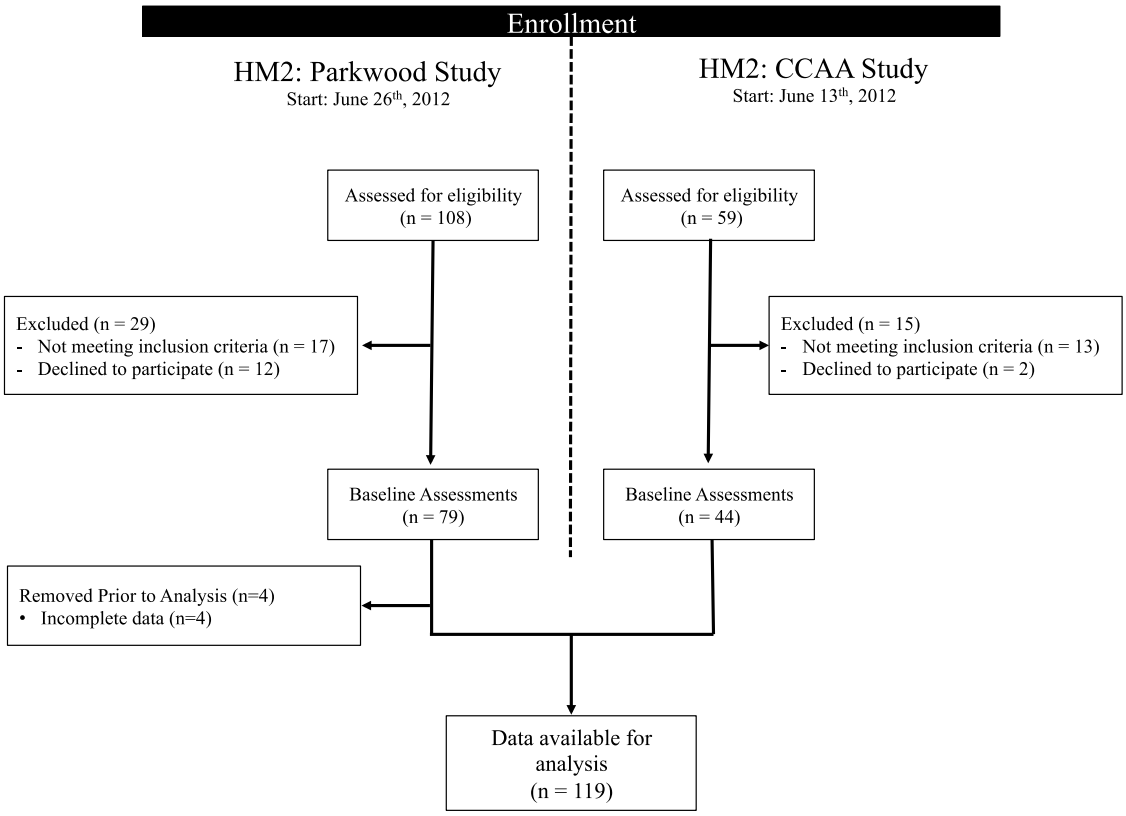

Figure 2.1. Participant Recruitment and Enrollment for the Laboratory- and Community-based Arms of the Healthy Mind, Healthy Mobility (HM2) trial.

Participant characteristics are presented in Table 2.1. Participants had a mean age of 71.5 (SD 7.0) years, 63% were female, most (96%) were Caucasian, and all were highly educated [mean (SD): 15.5 (3.2) years]. Slightly more than half (54.5%) of the participants reported a SCC, and, on average, CES-D scores were well below the cut-off of 16 [mean (SD): 6 (5)]. Participants had subtle indications of underlying cognitive impairment [MoCA scores, mean (SD): 25.0 (2.2)] but not dementia [MMSE scores, mean (SD): 28.5 (1.3)]. On average, performance on the TMT-B was similar to what could be expected for the participant's age and education level (Tombaugh, 2004), and UG performance (i.e., speed, step length, and stride time variability) was also comparable to normative data (Hollman, McDade, & Petersen, 2011). QRISK2 scores ranged from 6.8% to 59.4%, and were, on average, higher than the >20% threshold that is required to identify individuals at high 10-year CVD risk (Collins & Altman, 2012).

Table 2.1

Baseline Characteristics of the 119 Participants Enrolled in the HM2 Studies[a]

Characteristic	Participants (n = 119)
Age, mean (SD), yr	71.4 (7.0)
Female sex, no. (%)	77 (58.3)
Education, mean (SD), yr	15.5 (3.2)
Caucasian, no. (%)	115 (87.1)
Cognitive complaint (ref: 5 yr ago)[b], no (%)	66 (55.5)
MMSE score, mean (SD)	28.6 (1.3)
MoCA score, mean (SD)	25.0 (2.2)
Body mass index, mean (SD)	28.8 (4.5)
Fitness (pVO_{2max}) score[c], mean (SD)	28.0 (8.0)
QRISK2 score (%), mean (SD)	22.7 (12.6)
Usual gait performance, mean (SD)	
Velocity (m/sec)	1.14 (0.17)
Step length (cm)	63.0 (7.3)
Stride time variability (CoV)	2.4 (2.6)
Usual gait composite	-0.01 (0.34)
Medical history, no. (%)	
Hypertension-total[d]	54 (45)
Hypertension-uncontrolled[d]	36 (30)
Hypercholesterolemia	42 (35)
Type 2 diabetes	15 (13)
Myocardial infarction	9 (8)
Angina/coronary artery disease	8 (7)
Atrial fibrillation	4 (3)
Cerebrovascular disease	11 (9)
Depression[f]	7 (6)
Current smoker	4 (3)
Former smoker	63 (53)

Abbreviations: MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; pVO_{2max}, predicted maximal oxygen uptake

[a]Data is preseted as mean (SD) or frequency (%), where applicable

[b]Participants rated their memory on a scale of 5 (1 = much better, 5 = much worse)

[c]pVO_{2max} was determined using the Step Test and Exercise Prescription tool

[d]Total hypertension was defined as those who displayed systolic ambulatory BP measures >135 mmHg *or* those taking antihypertensive medication

[e]Uncontrolled hypertension was defined as 24-hour ambulatory systolic blood pressure >135 mmHg, regardless of medication status.

[f]Depression was defined as scores >16 on the Centre for Epidemiological Studies-Depression Scale

Bivariate Analysis

MoCA scores were negatively correlated with age ($r = -.233$, $p<.01$) and QRISK2 scores ($r = -.213$, $p<.02$), and positively correlated with education ($r = .188$, $p<.04$) and the UG composite score ($r = .210$, $p=.02$). CES-DS and uncontrolled hypertension were not correlated with MoCA scores (all $p>.05$). TMT-B scores were negatively correlated with the UG composite score ($r = -.275$, $p<.01$), and positively associated with age ($r = .462$, $p<.001$), and QRISK2 scores ($r = .469$, $p<.001$). Education, depressive status, and the presence of uncontrolled hypertension were not associated with TMT-B scores (all $p>.05$).

Hierarchal Regression

The results from the regression models are summarized in Table 2.2. All applicable assumptions were met for the two regression models. When examining the explained variance in MoCA scores provided by QRISK2 and UG performance, only age [$F_{(1,117)}=7.003$, $p=.009$] and years of education [$F_{(1,116)}=7.159$, $p=.009$] contributed to the explained variance in MoCA scores. Age contributed the highest degree of explained variance in global cognition (5.6%, R^2 change = 0.056), while years of education explained an additional 5.5% of the variance (R^2 change = 0.055). The overall model explained 13.9% of the variance in MoCA scores ($R^2 = 0.139$, or 13.9%, $p<.01$; Adjusted $R^2 = .093$ or 93%).

When examining the explained variance in TMT-B scores provided by QRISK2 and UG performance, only age [$F_{(1,117)}=31.637$, $p=<.001$] and QRISK2 scores [$F_{(1,113)}=4.89$, $p<.03$] contributed to the explained variance in TMT-B scores. Age contributed the highest degree of explained variance in executive function (21.3%, R^2

318 change = 0.213), while QRISK2 scores explained an additional 3.2% of the variance (R^2
319 change = 0.032). The overall model explained 28.4% of the variance in TMT-B scores
320 (R^2 = 0.284, or 28.4%, $p<.03$; Adjusted R^2 = .245 or 24.5%).
321

Table 2.2

Summary of hierarchal regression analyses for Montreal Cognitive Assessment and Trail Making Test Part B scores.[a]

Model	Step	Variable	R	R^2	R^2 Change	F Change	p-value
1[b]	1	Age	.238	.056	.056	7.003	.009
	2	Education	.334	.111	.055	7.159	.009
	3	Depression	.337	.114	.002	.289	.592
	4	Hypertension-UC	.360	.129	.016	2.069	.153
	5	QRISK2	.371	.138	.008	1.083	.300
	6	UG-Composite	.372	.139	.001	.143	.706
2[c]	1	Age	.461	.213	.213	31.637	<.001
	2	Education	.469	.220	.007	1.049	.308
	3	Depression	.475	.225	.006	.822	.367
	4	Hypertension-UC	.490	.240	.015	2.208	.140
	5	QRISK2	.521	.272	.032	4.890	.029
	6	UG-Composite	.533	.284	.012	1.875	.174

Abbreviations: Hypertension-UC, uncontrolled hypertension; UG-composite, usual gait composite score

[a]Data were missing for depression status in 4 participants.

[b]Dependent variable: MoCA score

[c]Dependent variable: TMT-B score

Discussion

Cardiovascular Disease Risk, Gait, and Global Cognition

The presence of chronic CVD risk factors has been implicated as a mechanism responsible for vascular-related neuropathological changes within the aging brain (Knopman et al., 2001). Recently, the management of CVD risk (Langa, 2015) and also gait dysfunction (Lord, Galna, & Rochester, 2013; Mielke et al., 2013) have emerged as promising avenues to prevent cognitive impairments in aging; however, specific risk factors that share the strongest relationship with cognition remain unknown.

In this study, QRISK2 scores and UG-composite scores were associated with MoCA scores in bivariate analyses; however, multivariable analyses suggest that neither provide a meaningful contribution to the explanation of variance in MoCA scores. Aging coincides with a gradual decline in the functioning of a number of cognitive domains (Sperling et al., 2011), and higher educational attainment is considered a protective factor against cognitive impairment (Brickman et al., 2011). The lack of contribution of either QRISK2 score or the UG-composite scores to the explained variance in MoCA scores was, however, in contrast to the a priori hypothesis and previous observations (Liu et al., 2013; McLennan et al., 2011). Liu and colleagues (2013) identified an association between a number of cardiovascular conditions (i.e., previous stroke, type 2 diabetes, history of smoking, and systolic hypertension) and global cognitive functioning among a large cohort (n = 3,145) of older, community-dwelling African Americans, while McLennen and colleagues (2011) observed low MoCA scores [mean (SD), 22.8 (3.8)] among a cardiovascular outpatient population. The discrepancies between these studies can be attributed to differences in the recruited populations and study design. There is a higher incidence and prevalence of CVD among African Americans compared to

Caucasians (Yusuf, Reddy, Ounpuu, & Anand, 2001), and the relationship between vascular health and cognition may be higher among CVD outpatient populations. However, the participants herein were predominantly Caucasian, attained higher levels of formal education [mean (SD), 15.5 (3.2) years], demonstrated relatively preserved cognitive functioning (i.e., MoCA scores), and had lower pre-existing CVD than those previously studied. Furthermore, the present study utilized the QRISK2 as an index of cumulative CVD risk rather than assessing the relationship between individual CVD risk factors. Although QRISK2 is an effective method to identify individuals at increased risk for CVD, its utility as an index of CVD risk to be used for the investigation of the relationship between vascular health and cognition remains uncertain. Furthermore, age is the strongest weighted factor when calculating the QRISK2. Although these variables did not share multicolinearity, having age entered in to the models first may have masked a portion of the relationship between QRISK2 and cognition.

In contrast to the current study, previous investigations have identified an association between gait dysfunction and poor cognitive functioning in older adults (Allali, Ayers, & Verghese, 2016; Mielke et al., 2013). These conflicting observations are also conceivably related to discrepancies in participant characteristics and study design, including differences in: i) the measure of global cognition, ii) the proportion of participants reporting SCCs, and iii) the methods used to quantify usual gait (i.e., raw data vs. composite performance score). The relatively well-preserved cognitive functioning of the older adults in the present study may have blunted the likelihood of observing a relationship between gait and cognition. Furthermore, previous studies have focused on individual measures of gait performance (Allali et al., 2016; Mielke et al.,

2013) rather than a multifactorial composite score. Although gait speed, step length, and stride time variability have been independently associated with poor global cognitive function (Allali et al., 2016; Mielke et al., 2013) the creation of a UG-composite score for use in this study may have masked these relationships.

Cardiovascular Disease Risk, Gait, and Executive Function

In bivariate analyses, TMT-B scores were positively associated with age, QRISK2 scores, and were negatively associated with UG-composite scores. Linear multiple regression analysis identified age and QRISK2 were the only dependent variables to contribute to the explained variance in TMT-B scores.

Intact EF is dependent upon the integrity of a number of neural networks; however, the prefrontal and dorsolateral prefrontal cortices are heavily relied upon for successful completion of the TMT tests (Hagen et al., 2014; Shibuya-Tayoshi et al., 2007). Thus, vascular-related neuropathology within these regions of the brain could contribute to impaired performance on the TMT-B. In addition to age, the QRISK2 score was the only additional factor that contributed to the explained variance in TMT-B scores. Although associations between TMT-B performance, age, and education have been previously reported (Tombaugh, 2004), the relatively high level of formal education attained by the participants in the current study likely diminished the possibility of observing this relationship. These observations are, however, aligned with previous works that identified an association between a number of indices of vascular health (i.e., aortic stiffness, hypertension, stroke, congestive heart failure and Framingham cardiovascular risk scores) and EF (i.e., TMT-B and Stroop task performance) (Gauthier et al., 2015; Viswanathan et al., 2015). Taken together, these observations suggest that

EF, but not global cognition, is most sensitive to vascular health and CVD risk in aging. These observations are critically important, as EF is one of the first cognitive domains affected by pathological cognitive decline (Li et al., 2004), and is the cognitive domain whose intact functioning is necessary for the maintenance of functional independence in aging (Mitchell & Miller, 2008). However, the low percentage of explained variance in TMT-B scores provided by QRISK2 suggests that other vascular risk factors that are not captured by CVD risk-scoring systems must be identified. Identifying novel vascular risk factors, determining their impact on brain health, and addressing CVD risk may serve to protect and benefit EF in older adults.

Gait performance reflects underlying neuropathology within the frontal cortices (Rosano et al., 2008), and thus, may be associated with cognitive functions that rely upon these regions. In contrast to the current study, previous research has identified an association between usual gait and measures of EF (Hajjar et al., 2009). This discrepancy can be attributed to a number of factors: i) the use of a composite score rather than a single gait characteristic (Hajjar et al., 2009), ii) the EF outcome used in the analysis, as well as iii) the relatively preserved cognitive functioning, and iv) the lack of gait dysfunction within participants. The UG-composite score was envisioned to comprehensively account for gait performance across a number of gait parameters that are affected as cognition declines (Mielke et al., 2013). However, the relatively preserved cognitive functioning of the participants within the current study could have diminished the previously reported relationship between UG performance and EF. Recent evidence suggests that UG performance is dependent upon the integrity of cortical regions that are associated with information processing rather than EF (Rosano et al., 2008). The

relationship between UG and EF becomes most pronounced while performing more complex motor tasks (i.e., walking while responding to cognitively challenging questions) (Springer et al., 2006), and among those with pre-existing gait dysfunction (Holtzer, Verghese, Xue, & Lipton, 2006). A lack of an observed association between our UG-composite score and TMT-B test performance likely arose from the single task requirements of the gait assessment, and the preserved functional status of the participants. In order to overcome these issues, a comprehensive evaluation of gait under a number of conditions, and investigating the relationship between usual and complex gait performance and cognitive functioning within a wide breadth of cognitive domains should be explored.

Conclusions

Identifying which risk factors contribute to increased risk for cognitive impairment, and whether the modification of these risk factors contribute to the prevention of cognitive impairment remains a significant priority in clinical practice (Smetanin et al., 2009). Although there is an increasing consensus on the role of vascular risk factors and gait in the establishment of cognitive impairment (Smetanin et al., 2009), the factors that are the most suitable targets for dementia-risk reduction remains equivocal. The observed relationship between cumulative CVD risk and EF suggests the potential for vascular risk factor management and CVD prevention to be the most promising strategies for the preservation of EF in aging.

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Chapter 3: Diurnal blood pressure dipping status as a novel risk factor for cognitive and mobility impairments in older adults without dementia

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Cognitive Impairment in Aging

Despite considerable efforts being directed towards the maintenance of cognitive health in aging, cognitive impairment continues to impart considerable strain on health care systems (Fisher et al., 2011; Werner, 2012) and the global economy (Brookmeyer, Johnson, Ziegler-Graham, & Arrighi, 2007; Prince et al., 2015). As such, the identification of modifiable risk factors for dementia and the development of effective methods to reduce the incidence and prevalence of cognitive impairment remains a significant priority for cognitive research and clinical practice (Lancet Neurology, 2012).

Although cardiovascular disease (CVD) risk factors are not the sole contributors to the development of cognitive impairment, they do appear to be some of the most promising modifiable dementia risk factor candidates (Chen et al., 2014; Hughes et al., 2014; King, 2014; Langbaum et al., 2012; Norton, Matthews, Barnes, Yaffe, & Brayne, 2014). Indeed this notion appears to have taken hold, as population-based studies suggest that recent reductions in the incidence of dementia in high-income nations can be attributed, in part, to increased rigor in the identification and management of CVD risk factors (Langa, 2015). A number of CVD risk factors (i.e., hypertension and arterial stiffening) contribute to progressive damage to the cortical microvasculature and have been associated with the development of lesions within the frontal and subcortical regions of the brain (Pugh & Lipsitz, 2002). The neural networks that are responsible for cognitive and motor control lay within close proximity to one another within these regions; thus, when these lesions accumulate within these regions, cognitive impairments and gait dysfunction can manifest (Pugh & Lipsitz, 2002). In addition to CVD risk factors, these observations have led to the identification of gait abnormalities as a

potentially modifiable dementia risk factor, and have solidified the importance of the interplay between vascular risk factor management, cognitive functioning, and gait. However, intervention efforts aimed at prevention would benefit from the further identification and characterization of other vascular risk factors that are potentially associated with cognitive and gait impairments in aging (Canavan et al., 2014; Langa, 2015; Prince et al., 2015).

Novel Vascular Risk Factors for Cognitive Impairment

Due to the intimate relationship between CVD risk factors and brain health, it is reasonable to surmise that a myriad of CVD risk factors may impose a significant negative impact on the aging brain. However, questions regarding the specific mechanisms of action by which these risk factors detrimentally affect the aging brain have yet to be answered. Furthermore, as a large number of vascular risk factors have also been implicated as dementia risk factors, it stands to reason that other novel vascular risk factors may also impose a pernicious effect on the aging brain and may play an equally important prognostic role.

Blood Pressure Dipping Status as a Risk Factor for Chronic Conditions in Aging

Ambulatory blood pressure (BP) monitoring has become an integral component of the clinical management of hypertension (National Institute for Health and Clinical Excellence, 2011; Public Health Agency of Canada, 2010), as it collects mean, maximum, and minimum 24-hour, daytime, and night time systolic and diastolic BP and heart rate. This data provides unique and comprehensive insight into a patient's diurnal BP pattern that reaches far beyond what could be obtained during resting office BP measures. Indeed, ambulatory BP monitoring consistently out-performs office BP

measures as an index of overall cardiovascular risk (Krakoff, 2013; O'Brien et al., 2013; Verdecchia, 2000), and has led to the identification of mean nocturnal BP as the most potent predictor of cardiovascular events (ABC-H Investigators et al., 2014; O'Brien et al., 2013).

BP dipping characterizes the diurnal BP pattern, and is expressed as the percentage-drop in mean systolic BP from day to night or the systolic day-to-night ratio (O'Brien et al., 2013). Several BP dipping patterns are commonly observed, including normal dipping status (DS; i.e., those who experience a 10% to 20% drop in mean systolic BP from day to night), extreme dipping status (i.e., those who experience a greater than or equal to 20% drop in mean systolic BP from day to night), non-dipping status (N-DS; i.e., those who experience a drop of less than 10% in mean systolic BP from day to night), and reverse dipping status (i.e., those who experience higher mean systolic BP levels at night compared to day, expressed as a negative blood pressure dipping percentage) (O'Brien et al., 2013; Salles et al., 2016). N-DS is considered an independent CVD risk factor (Salles et al., 2016), and has been associated with an increased risk of severe cardiovascular events, cerebrovascular events, and all-cause mortality (Fagard et al., 2008; Verdecchia, 2000; Salles et al., 2016). It is assumed that because of the exposure to higher BP levels during night time hours when individuals lie supine while sleeping, the brain is less protected from hydrostatic forces and the cerebral vasculature is exposed to pathologically higher pulsatile flow (Fagard et al., 2008). The sustained elevation in pulsatile flow subsequently damages the cerebral microvasculature and contributes to the development of vascular-related brain injury, including microbleeds, lacunar infarcts, and white matter hyperintensities (O'Rourke & Safar,

2005). Previous observations have also identified a negative relationship between N-DS and cognition. N-DS has been associated with worse global cognitive functioning among older adults with various degrees of cognitive and functional impairments (Ohya et al., 2001). In older hypertensive adults, N-DS has been associated with smaller total brain volumes (Nagai, Hoshide, Ishikawa, Shimada, & Kario, 2008), poorer global cognitive functioning (Bellelli et al., 2004), worse memory, and information processing speed (van Boxtel et al., 1998). Abnormal BP dipping may also be associated with the development of mild cognitive impairment (MCI), as the prevalence of MCI is greatest among community-dwelling older adults who are extreme dippers (32%), N-DS (30%), and reverse-dippers (50%) when compared to DS (13.2%; Guo et al., 2010). Although these initial observations suggest a negative relationship between N-DS and brain health, questions regarding the mechanisms that drive the association between N-DS and cognition remain. For instance, some have failed to identify an association between N-DS and cognitive functioning in older adults, and have suggested that this apparent association is mediated by the development of vascular-related cerebral lesions (van Boxtel et al., 2006). Although the mechanistic evidence to implicate N-DS as a pathological mechanism of cognitive impairment in aging exists, the relationship between diurnal BP variation and cognitive functioning in older adults remains equivocal.

Thus, the purpose of this study was two-fold: i) to determine whether differences in cognitive performance [i.e., global cognitive functioning, executive functioning (EF), information processing speed, verbal fluency, and memory] exist between community-dwelling older adults who display a diurnal BP dipping profile greater than 10% (DS), and those who do not (N-DS), and ii) to determine whether group differences exist

between DS (including extreme dippers) and N-DS (including reverse dippers) on usual and dual-task gait speed, step length, and stride time variability, 24-hour ambulatory systolic and diastolic BP, carotid intima-media thickness (cIMT), and carotid arterial compliance (CAC). It was hypothesized that compared to DS, N-DS would: i) perform worse on all cognitive tasks, and ii) demonstrate slower usual and dual-task gait speed, shorter usual and dual-task gait step length, greater usual and dual-task stride time variability, higher 24-hour ambulatory BP and cIMT, and lower CAC.

Methods

Study Design

A retrospective analysis was performed using pooled data collected from two, 6-month exercise interventions that took place in London, Ontario. Targeted recruitment efforts were focused on town-hall announcements, calls to past research participants, and the distribution of advertisements to other locations (i.e., Retirement Research Association of Western University, Boys & Girls Clubs, Kiwanis Clubs, and newspaper ads) within London Ontario, and the surrounding communities.

Participants

The inclusion and exclusion criteria for each of the parent studies were identical. Following consent, eligibility was determined during a pre-therapy visit via a medical history review, seated resting office BP measures, and a comprehensive sensory and motor function neurological exam (Hachinski et al., 2006), which included the Mini-Mental State Examination (MMSE; Appendix C; Folstein, Folstein, & McHugh, 1975), Montreal Cognitive Assessment (MoCA; Appendix D; Nasreddine et al., 2005), Centre of Epidemiological Studies-Depression scale (CES-D; Appendix E; Lewinsohn, Seeley,

Roberts, & Allen, 1997), and the Lawton-Brody Instrumental Activities of Daily Living scale (IADL; Appendix F; Lawton & Brody, 1969).

Older adults (60-90 years) without dementia [i.e., no previous dementia diagnosis and a MMSE score > 24 (Folstein et al., 1975)] and preserved IADLs [i.e., Lawton Brody IADL score ≥ 6 (Lawton & Brody, 1969)] were invited to participate. Individuals who presented with significant neurological conditions (Parkinson's), recent severe cardiovascular conditions (myocardial infarction, congestive heart disease), significant mobility limitations (severe osteoarthritis), clinical depression [i.e., >16 on CES-D scale (Lewinsohn et al., 1997) or at the discretion of the study physician], BP unsafe for exercise [i.e., > 180/100 mmHg or < 100/60 mmHg (Thompson, Gordon, & Pescatello, 2010)], or those unable to comprehend the questionnaire material were excluded. All participants provided written informed consent and the Western University Health Sciences (Appendix A) and Lawson Health Research Institute (Appendix B) Research Ethics Boards approved these studies.

Participant Characteristics

Participant demographics and anthropometrics were collected upon entry to each study, including: age, sex, ethnicity, education, self-reported cognitive complaints, and body mass index. Medical history and current prescribed medications were recorded and used to determine the presence of hypertension, type 2 diabetes, hypercholesterolemia, osteoarthritis, and a previous cardiovascular or cerebrovascular event within each group. Previous cardiovascular events included myocardial infarctions or bypass surgery; previous cerebrovascular events included stroke or transient ischemic attacks. Cardiovascular fitness [i.e., predicted maximal oxygen uptake] was determined using the

Step Test and Exercise Prescription (STEP; Appendix M) tool (Petrella, Koval, Cunningham, & Paterson, 2001).

Outcomes

All outcomes were collected over a span of two days, with cognition and gait evaluated on the first day of assessments, and vascular health evaluated on the second day of assessments. Each assessment session lasted approximately 60 minutes.

Cognition

Global cognition and domain-specific cognitive function (i.e., EF, information processing speed, verbal fluency, and memory) were assessed using traditional neuropsychological evaluations.

Global Cognition

MoCA scores that were collected during the screening and eligibility visit were used as a surrogate of global cognitive functioning. The MoCA is a valid and reliable (Costa et al., 2012; Freitas, Simões, Alves, Vicente, & Santana, 2012) cognitive screening questionnaire that assesses cognitive functioning within 8 sub-domains, including attention and concentration, orientation, short-term memory, visuospatial abilities, EF, working memory, and language. The maximum total score is 30, with higher scores indicating better global cognitive functioning.

Executive Function

EF was assessed using the Trail Making Tests (TMT) part B (Appendix H), TMT-B minus A (B-A), and TMT-B to A ratio (B/A), which has been deemed a valid and reliable method to evaluate set-shifting and executive control (Arbuthnott & Frank, 2000; Hagen et al., 2014). The TMT-B requires participants to draw a line between alternating

numbers and letters (e.g., 1, A, 2, B, 3, C, etc.) as quickly and accurately as possible. The time to test completion in seconds represents the outcome score for the test.

Information Processing Speed

Information processing speed was assessed using the TMT-A (Appendix G) and the Digit Symbol Substitution Test (DSST; Appendix J). The TMT-A requires participants to draw a line between consecutive numbers spanning from 1 to 25 as quickly and accurately as possible. Time to complete the TMT-A is used as the outcome score for the test. For the purposes of this study, the decision to include the TMT-A as a measure of information processing speed was due to the specific cognitive requirements of the TMT A task (i.e., simple motor task with lower perceptual complexity when compared to TMT B; Arbuthnott & Frank, 2000).

The DSST is a 120 second task that requires participants to decode a test section by using a legend to sequentially match numbers with their corresponding symbols as quickly and accurately as possible. Performance on the DSST is dependent upon a number of cognitive processes, including incidental memory, visuomotor coordination, perceptual organization, sustained attention, psychomotor speed, and information processing (Wechsler, 2003). The DSST has high test-retest reliability (Matarazzo & Herman, 1984) and a maximum total score is 133, with higher scores indicating better performance.

Verbal Fluency

Verbal fluency was assessed using semantic (Appendix K) and phonemic (Appendix L) verbal fluency tasks. For the semantic verbal fluency outcome, participants were required to provide as many unique responses to a category fluency task (i.e.,

naming animals) as possible in 60 seconds (Tombaugh, Kozak, & Rees, 1999). The Controlled Oral Word Association (COWA; Benton, Lester, DeSandoz Hamsher, & Sivan, 1994) test was used to evaluate phonemic verbal fluency, which required participants to provide as many unique words that started with the letter "C", excluding proper nouns, numbers, and suffix substitutions (e.g., love, loves, lover, loving, etc.). The total numbers of unique responses provided over 60 seconds for each test were used as the verbal fluency outcomes.

Memory

Memory was assessed using the Auditory Verbal Learning Test (AVLT; Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2005). The AVLT (Appendix I) requires participants to listen to a list of 15 monosyllabic words and provide as many correct responses as possible over five independent trials. After the fifth trial, an interference list containing 15 new monosyllabic words is presented, and participants are required to recall as many items from the interference list as possible. Approximately five minutes (immediate recall) and 30 minutes (delayed recall) after the administration of the interference trial, participants are required to provide as many items from the original 15 item list as possible without having received any cues. Responses from each of the five trials and the immediate and delayed recall trials were used as a measure of verbal learning and memory, respectively.

Gait

Spatiotemporal gait characteristics were collected using an electronic walkway system [GAITRite® System, Software version 4.7.1, CIR Systems, Peekskill, NY, USA] following previously published techniques (Gregory et al., 2016). Briefly, participants

completed two standard (i.e., usual gait, UG) walking trials across the GAITRite mat at usual preferred speed. Participants then performed three separate DT walking trials: one "familiarization" (i.e., counting backwards from 100 by 1's) and two separate experimental (i.e., naming animals and subtracting serial 7's from 100) DT conditions. Gait characteristics were collected over two walking trials for each experimental condition (i.e., usual, naming animals, serial 7's) and were averaged and used for analysis. In order to avoid capturing the acceleration and deceleration phases of the gait cycle, participant start and end points were positioned 1.5 metres from either end of the mat (Montero-Odasso et al., 2009). Footfalls that did not entirely fall on the walkway at the start and the end of each walk were removed prior to analyses. No instructions regarding task prioritization were provided during the DT trials.

Vascular Health

In an attempt to avoid the effect of extrinsic factors on ambulatory BP and the vascular ultrasonography assessments being performed on day 2, participants were asked to avoid the participation in vigorous intensity exercise for 24 hours, the consumption of alcohol and tobacco products for the final 12 hours, and the consumption of food for four hours prior to the ultrasonography assessments (Pickering et al., 2005).

Ambulatory Blood Pressure

Upon completion of the first assessment day, participants were fitted with an appropriately sized, valid and reliable (Iqbal, Fotherby, & Potter, 1996) ambulatory BP cuff and monitor (Spacelabs^{TM} 90207 Ambulatory Blood Pressure Monitor, SpaceLabs Inc), which they wore over the subsequent 24 hours. Ambulatory BP measures were collected twice per hour during the day (i.e., 06:00 to 22:00) and once per hour at night

(i.e., 22:00 to 06:00), and the percent drop in daytime to nighttime mean systolic BP was used to calculate DS. For instance, a participant would demonstrate a 10.4% dip in systolic BP if they presented with a mean daytime systolic BP of 135 mmHg and a mean night time systolic BP of 121 mmHg. Although mean daytime and night time systolic BP were used to determine DS, mean 24-hour systolic and diastolic BP were considered as outcomes for this study Participants were identified as N-DS if they demonstrated a < 10% reduction in systolic BP from daytime (i.e., 06:00 to 22:00) to night time (i.e., 22:00 to 06:00; O'Brien et al., 2013; Salles et al., 2016).

Carotid Arterial Compliance and Intima-Media Thickness

Immediately following the 24-hour ambulatory BP period, carotid arterial stiffness measures were obtained using B-mode ultrasonography following previously published techniques (Gregory et al., 2016). Briefly, participants were fitted with a 3-lead ECG and underwent 5 to 10 minutes of supine rest in a quiet, temperature controlled (20 to 23°C) room. A longitudinal B-mode image (Vingmed, GE Ultrasound A/S, Horton, Norway) of the cephalic portion of the right common carotid artery was then obtained 1-2 cm proximal to the carotid bifurcation (Gregory et al., 2016). Arterial diameters were measured leading-edge-to-leading-edge at peak systole and end diastole over three cardiac cycles and subsequently averaged. Following image acquisition, a single measure of resting supine brachial arterial systolic and diastolic BP was recorded using automated oscillometry (BPTru, Coquitlam, BC, Canada). Carotid arterial compliance (CAC) and carotid intima-media thickness (cIMT) were considered as outcomes for this study; arterial compliance was determined using the following equation:

$$\left[\pi\left(\frac{Dmax}{2}\right)^2 - \pi\left(\frac{Dmin}{2}\right)^2\right]\Delta P \qquad \text{(Equation 2)}$$

where D_{max} was the systolic carotid arterial diameter, D_{min} was the diastolic carotid arterial diameter, and ΔP was resting brachial pulse pressure. cIMT was determined by subtracting the carotid arterial lumen diameter from the outer arterial diameter at diastole from the far wall of the carotid artery (Gregory et al., 2016).

Analysis

All analyses were performed using SPSS version 20 (SAS Institute Inc., Cary, NC, USA). Participant characteristics and anthropometrics (i.e., age, sex, ethnicity, education, body mass index, cardiovascular fitness, CES-D scores, MoCA and MMSE scores) were compared between DS and N-DS using one-way ANOVA for continuous data, and Chi-squared tests for categorical data. The prevalence of vascular risk factors, mobility limitations (i.e., osteoarthritis), and previous cardiovascular or cerebrovascular events were compared between DS and N-DS using Chi-squared tests. For the primary outcomes, differences in cognitive performance (i.e., TMT-B, TMT-A, DSST, semantic fluency & COWA, and AVLT) between DS and N-DS were investigated using one-way ANOVA. For the secondary outcomes, differences in usual and dual-task (i.e., serial 7's) gait and vascular health (i.e., 24-hour ambulatory SBP & DBP, cIMT, and CAC) between DS and N-DS were investigated using one-way ANOVA. Means and standard deviations (SD) were determined and two-sided P-values less than 0.05 were claimed as statistically significant.

Results

Participant Characteristics

Participant enrolment began June 26th, 2012, and data collection was finalized September 23rd, 2014. Across studies, of the 167 individuals who responded to the recruitment efforts (Figure 3.1), 44 were excluded from the studies (30 did not meet inclusion criteria, 14 declined to participate). An additional 8 participants did not have complete ambulatory BP data, which precluded the determination of their dipping status and resulted in their removal from this study. The remaining 115 individuals had complete baseline data and were included in the analyses. All of the data that was used for this study (i.e., ambulatory BP data used for group and outcome measures) was collected at baseline within their respective intervention studies.

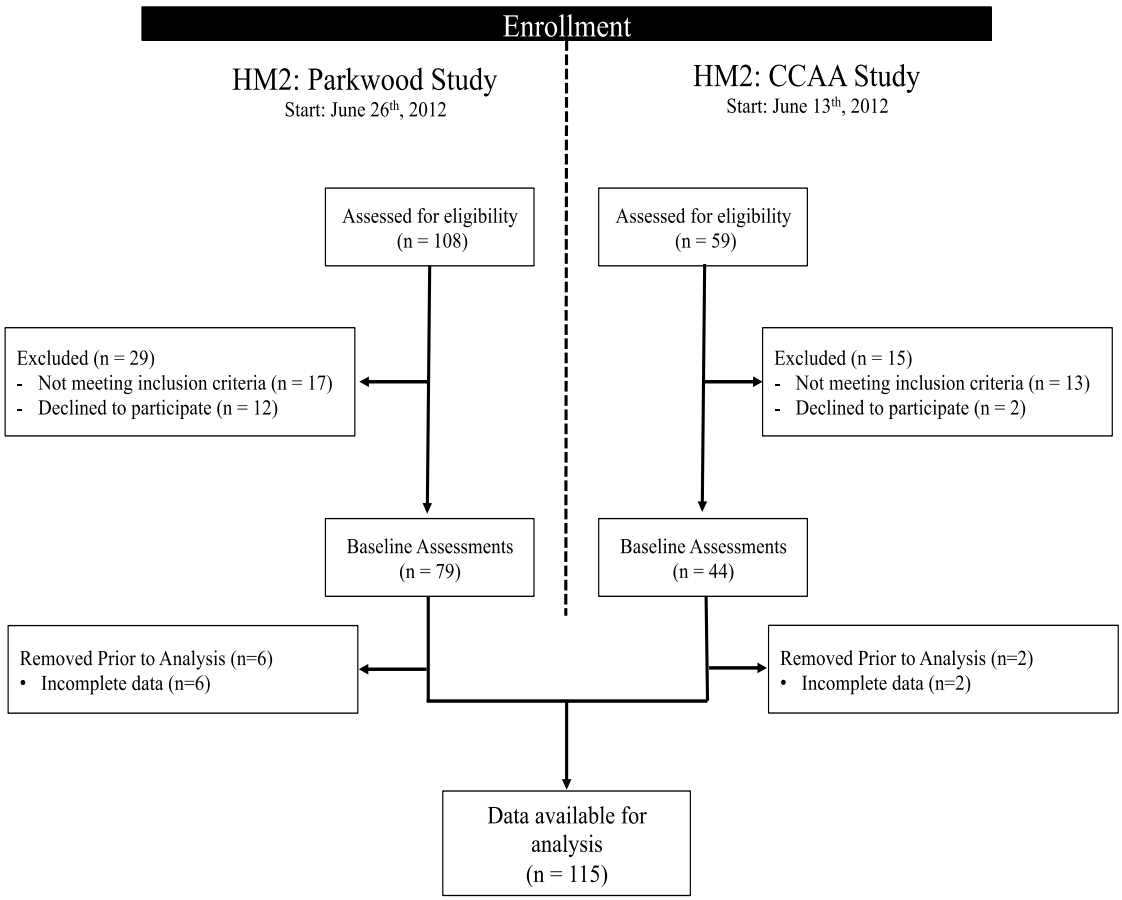


Figure 3.1. Participant recruitment for the Healthy Mind, Healthy Mobility (HM2) Laboratory- and Community-based Exercise Interventions.

Participant characteristics are presented in Table 3.1. Participants were older [mean (SD), 71.7 (6.9) years] and approximately 73% were female; most (96%) were Caucasian, and all were highly educated [mean (SD): 15.5 (3.3) years of formal education]. Educational attainment was the only participant characteristic that differed between groups, with N-DS achieving a higher level of formal education compared to DS [mean (SD); DS: 16.1 (3.3) vs. N-DS: 14.9 (3.1), p = .04]. On average, the participants in the study scored well within the range to indicate the absence of clinical depression on the CES-D [mean (SD): 5.8 (5.2)]. Over half (54.7%) of the participants reported that their memory was worse than 5 years earlier. Objective cognitive screening corroborated these subjective concerns, as participants had, on average, subtle indications of underlying cognitive impairment [MoCA scores, mean (SD): 24.8 (2.2)] but not dementia [MMSE scores, mean (SD): 28.5 (1.3)]. Vascular risk factors and medical comorbidities were also prevalent among participants in this study; approximately half (47%) had hypertension, 37% had hypercholesterolemia, 17% had type 2 diabetes, and 15% had osteoarthritis. The occurrences of previous cardiovascular or cerebrovascular events were rare among participants (6% and 10%, respectively). The prevalence of hypertension and the occurrence of a previous cardiovascular events were the only two clinical characteristics to differ between groups, with a higher proportion of those with N-DS having hypertension [n (%); DS: 17 (35) vs. N-DS: 37 (56), p = .02] and only N-DS reported having experienced a previous cardiovascular event [n (%); DS: 0 (0) vs. N-DS: 7 (11), p = .02].

Table 2.1

Participant characteristics and medical history for the Total Sample, Older Adults with Normal Blood Pressure Dipping Status (DS), and Those with Reduced Blood Pressure Dipping Status (N-DS).[a]

Characteristic	Total (n=115)	DS (n=49)	N-DS (n=66)	Group difference (p-value)
Age, y, mean (SD)	71.7 (6.9)	70.5 (6.6)	72.5 (7.0)	.13
Female sex, No. (%)	73 (63)	33 (67)	40 (61)	.46
Caucasian, No. (%)	110 (96)	45 (92)	65 (98)	.10
Body mass index[a], mean (SD)	28.9 (4.5)	28.5 (4.0)	29.2 (4.8)	.43
Baseline fitness[b], mean (SD)	27.9 (8.0)	28.7 (9.1)	27.2 (6.9)	.30
Education, y, mean (SD)	15.5 (3.3)	14.9 (3.1)	16.1 (3.3)	**.04**
MMSE score[c], mean (SD)	28.5 (1.3)	28.5 (2.3)	28.5 (1.2)	.94
MoCA score[c], mean (SD)	24.8 (2.2)	25.1 (2.3)	24.7 (2.2)	.36
Memory complaint, No. (%)	63 (55)	25 (51)	38 (58)	.50
CES-D score[d], mean (SD)	5.8 (5.2)	5.6 (4.6)	5.9 (5.6)	.76
Medical History				
Osteoarthritis, No. (%)	17 (15)	7 (14)	10 (15)	.90
Hypertension, No. (%)	54 (47)	17 (35)	37 (56)	**.02**
Hypercholesterolemia, No. (%)	42 (37)	13 (27)	29 (44)	.06
Type 2 diabetes, No. (%)	19 (17)	8 (16)	11(17)	.96
Previous cardiovascular event[e], No. (%)	7 (6)	0 (0)	7 (11)	**.02**
Previous cerebrovascular event[f], No. (%)	11 (10)	4 (8)	7 (11)	.66

Abbreviations: DS, Dippers; N-DS, Non-Dippers; SD, Standard Deviation; MMSE, Mini-Mental Status Examination; MoCA, Montreal Cognitive Assessment; CES-D, Centre for Epidemiological Studies Depression Scale

[a] Body Mass Index measured in kg/m^2

[b] Baseline fitness was estimated using the Step Test and Exercise Prescription (STEP) tool, and is measured in $mlO_2/kg/min$. Four participants from the N-DS group did not complete the STEP test and were missing data for this outcome

[c] Range from 0 to 30; lower scores indicate greater cognitive impairment

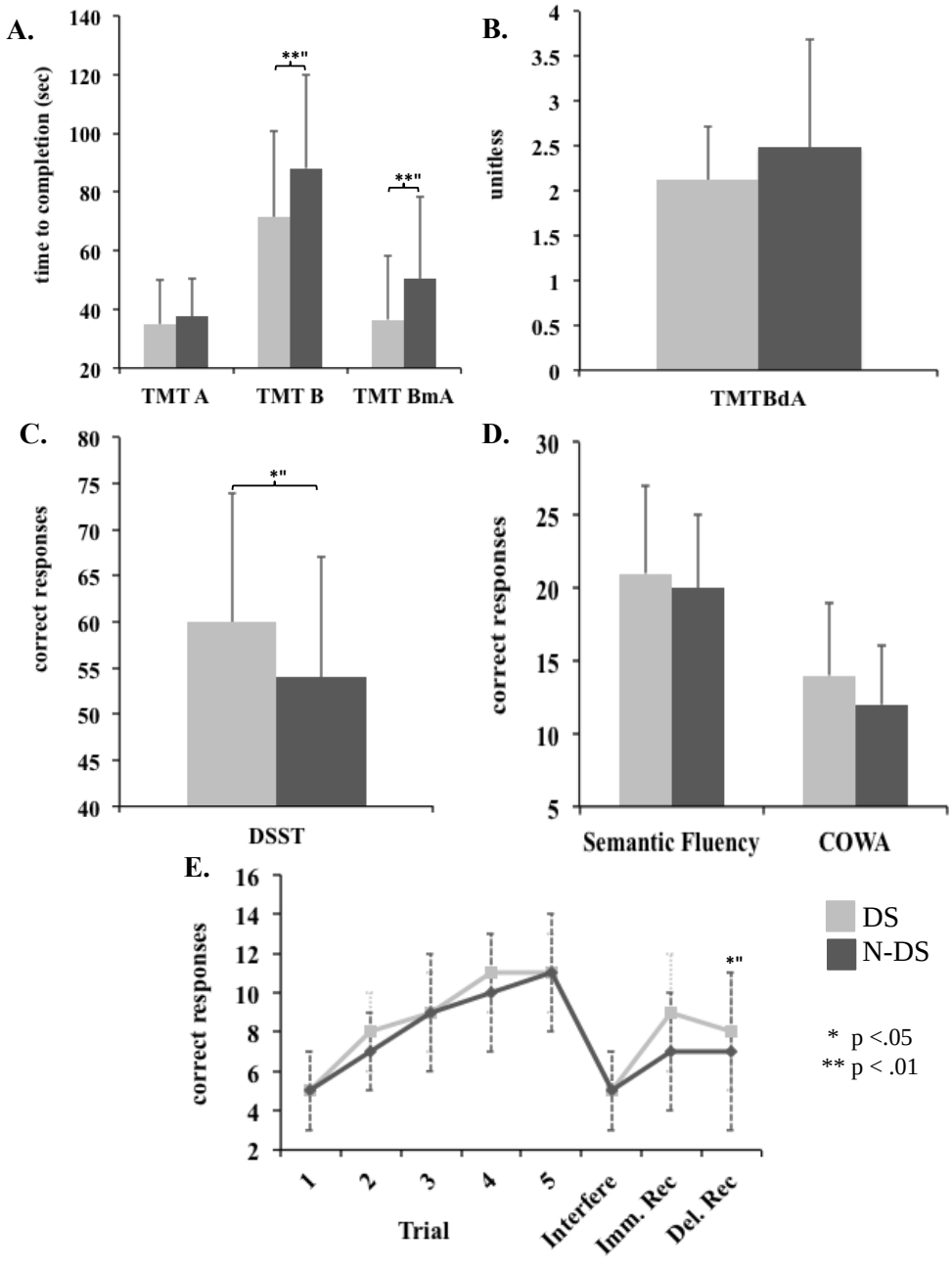
[d] Scores above 15 indicate clinical depression. Four participants from the N-DS group did not complete the CES-D and were missing data for this outcome

[e] Previous cardiovascular events included myocardial infarction, bypass surgery, or coronary artery stent implantation

[f] Previous cerebrovascular events included strokes or transient ischemic attacks (TIA)

315 ***Group Differences in Cognition***

316 Differences in cognitive performance between DS and N-DS are presented in
317 Figure 3.2 and Table 3.2. N-DS performed worse on measures of EF [TMT B, mean
318 (SD); DS: 71.5 (29.2) sec vs. N-DS: 88.1 (31.8) sec, p=.005; TMT B-A, mean (SD); DS:
319 36.5 (21.6) sec vs. N-DS: 50.5 (28.0) sec, p=.004], information processing speed [DSST,
320 mean (SD); DS: 60 (14) correct vs. N-DS: 54 (13) correct, p=.03], and memory [AVLT
321 delayed recall, mean (SD); DS: 8 (3) correct vs. N-DS: 7 (4) correct, p=.02].
322 Performances on measures of verbal fluency, as well as other measures of information
323 processing speed and memory (i.e., TMT A and AVLT immediate recall) were not
324 significant (all p>.05).



Abbreviations: TMT, Trail Making Test; DSST, Digit Symbol Substitution Test; COWA, Controlled Oral Word Association Test; Imm. Rec, immediate recall; Del. Rec, delayed recall. A. Executive function (TMT A, TMT B, TMT B-A), B. Executive function (TMT B/A), C. Information Processing Speed (DSST), D. Verbal Fluency (semantic: naming animals; phonetic: COWA), E. Memory (AVLT immediate and delayed recall).

Figure 3.2. Group differences in cognition between older adults with normal blood pressure dipping status (DS) and those with reduced blood pressure dipping status (N-DS).

Table 3.2

Performance on the Cognitive Tasks for the Total Sample, Older Adults with Normal Blood Pressure Dipping Status (DS), and Those with Reduced Blood Pressure Dipping Status (N-DS).[a]

Outcome	Total (n=115)	DS (n=49)	N-DS (n=66)	Group difference (p-value)
Executive Function				
TMT A (sec)	36.5 (13.7)	35.0 (14.9)	37.6 (12.7)	.32
TMT B (sec)	81.0 (31.7)	71.5 (29.2)	88.1 (31.8)	**.005**
TMT BmA (sec)	44.5 (26.2)	36.5 (21.6)	50.5 (28.0)	**.004**
TMT BdA (unitless)	2.32 (1.0)	2.12 (.60)	2.48 (1.19)	.054
Information Processing				
DSST (no. correct)	57 (14)	60 (14)	54 (13)	**.03**
Verbal Fluency				
Semantic fluency (no. correct)[b]	20 (6)	21 (6)	20 (5)	.37
COWA (no. correct)[c]	13 (5)	14 (5)	12 (4)	.06
Verbal Learning & Memory				
Trial 1 (no. correct)	5 (2)	5 (2)	5 (2)	.39
Trial 2 (no. correct)	8 (2)	8 (2)	7 (2)	.15
Trial 3 (no. correct)	9 (3)	9 (2)	9 (3)	.15
Trial 4 (no. correct)	10 (3)	11 (2)	10 (3)	.06
Trial 5 (no. correct)	11 (3)	11 (2)	11 (3)	.08
Interference trial (no. correct)	5 (2)	5 (2)	5 (2)	.08
Immediate recall (no. correct)[d]	8 (3)	9 (3)	7 (3)	.08
Delayed recall (no. correct)[e]	7 (4)	8 (3)	7 (4)	**.02**

Abbreviations: TMT, Trail Making Test; BmA, TMT B score minus A score; BdA, TMT B score divided by A score; DSST, Digit Symbol Substitution Test; COWA, Controlled Oral Word Association Test

[a] All data is presented as mean (standard deviation)

[b] Semantic verbal fluency was assessed using "animals" as the category

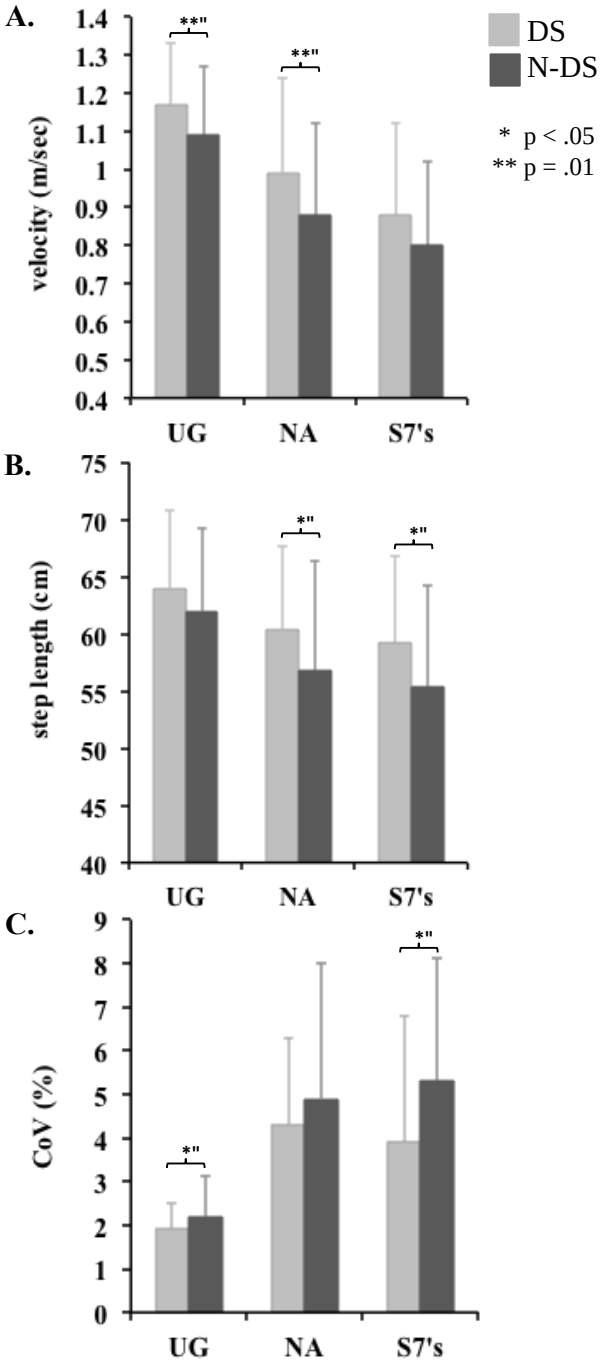
[c] COWA required participants to provide unique words starting with the letter "C", excluding proper nouns, numbers, and simple suffix changes

[d] Immediate verbal recall was performed approximately 5 minutes following the interference trial

[e] Delayed verbal recall was performed approximately 30 minutes following the interference trial

340 ***Group Differences in Usual and Dual-task Gait***

341 Differences in usual and dual task (i.e., naming animals and serial 7's) gait
342 performance between DS and N-DS are presented in Figure 3.3 and Table 3.3. Compared
343 to DS, N-DS had slower usual gait speed [mean (SD); DS: 1.17 (.16) vs. 1.09 (.18) m/sec,
344 p=.01] and greater usual gait stride time variability [CoV (%), mean (SD); DS: 1.9 (.6)
345 vs. N-DS: 2.2 (.9) %, p=.03]. Compared to DS, N-DS also demonstrated shorter step
346 length while performing both dual tasks [naming animals, mean (SD); DS: 60.4 (7.2) vs.
347 N-DS: 56.8 (9.6) cm; serial 7's mean (SD); DS: 59.2 (7.2) vs. N-DS: 55.4 (9.6) cm, both
348 p=.02]. N-DS also demonstrated slower gait speed while performing the verbal fluency
349 task but not the serial 7's subtraction task, and greater stride time variability while
350 performing the serial 7's subtraction task but not the verbal fluency task when compared
351 to DS.



Abbreviations: UG, usual gait; NA, naming animals, S7's, serial sevens; m/sec, metres per second; cm, centimetres; CoV, coefficient of variation (%). A. Usual and dual-task gait speed, B. Usual and dual-task step length, C. Usual and dual-task stride time variability. Naming animals and serial seven subtractions were used as verbal fluency and arithmetic dual-task conditions during the gait assessments.

Figure 3.3. Group differences in usual and dual-task gait performance between older adults with normal blood pressure dipping status (DS) and those with reduced blood pressure dipping status (N-DS).

Table 3.3

Usual and Dual-task Gait Characteristics for the Total Sample, Older Adults with Normal Blood Pressure Dipping Status (DS), and Those with Reduced Blood Pressure Dipping Status (N-DS).[a]

Characteristic	Total (n=115)	DS (n=49)	N-DS (n=66)	Group difference (p-value)
Usual gait				
Velocity (m/sec)	1.13 (.18)	1.17 (.16)	1.09 (.18)	**.01**
Step length (cm)	62.6 (7.1)	64.0 (6.8)	62.0 (7.3)	.11
Stride time variability (CoV, %)[b]	2.2 (1.0)	1.9 (.6)	2.2 (.9)	**.03**
Dual-task (naming animals) gait				
Velocity (m/sec)	.93 (.23)	.99 (.25)	.88 (.18)	**.01**
Step length (cm)	58.3 (8.5)	60.4 (7.2)	56.8 (9.6)	**.02**
Stride time variability (CoV, %)[c]	4.7 (2.8)	4.3 (2.0)	4.9 (3.1)	.25
Dual-task (serial 7's) gait				
Velocity (m/sec)	.83 (.24)	.88 (.25)	.80 (.24)	.11
Step length (cm)	57.0 (8.8)	59.2 (7.2)	55.4 (9.6)	**.02**
Stride time variability (CoV, %)[d]	4.7 (3.1)	3.9 (2.0)	5.3 (3.1)	**.03**
Vascular Health				
24-hour systolic BP (mmHg)	129 (12)	127 (12)	131 (12)	.10
24-hour diastolic BP (mmHg)	72 (8)	71 (8)	73 (8)	.20
Carotid IMT (mm)	.65 (.13)	.66 (.12)	.65 (.14)	.88
Carotid AC (mm^2/mmHg x 10^{-1})	.86 (.54)	.89 (.67)	.83 (.43)	.57

Abbreviations: AC, arterial compliance; CoV, coefficient of variation; mmHg, millimeters of mercury; IMT, intima-media thickness

[a] All data is presented as mean (standard deviation)

[b] n = 47 for Dippers and n = 64 for Non-Dippers following the removal of outliers

[c] n = 44 for Dippers and n = 62 for Non-Dippers following the removal of outliers

[d] n = 41 for Dippers and n = 63 for Non-Dippers following the removal of outliers

Group Differences in Vascular Health

Differences in 24-hour ambulatory systolic and diastolic BP, cIMT and CAC between DS and N-DS are also presented in Table 3.3. Despite participants having been stratified into groups by ambulatory BP dipping status (a known CVD risk factor), there were no differences between DS and N-DS on 24-hour systolic and diastolic BP, cIMT, or CAC (all $p > .05$).

Discussion

Until effective prevention and management strategies for cognitive impairment are developed, dementia is expected to continue to place a significant burden on the global health-care systems and economy (Brookmeyer et al., 2007; Fisher et al., 2011; Prince et al., 2015; Werner, 2012). Thus, developing a thorough understanding of the pathological processes and risk factors that are associated with the development of subclinical cerebrovascular disease and dementia is of significant clinical importance. CVD risk factors have been implicated as mechanisms that drive the development and progression of neuropathological changes in the brain, which predispose individuals to cognitive impairment and an increased risk of dementia. Despite these observations, the specific mechanisms by which traditional CVD risk factors impart detrimental effects on the aging brain have yet to be fully elucidated.

Hypertension is a known risk factor for a number of chronic conditions in aging, including cardiovascular morbidity (i.e., left ventricular hypertrophy), coronary heart disease, and stroke (ABC-H Investigators et al., 2014; Verdecchia et al., 1990; Verdecchia et al., 1994); recent evidence also implicates hypertension as a risk factor for neuropathological changes to the brain and dementia (Beauchet et al., 2013; Brickman et

al., 2010; Dai et al., 2008; Dufouil et al., 2001; Goldstein, Bartzokis, Hance, & Shapiro, 1998; Langbaum et al., 2012; Petrovitch et al., 2000; van Dijk et al., 2004). In addition to poor BP control, other CVD risk factors (i.e., arterial stiffness, diabetes) contribute to the development and accumulation of vascular-related brain injury and subsequent cognitive impairment (Crane et al., 2013; Daviglus et al., 2011; Hooshmand et al., 2013; Tsao et al., 2013). Collectively, these observations suggest that the health of the cardiovascular and cognitive systems is intimately linked, and the accumulation of any given CVD risk factor can detrimentally affect the brain. Thus, investigating the association between cognitive functioning and the presence of other established and novel CVD risk factors may help to characterize the mechanisms by which vascular health influences cognitive health and functioning in aging.

Although N-DS has been identified as an independent CVD risk factor (Verdecchia et al., 1994; Verdecchia et al., 1990) and has been implicated as a mechanism that contributes to the development white matter hyperintensities (Goldstein et al., 1998), the association between blunted BP dipping and cognitive functioning remains poorly understood. In the current study, community-dwelling older adults with N-DS scored worse on a number of diverse cognitive outcomes, including measures of EF, information processing speed, and verbal memory delayed recall when compared to their DS peers, despite having significantly higher levels of formal education. These results are, however, aligned with previous observations that have suggested that specific components of BP regulation may be more appropriate to consider when evaluating chronic disease risk than merely systolic BP in isolation. For instance, recent meta-analyses and observational studies have suggested that nighttime systolic BP outperforms

day time systolic BP as a predictor of all-cause mortality, cardiovascular mortality, coronary heart disease and stroke in older hypertensive adults (ABC-H et al., 2014; Fagard et al., 2008). Higher pulse pressure (i.e., the difference between systolic and diastolic BP) has also been associated with the accumulation of fibrillar amyloid beta burden and impaired glucose metabolism within the cortex (Langbaum et al., 2012), both of which are hallmarks of Alzheimer's disease pathology. Last, higher BP variability (i.e., a greater degree in the fluctuations of BP) at baseline has also been associated with a higher prevalence of cerebral infarctions and white matter hyperintensities over 6 years of follow-up (Brickman et al., 2010). Collectively, these observations and those presented within the current study support the notion that discrete BP characteristics may provide additional prognostic utility for the development of CVD and neuropathological changes to the aging brain, beyond what can be achieved using systolic BP alone. Indeed, previous studies have identified a negative relationship between N-DS and global cognition, memory, and information processing speed that were not apparent when considering other measures of BP in older adults with and without hypertension (Bellelli et al., 2004; Nagai et al., 2008; Ohya et al., 2001; van Boxtel et al., 1998). However, questions regarding the specific association between N-DS and brain health and functioning, and the mechanisms that drive the association between N-DS and cognition in aging remain. Further research is required to characterize the relationship between specific components of BP and brain health and function in those with and without pre-existing CVD and cognitive impairment.

The exposure to both protective and risk factors for dementia over the course of one's life differentially affect the probability of developing dementia in aging

(Fratiglioni, Winblad, & von Strauss, 2007). However, the relationship between these protective and risk factors, and the nature by which they cumulatively affect the aging brain remains poorly understood. In the current study, participants with N-DS demonstrated worse cognitive performance despite having achieved significantly higher levels of formal education. This observation suggests two likely possibilities: i) that physiological risk factors are of greater clinical and prognostic importance to brain aging than experiential factors or ii) the time course of exposure to protective and risk factors influences the degree by which these factors affect brain health; the benefits of higher formal education in young adulthood are undone by the sustained exposure to risk factors in middle to older age. However, this observation must be replicated, and further study into the interplay between physiological and experiential dementia risk factors is required to definitively determine how these factors cumulatively influence the aging brain.

Mobility impairments, specifically gait dysfunction, manifest as cognitive function declines. For instance, impaired gait, specifically, reductions in gait speed, step length, and elevations in stride time variability is a common characteristic of those with mild cognitive impairment and dementia (Muir et al., 2012; Verghese et al., 2008), and is amplified under dual-task conditions (Hausdorff, Schweiger, Herman, Yogev-Seligmann, & Giladi, 2008). Gait abnormalities have also been suggested as potentially modifiable dementia risk factors (Mielke et al., 2013). For instance, reductions in gait speed develop prior to the establishment of objective cognitive impairment (Mielke et al., 2013), and have been linked with the presence of CVD risk factors (Rosano et al., 2011), vascular-related neuropathological changes to the brain (Holtzer, Epstein, Mahoney, Izzetoglu, & Blumen, 2014; Rosano, Brach, Studenski, Longstreth, & Newman, 2007; Rosano, Rosso,

& Studenski, 2014), and poorer objective cognitive functioning (Mielke et al., 2013; Holtzer, Verghese, Xue, & Lipton, 2006; Montero-Odasso, Verghese, Beauchet, & Hausdorff, 2012; van Iersel, Kessels, Bloem, Verbeek, & Olde Rikkert, 2008). EF appears to play a specific and intimate role in gait performance, as the cognitive control of gait has been localized within the regions of the brain that are involved with executive control processes (Persad, Jones, Ashton-Miller, Alexander, & Giordani, 2008; Montero-Odasso et al., 2012; Rosano et al., 2008). Collectively, these observations suggest that the control of gait under usual and dual-task conditions is dependent upon the functional and structural integrity of the regions of the brain associated with EF, and the accumulation of vascular-related injury within these regions can contribute to the simultaneous development of gait dysfunction and cognitive impairment.

Results from the present study corroborate these previous observations, as N-DS exhibited slower gait speed and higher gait variability under usual and dual-task conditions, and reduced step length under dual task conditions when compared to DS. Of particular interest, the participants within the current study did not exhibit significant objective cognitive impairment [total sample MMSE = 29 (1); total sample MoCA: 26 (2)] and there were no observable differences in global cognitive functioning between older adults with DS and N-DS.

Together, these observations suggest that N-DS may be a risk factor that drives the initial development subclinical cerebrovascular disease that can affect both cognition and mobility in older adults prior to the establishment of significant objective cognitive impairment. Thus, BP dipping status may be more a more effective surrogate of vascular-related cognitive risk in aging than ambulatory BP indices or central arterial health (i.e.,

cIMT and CAC). Future prospective cohort studies are required to definitively determine the temporal relationship between BP dipping and changes in cognition and mobility in older adults with and without cognitive impairment.

Future Directions and Recommendations

N-DS is associated with poor objective cognitive functioning and gait dysfunction in community-dwelling older adults without dementia. However, several limitations must be addressed before the nature of the relationship between N-DS and brain health in aging can be thoroughly understood. First, this secondary analysis was cross-sectional and is thus limited by an inability to determine causality. Furthermore, the predominantly Caucasian, relatively healthy, well-educated and functionally independent older adults within this study will limit the ability to generalize these findings. Prospective cohort studies that define their objectives *a priori*, incorporate appropriately spaced longitudinal follow-up visits, and recruit a number of clinical populations will be required to overcome these issues (Goldstein et al., 1998). Second, other BP dipping phenotypes (i.e., extreme dippers, reverse dippers) have been associated with the incidence of total cardiovascular events, but their relationship with brain health and functioning has yet to be investigated. In the current study, only three of the 49 DS participants were extreme dippers (i.e., >20% drop is systolic BP from daytime to night time) and only 14 of the 66 N-DS participants were reverse dippers (i.e., rise in systolic BP from daytime to night time). The small sizes of these two dipping phenotypes precluded the ability to perform meaningful subgroup analyses. In order to comprehensively characterize the influence of diurnal BP variation on brain health, the recruitment of older adults who demonstrate other BP dipping phenotypes should be a priority. Third, previous observations suggest

that the relationship between N-DS and cardiovascular health may be sex-specific, with N-DS women being at greater risk for cardiovascular morbidity than men (Verdecchia et al., 1994; Verdecchia et al., 1990); future works should be specifically designed and powered to investigate the possibility of sex-specific relationship between N-DS, cognition, and mobility. Fourth, the possibility for confounders and covariates to influence the relationship between dipping status and cognition were not accounted for in this investigation, and should be considered when interpreting these findings. Finally, the relationship between N-DS, dementia risk factor candidates, and brain health remains relatively understudied. Future work should aim to determine the extent by which N-DS drives neuropathological changes in the aging brain, and to determine the degree by which N-DS pathologically influences brain health in aging when compared to other potential vascular-related dementia risk factors (i.e., hypertension, type 2 diabetes, hypercholesterolemia, etc.).

Conclusions

The establishment and progression of pathological cognitive decline in aging is intimately linked with cardiovascular health and the detrimental influence of the presence of chronic CVD risk factors. Continuing to define the risk factors for dementia and determining the specific mechanisms by which known risk factors influence the brain remains a significant research and clinical priority. Diurnal BP variation appears to be a promising potential candidate, as N-DS was associated with poorer performance on measures of EF, information processing speed, and memory, and usual and dual-task gait impairments in this sample of community-dwelling older adults without dementia in this study. However, this work is cross-sectional and does not allow for the establishment of

causality in this relationship; further work is required in order to solidify blunted BP dipping as a risk factor for cognitive and functional impairment in aging. The development of interventions that can beneficially impact BP control while simultaneously mitigating the burden of other CVD-related dementia risk factors in older adults prior to the establishment of vascular-related cerebral pathology (i.e., middle-aged) may be one of the most promising strategies to prevent pathological cognitive impairment in the elderly. Lifestyle modifications, including a well-balanced diet (Bacon, Sherwood, Hinderliter, & Blumenthal, 2004) and the habitual participation in physical exercise training (Wang, Li, Dong, Zhang, & Zhang, 2015) can reduce vascular risk factor burden, and evidence suggests that these interventions and cognitive training can also benefit brain health and functioning (Gregory, Gill, & Petrella, 2013). Future work should aim to determine whether combined lifestyle interventions (i.e., nutritional or dietary counseling with multiple modality exercise training) could benefit vascular health and restore diurnal BP variation, and whether these improvements mediate the maintenance of or beneficial changes to the structure and function of the brain.

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Chapter 4: The effects of combined dual-task gait training and aerobic exercise on cognition, mobility, and vascular health in community-dwelling older adults at risk for future cognitive decline

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The Global Burden of Cognitive Impairment in Aging

As the global population continues to age, the incidence of dementia is expected to continue to rise. Currently, there are more than 46 million cases of dementia worldwide, a number that is expected to double every two decades to reach approximately 131.5 million by 2050 (Prince et al., 2015). This forecast is coupled with projections that estimate 9.9 million new cases of dementia will be diagnosed globally each year, and suggests that there will be one new case of dementia diagnosed every 3.2 seconds (Prince et al., 2015). These predictions are also accompanied by a considerable economic burden; the global costs of dementia have risen by 35.4% over the past five years, reaching $818 billion dollars (United States dollars) in 2015 (Prince et al., 2015). Dementia has gained considerable global recognition, as recent work from the G7 has led to a "Global Action Against Dementia" plan that aims to identify effective dementia treatment and prevention strategies within the next 10 years (Prince et al., 2015). An integral component to dementia prevention efforts will be the identification of modifiable risk factors for dementia (Daviglus et al., 2010; Daviglus et al., 2011; Lehert, Villaseca, Hogervorst, Maki, & Henderson, 2015; Prince et al., 2015; Xu et al., 2015) and the development of interventions that can reduce risk factor burden and benefit brain health and functioning in older adults who are at risk for future cognitive impairment (Gregory, Gill, & Petrella, 2013).

Risk Factors for Cognitive Impairment and Dementia

Cardiovascular disease (CVD) risk factors have been recognized as some of the most readily modifiable risk factors for dementia (Montine & Larson, 2009; Xu et al., 2015); developing a thorough understanding of the link between CVD and cognitive

impairment is a significant research priority. Indeed, an association between heart and brain health has been identified, as greater vascular risk factor burden is associated with greater task-related activation and poorer task performance on executive function (EF) tasks in community-dwelling older adults (Chuang et al., 2014), and has been found to increase the risk of incident dementia over five years of follow-up among older adults with mild cognitive impairment (Li et al., 2011).

Exercise Training and Cognitive Function in Older Adults

Healthy lifestyle choices, such as the habitual participation in aerobic exercise (AE), consistently reduces CVD risk factor burden, and evidence suggests that exercise may also be an important strategy to reduce the risk of cognitive impairment and slow the progression of dementia (Barnes, Yaffe, Satariano, & Tager, 2003; Xu et al., 2015). Previous meta-analyses suggest that AE can improve cognitive function within a number of cognitive domains, including processing speed, memory, and EF in healthy older adults (Colcombe & Kramer, 2003; Hindin & Zelinski, 2012; Smith et al., 2010) and can improve verbal fluency in those with indications of underlying cognitive impairment (Gates, Fiatrone Singh, Sachdev, & Valenzuela, 2013). Of particular interest, EF appears to be particularly responsive to AE training (Colcombe & Kramer, 2003) and can also improve following cognitive training (CT; Kelly et al., 2014a). Furthermore, cognitive training (or cognitive exercise) has also been found to lead to improvements in EF and memory in healthy older adults (Kelly et al., 2014a; Willis et al., 2006) and in those with cognitive impairment (Klusmann et al., 2010). Although the evidence from these reviews is promising, recent meta-analyses have revealed inconsistencies regarding the impact of AE interventions and improvements in aerobic fitness on cognitive functioning in older

adults, and the specific exercise training modality that is best suited to benefit the brain remains to be determined (Kelly et al., 2014b; Snowden et al., 2011; Young, Angevaren, Rusted, & Tabet, 2015).

Novel Exercise Modalities to Improve Cognition in Older Adults

In addition to AE and CT, the effect of novel exercise modalities [i.e., dual-task (DT) training] on cognition and mobility in older adults has received increasing attention. DT training is a multi-dimensional intervention that combines physical and cognitive tasks in order to directly train the parieto-frontal networks of the brain (Collette et al., 2005) to divide attention and co-ordinate actions more efficiently (Erickson et al., 2007; Kramer, Larish, & Strayer, 1995). For instance, Erickson et al. (2007) observed a DT training-related 'shift' in the location of DT-related brain activity (i.e., reduced activation within the right ventral inferior gyrus, right and left superior parietal lobules, and right dorsal inferior gyrus accompanied by increased activation within the dorsolateral prefrontal cortex from pre- to post-training), and suggested that this may represent a training-induced reorganization of the cortical areas involved in dual-tasking processing. DT exercise training has been found to benefit memory (Eggenberger, Schumacher, Angst, Theill, & de Bruin, 2015; Nishiguchi et al., 2015), EF (Eggenberger et al., 2015; Forte et al., 2013; Nishiguchi et al., 2015; Silsupadol et al., 2009a), and global cognition (Gill et al., 2016), and can reduce the activation within regions of the brain associated with short-term memory functioning (Nishiguchi et al., 2015), and increase DT gait speed (Silsupadol et al., 2009b) in cognitively healthy older adults. DT exercise training has also been shown to benefit memory and EF, as well as usual and dual task gait speed among elderly fallers (Dorfman et al., 2014) and improve DT performance (i.e., reduced

DT cost on gait speed while walking and performing serial 3 subtractions) among older adults with dementia (Schwenk, Zieschang, Oster, & Hauer, 2010). Collectively, these observations suggest that DT exercise programs can benefit neural functioning, which may in turn mediate improvements in objective cognitive functioning, dynamic balance, and usual and DT gait performance among older adults.

Despite these initial observations, several limitations within the current literature must be addressed before the cognitive benefits of aerobically based exercise training can be fully understood. Specifically, longer duration interventions that incorporate well-validated cognitive outcome measures and longitudinal follow-up are required to determine the trajectory of cognitive change throughout the course of the intervention, and whether any cognitive benefits are maintained following the cessation of exercise training (Gregory et al., 2013; Kelly et al., 2014b; Snowden et al., 2011; Young et al., 2015). Furthermore, it is crucial to determine the efficacy of interventions aimed at simultaneously reducing the burden of modifiable dementia risk factors (i.e., CVD risk factors) and improving cognition and mobility in older adults at increased risk for future cognitive decline.

Thus, the primary objective of this study was to determine whether 26 weeks of DT gait training and aerobic exercise (DAE) training can improve performance on an EF task. It is hypothesized that 26 weeks of DAE training will stimulate improvements in EF. The secondary objectives include determining whether 26 weeks of DAE training can: i) improve performance on cognition tasks across multiple domains, including, information processing, verbal fluency, and memory; ii) improve usual and DT gait performance; iii) reduce 24-hour ambulatory systolic and diastolic blood pressure (BP),

and decrease vascular stiffness (i.e., carotid arterial compliance and intima media thickness; and iv) stimulate changes in cognition, mobility, and vascular outcomes that are maintained six months following the cessation of training. It is hypothesized that DAE training will: i) improve performance across all of the measured cognitive domains; ii) improve usual and DT gait performance; iii) reduce 24-hour ambulatory BP and decrease vascular stiffness (i.e., increase compliance and reduce intima media thickness); and iv) provide cognitive, mobility, and vascular benefits that will be maintained for six months following training.

Methods

Study Design

This study was a 6-month experimental case series coupled with a 6-month no-contact follow-up. Participants were assessed at four time points throughout the intervention and follow-up period: i) baseline, ii) interim (3 months), iii) intervention endpoint (6 months), and iv) study endpoint (12 months).

Participants

Participants were recruited from London, ON through the use of town hall announcements, calls to past research participants, and the distribution of advertisements to various locations throughout the community (i.e., Boys & Girls Clubs, Kiwanis Clubs, media outlets). Community-dwelling older adults (60-90 years) without dementia [i.e., no previous dementia diagnosis and a Mini Mental State Examination (MMSE) score > 24 (Appendix C; Folstein, Folstein, & McHugh, 1975)], and preserved instrumental activities of daily living [Lawton-Brody Instrumental Activities of Daily Living (IADL) scale (Appendix F; Lawton & Brody, 1969)] were invited to participate. Older adults who

demonstrated significant neurological (i.e., Parkinson's) or orthopaedic (i.e., severe osteoarthritis) conditions, clinical depression [i.e., >16 on Center for Epidemiologic Studies-Depression (CES-D) Scale (Appendix E; Radloff, 1977)] or at the discretion of the study physician), or BP unsafe for exercise [i.e., 180/100 mmHg or < 100/60 mmHg (Thompson, Gordon, & Pescatello, 2010)], and those who reported a recent severe cardiovascular complication (i.e., congestive heart failure, stroke), or could not comprehend the questionnaire material were excluded from participation.

Sample Size

No study to date has observed the impact of laboratory-based DAE on EF in older adults; however, following reviews of studies using AE (Baker et al., 2010; Colcombe & Kramer, 2003) and other cycle-based exergaming (Anderson-Hanley et al., 2012) to improve cognition [i.e., EF measured via the Trail Making Test Part B (TMT B; Appendix H)] in older adults allowed for the selection of an effect size of d=0.66 for our calculations. The valid and reliable TMT-B (Arbuthnott & Frank, 2000; Reitan, 1958; Shibuya-Tayoshi et al., 2007) is specific to EF processes due to its requirements for switching sets and mental tracking throughout the task (Arbuthnott & Frank, 2000; Hagen et al., 2014) and was considered the primary outcome measure. Assuming an alpha of 0.05, 80% power, and a drop out rate of 10%, 84 participants were required for this study [G*Power ver. 3.1.9.2 (Faul, Erdfelder, Lang, & Buchner, 2007)].

Baseline Variables

Participant medical history and demographics were collected at baseline, and include: age, sex, ethnicity, years of formal education, body mass index, global cognitive functioning, the presence of subjective cognitive complaints, and estimated

cardiorespiratory fitness [i.e., predicted maximal oxygen uptake (VO_2 max)]. Global cognitive functioning was assessed using the Montreal Cognitive Assessment (MoCA; Appendix D; Nasreddine et al., 2005). Predicted VO_2max was estimated using the Step Test and Exercise Prescription (STEP) tool (Appendix M; Stuckey, Knight, & Petrella, 2012), which requires participants to climb and descend a set of standardized steps twenty times at a self-selected moderate pace, and uses time to completion, post-test heart rate, age, and sex within the prediction algorithm to estimate VO_2 max.

Cognition: Cognition was assessed across 4 domains, including EF, information processing speed, verbal fluency, and memory.

EF was assessed using Trail Making Tests (TMT), which requires participants to draw a line between 25 consecutive encircled numbers on a piece of paper (TMT-A; Appendix G), and between alternating numbers and letters (TMT-B; Appendix H). The time to test completion in seconds represents the outcome score for each part of the test. For the purposes of this study, TMT-B served as a surrogate of EF and the primary cognitive outcome, while TMT-A served as an index of information processing and a secondary cognitive outcome.

Information processing speed was also assessed using the valid and reliable (Matarazzo & Herman, 1984) Digit-Symbol Coding (DSC; Appendix J) from the Weschler Adult Intelligence Scale, 3rd Ed. (Wechsler, 2003). The DSC required participants to decode the test section by using a legend to sequentially match the numbers with the corresponding symbols as quickly and accurately as possible. Maximum total score obtained in 120 seconds was used as the outcome.

Semantic (animal naming; Appendix K) and phonetic [Controlled Oral Word Association Test; Appendix L; Benton, Hamsher, & Sivan, 1994)] fluency tasks were used to evaluate lexical verbal fluency. For the phonetic verbal fluency task, participants were required to exclude proper nouns and suffix substitutions (i.e., love, loves, lover, loving, etc.) from the responses that were provided. The total number of correct responses provided over 60 seconds was used as the outcome score for each task, and repeated responses were not considered in the final score.

Memory was assessed using the Auditory Verbal Learning Test (AVLT; Appendix I; Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2005). This test contains 15 monosyllabic words that are presented over five subsequent trials. After each trial, participants were required to freely recall as many words from the list as possible without receiving any cues from the administrator. Following the fifth trial, an interference trial was performed, whereby a new 15-item word list was read and participants were required to freely recall as many items from this list as possible. Approximately five minutes after the interference trial, an immediate recall trial was performed, where participants were required to provide as many items from the original 15 word list as possible, without receiving cues by the administrator. Approximately 30 minutes following the immediate recall trial, a delayed recall trial of the original list was performed. Responses from the immediate and delayed recall trials were tallied separately and served as the memory outcomes.

<u>Mobility (gait):</u> Usual and DT gait analysis was used to assess mobility.

Spatiotemporal gait characteristics were collected using a valid and reliable (Brach, Perera, Studenski, & Newman, 2008) portable electronic walkway system

[GAITRite® System; 580 x 90 x .63cm (L x W x H), that has an active electronic surface area 792 x 610 cm (L x W), with a total of 29,952 pressure sensors, and scanning frequency of 60 Hz, Software version 4.7.1, CIR Systems, Peekskill, NY, USA]. In order to avoid capturing acceleration and deceleration phases of the gait cycle, participant start and end points were placed 1.5 metres before and after the mat. Participants were required to complete two usual walking trials at a comfortable pace, and then performed three separate DT walking trials: a "sham" DT condition (i.e., counting backwards from 100 by 1's), and two experimental DT conditions (i.e., naming animals and subtracting serial 7's from 100). For the usual and two experimental DT conditions, gait performance over two walks were averaged and used for analysis. The sham DT condition was incorporated as an attempt to familiarize the participants to the requirements of the DT condition and was not considered for analysis. There was no instruction to prioritize gait or responses to the cognitive tasks during the DT trials, and any footfalls that did not entirely fall on the walkway during data collection were removed prior to analysis.

A total of three outcomes for each gait condition were considered as outcomes: i) velocity (m/sec), ii) step length (cm), and iii) stride time variability (CoV, %). Gait performance during the second experimental condition (serial 7s from 100) was selected to serve as the DT gait outcome for two reasons: i) recent literature followed a similar approach for the DT condition used during a gait assessment (i.e., arithmetic-based task) following an treadmill based exercise intervention (Dorfman et al., 2014); and ii) as an attempt to reduce the probability of false-positive results or committing a Type I error by reducing the number of gait outcomes considered for analysis.

Vascular Health: 24-hour ambulatory BP and carotid ultrasonography were used to evaluate vascular health.

Following the gait assessment, participants were fitted with an appropriately sized, valid and reliable (Iqbal, Fotherby, & Potter, 1996) ambulatory BP cuff and monitor (Spacelabs^{TM} 90207 Ambulatory Blood Pressure Monitor, SpaceLabs Inc.). Measurements were recorded two times an hour during the daytime (i.e., 06:00 to 22:00), and once an hour during the nighttime (i.e., 22:00 to 06:00) over the subsequent 24-hour period, and mean 24-hour systolic and diastolic BP were considered as outcomes. Following the ambulatory BP assessment, carotid arterial diameters were following previously published techniques (Gregory et al., 2016). Briefly, after 10 minutes of supine rest, a 10 MHz linear array B-mode ultrasonography (Vingmed, GE Ultrasound A/S, Horton, Norway) transducer was used to collect a longitudinal two-dimensional image of the cephalic portion of the right common carotid artery, 1-2 cm proximal to the carotid bifurcation. Arterial diameters were measured leading-edge-to-leading-edge at peak systole and end diastole and averaged across three cardiac cycles. Following the acquisition of the arterial diameters, carotid arterial pulse pressure was inferred through the collection of a single measure of resting supine brachial pulse pressure obtained using automated oscillometry (BPTru, Coquitlam, BC, Canada). Anatomical land marking was used to ensure accurate comparisons over time. Carotid arterial compliance (CAC) was determined using the following equation:

$$\left[\pi\left(\frac{Dmax}{2}\right)^2 - \pi\left(\frac{Dmin}{2}\right)^2\right]\Delta P \qquad \text{(Equation 1)}$$

where D_{max} was the systolic carotid arterial diameter, D_{min} was the diastolic carotid arterial diameter, and ΔP was resting brachial pulse pressure (Gregory et al., 2016).

Carotid intima-media thickness (cIMT) was determined by subtracting the carotid arterial lumen diameter from the outer arterial diameter at end diastole. In attempts to control for external factors, vascular assessments were performed in a quiet, temperature controlled room (20 to 23°C), and participants were asked to refrain from the consumption of alcohol or participation in moderate-vigorous intensity exercise in the preceding 24 hours, and the consumption of caffeine over the preceding 12 hours (Pickering et al., 2005).

Intervention

Laboratory-based DAE Program: Exercise training utilized a Biodex GaitTrainer2 treadmill (providing visual-spatial feedback related to the user's step length on a screen fixed atop of the treadmill) under the supervision of research personnel.

During each session, participants worked through a 5-minute (min) warm-up period, one 15-min stage of DAE, one 15-min stage of moderate intensity AE [i.e., 75-85% maximal heart rate determined using the STEP test protocol (Knight, Stuckey, & Petrella, 2014; Petrella, Koval, Cunningham, & Paterson, 2003; Stuckey et al., 2012)], and a 5-min cool down stage. During the DAE stage, participants walked at a self-selected pace while receiving visuospatial step-length feedback and answering cognitively challenging questions (i.e., verbal fluency and arithmetic). The variable priority DT training was used during DAE portion of the exercise sessions (Silsupadol et al., 2009a); for the first 7-min, participants prioritized providing correct responses to the verbal fluency and arithmetic tasks, and after a 1-min break (walk without answering questions), participants prioritized modifying their step length to achieve or surpass an individualized step length goal (for the remaining 7-min).

Following the DAE component, the visuospatial step length feed back was removed and participants performed 15-min of moderate intensity AE. The incline and speed of the treadmill was increased until training heart rate was achieved, and the training intensity was monitored every 5-min throughout the 15-min of AE using a 10-point RPE scale and the built-in handgrip heart rate monitor on the Biodex treadmill. Duration/Frequency/Length of Intervention: *40-min/session; 3x/week; 26-weeks*.

Analysis

All analyses were performed using SPSS version 20 (SAS Institute Inc., Cary, NC, USA). Demographic variables at baseline were summarized as means and standard deviations or medians and interquartile ranges, where applicable.

Primary Analysis: To determine the efficacy of DAE on EF and whether changes in TMT-B scores were maintained after the no-contact follow-up, changes in TMT-B scores (time to complete test in seconds) were compared from baseline (V0) to 12-weeks (V1; interim assessment), 26-weeks (V2; intervention endpoint) and 52-weeks (V3; study endpoint) using a one-way repeated measures analysis of variance (ANOVA) using time as a main effect and post hoc tests that employ Bonferroni alpha adjustments.

Secondary and Tertiary Analyses: Secondary and Tertiary efficacy parameters included: i) change in other cognitive tests [information processing: DSC and TMT-A; verbal fluency: semantic (animal naming) & phonemic (COWA) fluency; memory: AVLT immediate and delayed recall]; ii) change in mobility measures [usual and DT gait speed, step length, and strive time variability]; and iii) change in vascular measures [24-hour systolic and diastolic BP; CAC and cIMT] at V2 and V3. The same analysis

approach was followed to determine the efficacy of DAE on the secondary and tertiary outcome measures.

Outliers for each outcome were identified and removed prior to analyses, and Greenhouse-Geiser epsilon adjusted degrees of freedom were interpreted from the omnibus ANOVA tests. Friedman tests with alpha adjusted Wilcoxon sign ranked tests were used when violations of normality were encountered.

Results

Participant enrollment began June 26th, 2012, and data collection was completed on October 8th, 2015. Figure 4.1 describes participant flow through the intervention. A total of 109 participants were assessed for eligibility, and 30 were excluded from participation (n = 17 did not meet the inclusion criteria; n= 12 declined to participate, primarily due to the time commitment required for the intervention). This left 79 participants who were enrolled for the study. Following attrition throughout the intervention and follow-up period, 56 participants completed the entire 52-week study. There were no study-related adverse events experienced by any of the participants throughout the intervention and follow-up period.

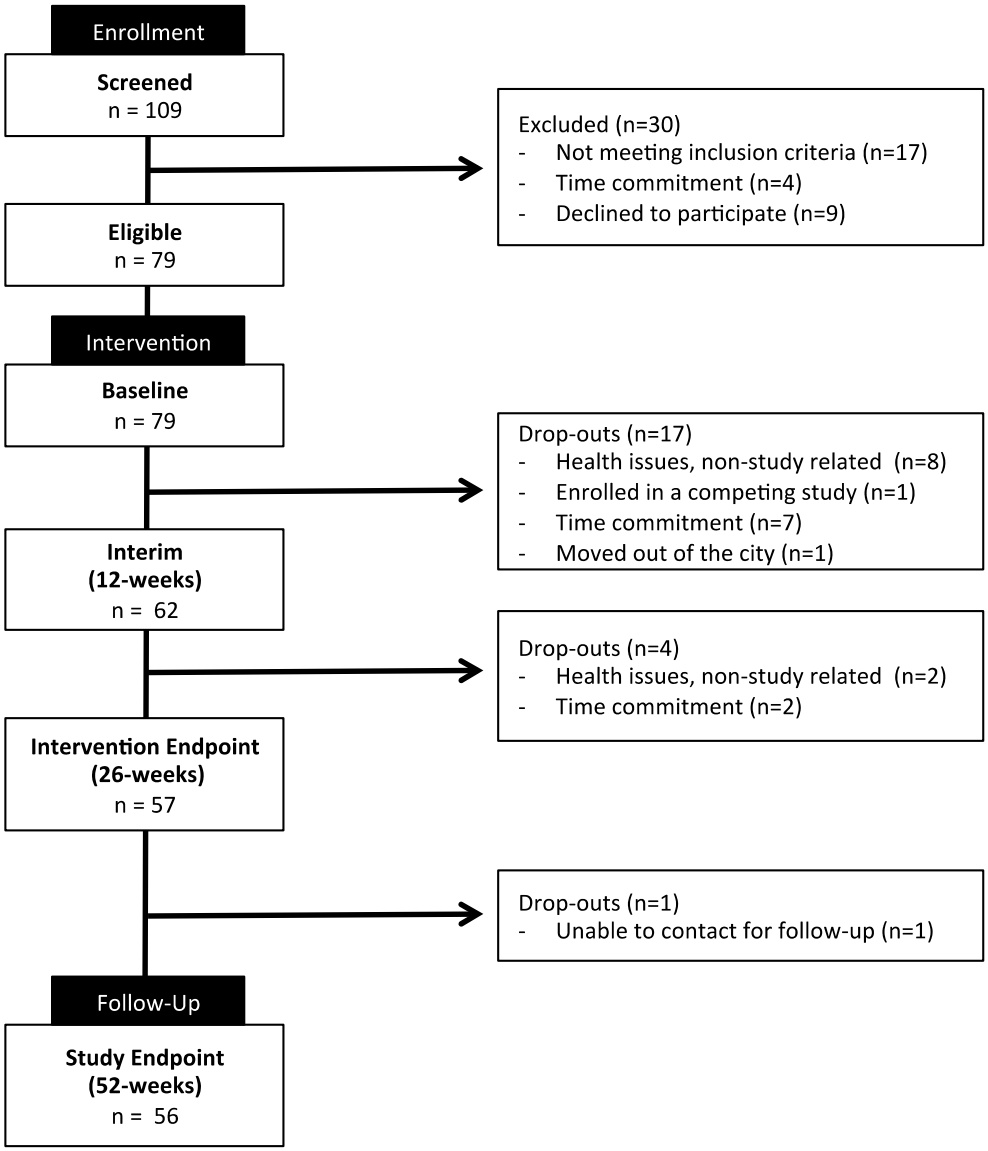


Figure 4.1. Participant flow through the dual-task and aerobic exercise (DAE) intervention and follow-up period.

Participant characteristics are reported in Table 4.1. Participants had a mean age of 70.4 (SD 6.2) years, were just under two-thirds female, and were primarily (96%) Caucasian. Participants were on average highly educated [mean (SD) years: 14.7 (3.2)], and just over half reported that their memory has gotten worse over the past five years. On average, the participants had relatively preserved objective cognition [MoCA score, mean (SD): 25 (3.2)] and did not display any indications of the presence of unidentified dementia [MMSE score, mean (SD): 28.5 (1.3)].

Table 4.1

Baseline characteristics of the 56 participants who completed the 26-week dual-task gait training and aerobic exercise (DAE) intervention and the 24-week no-contact follow-up.

Characteristic	Participants (n = 56)
Age, mean (SD), yr	70.4 (6.2)
Female sex, no. (%)	22 (61)
Education, mean (SD), yr	14.7 (3.2)
Caucasian, no. (%)	53 (95)
Body mass index[a], mean (SD)	29.6 (4.7)
Fitness (pVO_{2max}) score[b], mean (SD)	28.9 (7.8)
Cognitive complaint (ref: 5 yr ago)[c], no (%)	31 (55)
MMSE score[d], mean (SD)	29 (1.3)
MoCA score[d], mean (SD)	25 (2.5)
CES-D score[e], mean (SD)	6.4 (5.3)
Medical history, no. (%)	
Hypertension	32 (57)
Hypercholesterolemia	23 (41)
Type 2 diabetes	7 (12.5)
Previous cardiovascular event	3 (5)
Previous stroke	6 (11)
Osteoarthritis	9 (16)

Abbreviations: SD, Standard Deviation; MMSE, Mini-Mental Status Examination; MoCA, Montreal Cognitive Assessment; CES-D, Centre for Epidemiological Studies Depression Scale

[a] Body Mass Index measured in kg/m^2

[b] pVO_{2max} was determined using the Step Test and Exercise Prescription tool, and is measured in $mlO_2/kg/min$

[c] Participants rated their memory on a scale of 5 (1 = much better, 5 = much worse)

[d] Range from 0 to 30; lower scores indicate greater cognitive impairment

[e] Scores above 15 indicate clinical depression

Cognition Outcomes

Baseline cognitive scores are summarized in Table 4.2. Compared to age and education-matched normative data, the study participants demonstrated on average better baseline performance on TMT-A and -B (Tombaugh, 2004) and semantic verbal fluency task (letters starting with "C"; Tombaugh, Kozak, & Rees, 1999), comparable performance on the DSC (Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2006) and the AVLT (Van der Elst et al., 2005), and poorer performance on the phonemic verbal fluency task (naming animals; Tombaugh et al., 1999).

Table 4.2

Baseline performance on all outcome measures for participants in the dual-task gait training and aerobic exercise (DAE) intervention.

Outcome[a,b]	Score
Executive Function	
TMT-B[c], median (IQR), (n = 51)	65.6 (53.9 to 87.0)
Information Processing Speed	
TMT-A[c], median (IQR), (n = 50)	30.5 (26.7 to 36.2)
DSC[d], mean (SD), (n=55)	56.9 (13.8)
Verbal Fluency	
Semantic VF[e], mean (SD), (n = 53)	20.4 (5.1)
COWA[e], mean (SD), (n = 53)	13 (4.5)
Memory	
AVLT immediate recall[f], median (IQR), (n = 51)	7 (5.3 to 10.8)
AVLT delayed recall[f], median (IQR), (n = 56)	8 (4.3 to 10)
Usual Gait	
Speed[g], mean (SD), (n = 56)	1.11 (.19)
Step length[h], mean (SD), (n = 56)	62.2 (7.1)
Stride time variability[i], median (IQR), (n = 45)	1.8 (1.5 to 2.3)
Dual-task Gait	
Speed[g], mean (SD), (n = 55)	.81 (.27)
Step length[h], mean (SD), (n = 53)	56.1 (8.3)
Stride time variability[i], median (IQR), (n = 44)	3.5 (2.5 to 7)
Vascular Health	
24-hour systolic BP[j], mean (SD), (n = 45)	128 (10)
24-hour diastolic BP[j], mean (SD), (n = 50)	71 (6)
CAC[k], median (IQR), (n = 54)	.73 (.54 to .96)
cIMT[l], median (IQR), (n = 54)	.63 (.55 to .74)

Abbreviations: IQR, Interquartile Range; TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B; DSC, Digit Symbol Coding; SD, Standard Deviation; VF, verbal fluency; COWA, Controlled Oral Word Association test; VLT, Verbal Learning Test

[a] Data that violated normality are presented as median and IQR

[b] Differing sample sizes for outcomes were due to the identification and removal of outliers prior to analysis

[c] Units for the TMT tests are seconds; lower time to completion indicates greater performance

[d] Scores range from 0 to 144; higher scores indicate greater performance

[e] Scored as the correct number of unique responses provided in 60 seconds

[f] Range from 0 to 15; higher scores indicate greater performance

[g] Units are in metres per second (m/sec)

[h] Units are in centimetres (cm)

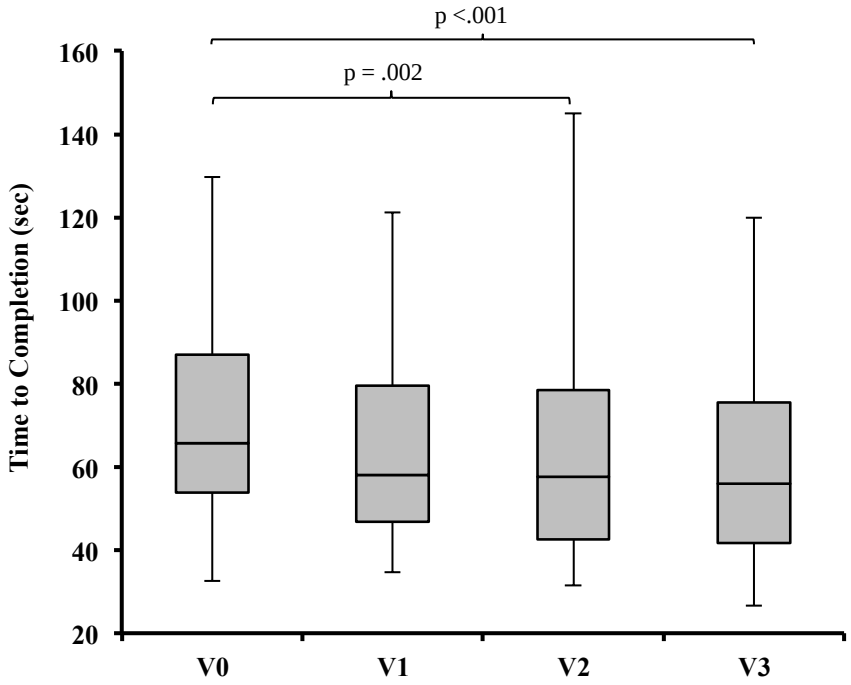
[i] Units are the CoV, expressed as a percentage

[j] Units are in millimetres of mercury (mmHg)

[k] Units are in millimetres squared per millimetre of mercury ($mm^2/mmHg \times 10^{-1}$)

[l] Units are in centimetres (cm)

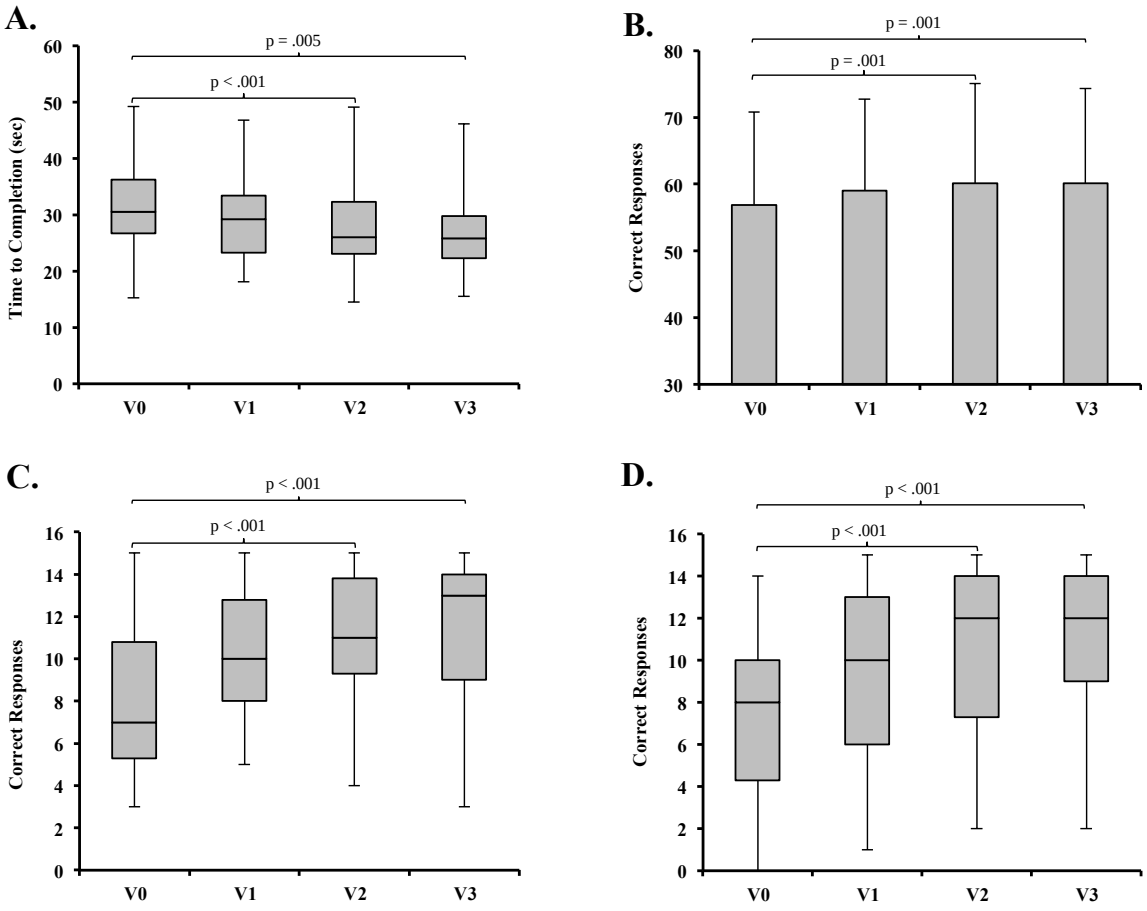
The effects of 26-weeks of DAE training on the primary and secondary cognitive outcomes are reported in Table 4.3a. The observed change in TMT-B performance from V0 to V1, V2, and V3 is shown in Figure 4.2. A significant difference between TMT-B scores was observed ($\chi^2_{(3)} = 19.49$, $p < .001$). Post hoc tests with Bonferroni corrections (significance set at $p < .008$) revealed significant reductions in the time to complete TMT-B from baseline to intervention endpoint [median (IQR); V0: 65.6 (53.9 to 87.0), V2: 57.7 (42.6 to 78.4), $p = .002$], and a significant difference from baseline was maintained through the no-contact follow-up period [median (IQR): V0: 65.6 (53.9 to 87.0), V3: 55.8 (41.6 to 74.5), $p<.001$]. There were no significant differences in TMT-B scores at any other time points (all $p > .05$).



Abbreviations: sec, seconds

Figure 4.2. Trail Making Test (TMT) Part B performance at baseline, interim (12-weeks), intervention endpoint (26-weeks), and study endpoint (52-weeks).

The observed changes in the secondary cognitive outcomes from V0 to V2 are summarized in Table 4.3a are presented in Figure 4.3. Significant reductions in TMT-A scores were observed following 26-weeks of DAE training [median (IQR); V0: 30.5 (26.7 to 36.2), V2: 26.0 (23.0 to 32.3), $p < .001$], and these changes were maintained over the 6-month follow-up [median (IQR); V3: 25.8 (22.3 to 29.8), $p = .005$]. At 26-weeks, the participants showed significant improvements DSC scores [mean (SD); V0: 56.9 (13.8), V2: 61.7 (15.0), $p = .001$], phonemic verbal fluency [mean (SD); V0: 13.2 (4.6), V2: 17.0 (4.7), $p < .001$], and immediate [median (IQR); V0: 7.0 (5.3 to 10.8), V2: 11.0 (9.3 to 13.8), $p < .001$] and delayed recall [median (IQR); V0: 8.0 (4.3 to 10.0), V2: 12.0 (7.3 to 14.0), $p < .001$], but not semantic verbal fluency [mean (SD); V0: 20.4 (5.1), V2: 21.8 (5.1), $p > .05$). Compared to baseline performance, the observed improvements DSC scores, phonemic verbal fluency, and immediate and delayed recall following DAE training were maintained after 6-months of follow-up (all $\leq .001$).



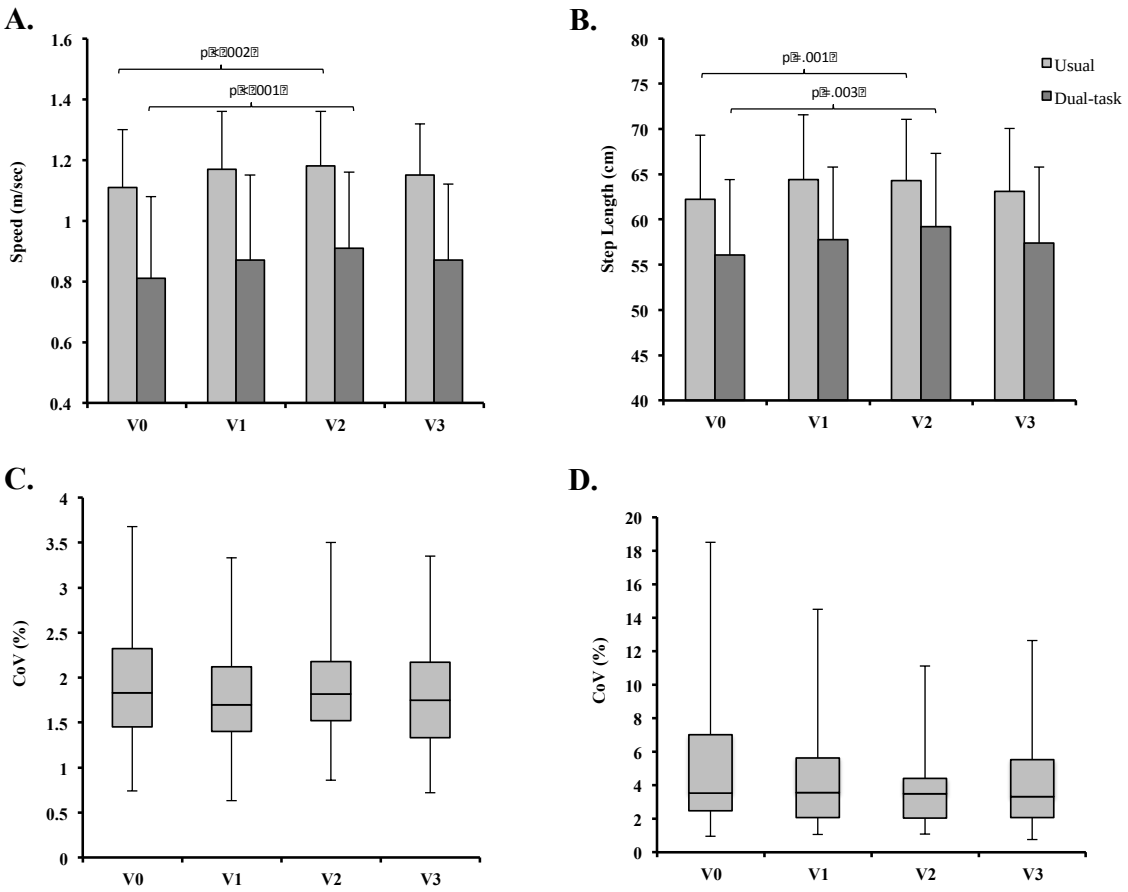
Abbreviations: sec, seconds. A. Trail Making Test Part A; B. Digit Symbol Coding; C. Auditory Verbal Learning Test immediate recall; D. Auditory Verbal Learning Test delayed recall; E. Semantic and Phonemic verbal fluency.

Figure 4.3. Performance on secondary cognitive outcomes at baseline, interim (12-weeks), intervention endpoint (26-weeks), and study endpoint (52-weeks).

Usual and Dual-Task Gait Outcomes

Changes in usual and DT gait speed, step length, and stride time variability from V0 to V2 are summarized in Table 4.3b. Changes in usual and DT gait and stride-time variability from V0 to V1, V2, and V3 are presented in Figure 4.4. Compared to age-matched data, the study participants demonstrated on average comparable usual gait speed, step length and stride time variability (Verlinden et al., 2013), and dual task gait speed, step length, and stride time variability (Gregory et al., 2016).

Increased usual gait speed [mean (SD); V0: 1.11 (.19) m/sec, V2: 1.18 (.18) m/sec, p = .002] and step length [mean (SD); V0: 62.2 (7.1) cm, V2: 64.3 (6.8) cm, p = .001] were observed following 26-weeks of DAE training; however, after the 6-months of follow-up the improvements in usual gait speed and step length no longer remained [mean difference (95% CI); gait speed: .41 (.90 to -.078) m/sec, p = .15; step length: .96 (2.5 to -.54), p = .51]. Increased DT (serial 7's subtraction) gait speed [mean (SD); V0: .81 (.27) m/sec, V2: .91 (.25) m/sec, p < .001] and step length [mean (SD); V0: 56.1 (8.3) cm, V2: 59.2 (8.1) cm, p = .003] were observed following 26-weeks of DAE training. After the 6-month follow-up, the improvements in DT gait speed and step length no longer remained [mean difference (95% CI); gait speed: .63 (.13 to - .08) m/sec; step length: 1.3 (3.6 to -1.1) cm, all p > .05]. There were no observable reductions in usual stride time variability [median (IQR); V0: 1.87 (1.47 to 2.45), V2: 1.88 (1.51 to 2.37)] or dual task stride time variability [median (IQR); V0: 3.5 (2.5 to 7.0), V2: 3.5 (2.0 to 4.4)] following 26-weeks of DAE training (both p > .05).

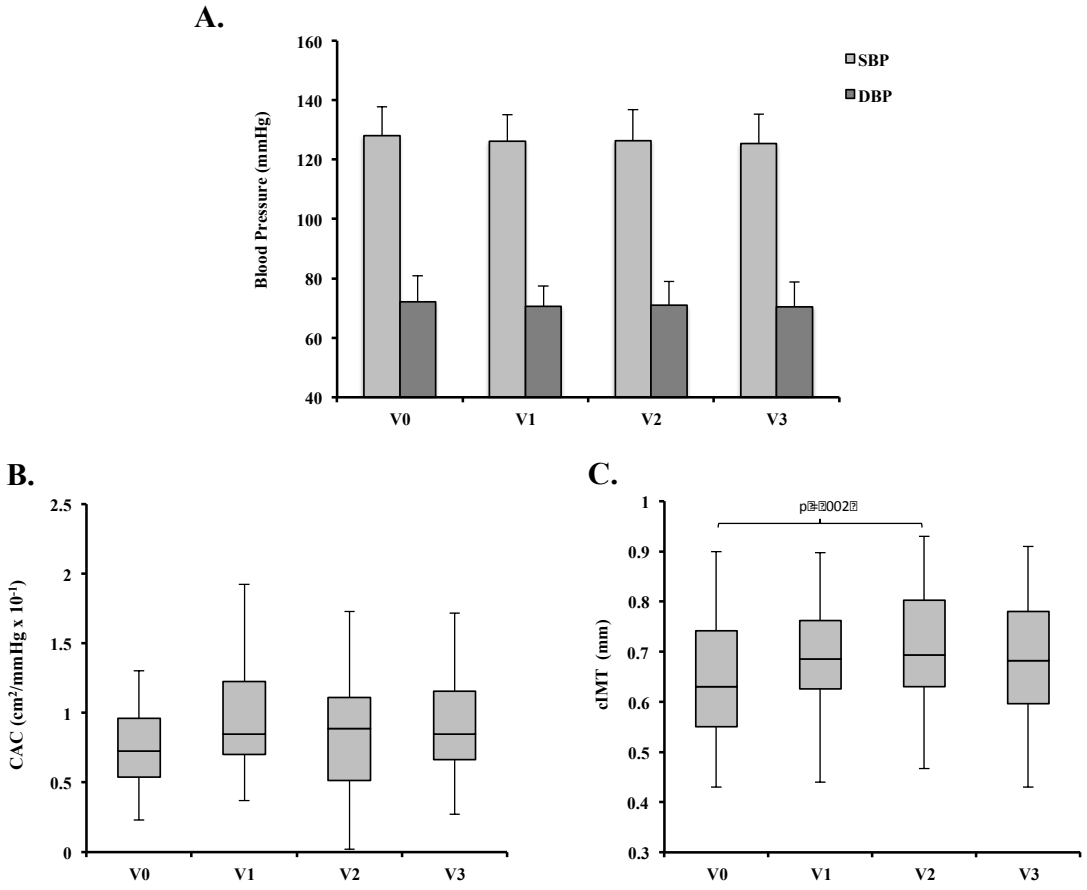


Abbreviations: CoV, coefficient of variation; m/sec, metres per second; cm, centimetres. A. Usual and dual-task gait speed; B. Usual and dual-task step length; C. Usual gait stride time variability; D. Dual-task gait stride time variability.

Figure 4.4. Changes in usual and dual-task (serial 7 subtraction) gait speed, step length, and stride time variability from baseline (V0), interim (V1; 12-weeks), intervention endpoint (V2; 26-weeks), and study endpoint (V3; 52-weeks).

Vascular Health Outcomes

Differences in 24-hour systolic BP, diastolic BP, CAC and cIMT from V0 to V2 are summarized in Table 4.3c. Changes in vascular health outcomes from V0 to V1, V2, and V3 are presented in Figure 4.5. Compared to age-matched data, the study participants demonstrated on average lower cIMT (Lim, Lim, Dwivedi, Kooner, & Senior, 2008), and similar 24-hour systolic BP, 24-hour diastolic BP, and CAC (Gregory et al., 2016). There were no significant changes in 24-hour systolic BP, 24-hour diastolic BP, or CAC following 26-weeks of DAE training (all $p > .05$). Compared to baseline, cIMT was higher after 26-weeks of DAE training [median (IQR); V0: .63 (.55 to .74) mm, V2: .69 (.63 to .80) mm, $p = .002$], but not after the 6-month follow-up ($p > .05$).



Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; CAC, carotid arterial compliance; cIMT, carotid intima-media thickness. A. 24-hour ambulatory systolic and diastolic blood pressure; B. Carotid arterial compliance; C. Carotid intima-media thickness.

Figure 4.5. Changes in 24-hour ambulatory systolic and diastolic blood pressure (A), carotid arterial compliance (B), and carotid intima-media thickness (C) from baseline (V0) to interim (V1; 12-weeks), intervention endpoint (V2; 26-weeks), and study endpoint (V3; 52-weeks).

Table 4.3a, b, c

Observed changes in cognition, gait, and vascular health outcomes from baseline (V0) to intervention endpoint (V2; 26-weeks)[a, b]

	V0	V2
A. Cognitive Test		
Executive Function		
TMT Part B[c], (n = 51)	65.6 (53.9 to 87.0)	57.7 (42.6 to 78.4)
Information Processing		
TMT Part A[c], (n = 50)	30.5 (26.7 to 36.2)	26.0 (23.0 to 32.3)
DSC[a,d], (n = 55)	56.9 (13.8)	60.7 (15.0)
Verbal Fluency		
Semantic VF[e,g], (n = 53)	20.4 (5.1)	21.8 (5.1)
COWA[f,g], (n = 53)	13.0 (4.5)	16.5 (4.0)
Memory		
AVLT, immediate recall[a,h], (n = 51)	7.0 (5.3 to 10.8)	11.0 (9.3 to 13.8)
AVLT, delayed recall[a,h], (n = 56)	8.0 (4.3 to 10.0)	12.0 (7.3 to 14.0)
B. Gait Performance		
Usual Gait		
Speed[i], (n = 56)	1.11 (.19)	1.17 (.18)
Step length[j], (n = 56)	62.2 (7.1)	64.3 (7.2)
Stride time variability[a,k], (n = 45)	1.8 (1.5 to 2.3)	1.8 (1.5 to 2.2)
Dual-task (serial 7's) Gait		
Speed[i], (n = 55)	.81 (.27)	.91 (.25)
Step length[j], (n = 53)	56.1 (8.3)	59.2 (8.1)
Stride time variability[a,k], (n = 44)	3.5 (2.5 to 7)	3.5 (2.0 to 4.4)
C. Vascular Health		
24-hour systolic BP[l], (n = 45)	128 (10)	126 (10)
24-hour diastolic BP[l], (n = 50)	71 (6)	70 (7)
CAC[a,m], (n = 54)	.73 (.54 to .96)	.89 (.52 to 1.2)
cIMT[a,n], (n = 54)	.63 (.55 to .74)	.69 (.63 to .80)

Abbreviations: DAE, dual-task gait training and aerobic exercise; TMT, Trail Making Test; DSC, Digit Symbol Coding; VF, verbal fluency; COWA, Controlled Oral Word Association test; AVLT, auditory verbal learning test; BP, blood pressure; CAC, carotid arterial compliance; cIMT, carotid intima-media thickness.

[a] Data that violated normality are presented as median and IQR

[b] The removal of outliers results in differing sample sizes for the outcomes

[c] Units for the TMT tests are seconds; lower time to completion indicates greater performance

[d] Scores range from 0 to 144; higher scores indicate greater performance

[e] The semantic verbal fluency task required participants to provide as many unique responses to the given category (i.e., naming animals) in 60 seconds

[f] The phonemic verbal fluency task required participants to provide as many unique responses that started with a pre-specified letter (i.e., words starting with C) in 60 seconds

[g] Scored as the correct number of unique responses provided in 60 seconds

[h] Range from 0 to 15; higher scores indicate greater performance

[i] Units are in metres per second (m/sec)

[j] Units are in centimetres (cm)

[k] Units are the CoV, expressed as a percentage

[l] Units are in millimetres of mercury (mmHg)

[m] Units are in centimetres squared per millimetre of mercury (cm^2/mmHg x 10^{-1})

[n] Units are in centimetres (cm)

Discussion

The Effect of DAE Training on Cognition

Following 26 weeks of treadmill based DAE for older adults without dementia, improvements in EF were observed and were maintained over 26 weeks of follow-up. Performance on the EF task was not significantly different from baseline following 12 weeks of training. Improvements in other cognitive processes, including information processing speed, verbal fluency, and memory were also observed following 26 weeks of DAE training, and these improvements were maintained for at least 26 weeks following the completion of the intervention. Performance on the semantic verbal fluency task was the only outcome that remained unchanged following the intervention, as well as the 26-week no contact follow-up period.

Evidence continues to suggest that AE training alone (Chapman et al., 2013; Colcombe & Kramer, 2003; Erickson & Kramer, 2009; Iuliano et al., 2015), or in combination with cognitive or DT training (Gill et al., 2016) can benefit brain health and improve cognition in cognitively healthy older adults, and even among those with objective cognitive impairment (Baker et al., 2010; Nagamatsu et al., 2013; Ten Brinke et al., 2014). Although recent meta-analyses have suggested that there is limited high-quality evidence to support the use of AE training alone as a method to improve cognition in older adults with (Gates et al., 2013) or without (Young et al., 2015) cognitive impairment, recent observations suggest that combined cognitive and physical exercise training interventions may provide the greatest cognitive benefit (Gregory et al., 2013; Law, Barnett, Yau, & Gray, 2014).

435 The results from the current study expands our understanding of the influence of
436 combined physical and cognitive exercise training on cognitive functioning in older
437 adults. The 26-week DAE training program combined moderate intensity AE with a DT
438 gait training component that required participants to actively modify their step length
439 using real-time biofeedback while simultaneously responding to a variety of verbal
440 fluency and arithmetic tasks. Although this is the only study that the authors are aware of
441 that has investigated the cognitive effects of such a unique DT stimulus in combination
442 with an AE intervention, previous studies have investigated the cognitive benefits
443 associated with other combined cognitive and physical exercise training interventions
444 (Barnes et al., 2013; Dorfman et al., 2014; Fabre, Chamari, Mucci, Masse-Biron, &
445 Prefaut, 2002; Gill et al., 2016; Nishiguchi et al., 2015; Rahe et al., 2015; Shah et al.,
446 2014; Theill, Schumacher, Adelsberger, Martin, & Jancke, 2013). Although a number of
447 exercise training modalities can benefit the brain, previous observations and those from
448 the current study collectively suggest that the cognitive response to these interventions
449 appear to be unique and is likely dependent upon several key factors: i) the duration of
450 the intervention, ii) the exercise intensity, and iii) the specific task requirements of the
451 cognitive training components of each intervention. In contrast to several previous shorter
452 duration studies (Barnes et al., 2013; Dorfman et al., 2014; Fabre et al., 2002; Nishiguchi
453 et al., 2015; Rahe et al., 2015; Shah et al., 2014; Theill et al., 2013), improvements in
454 cognitive functioning following DAE training were not apparent after 12 weeks of
455 training, and did not emerge until the completion of the 26-week intervention. In lieu of
456 these observations, several methodological differences may have contributed to the
457 delayed cognitive response to DAE training, specifically: i) the cognitive and functional

status of the participants in the current study was relatively preserved and exercise-related improvements may have required more time to manifest; ii) the AE component was relatively short; iii) the use of a moderate intensity AE component, which was gradually progressed over the first two weeks of the intervention until the proper training intensity could be comfortably performed; and iv) the evaluation of cognition using different neuropsychological tests where performance may be more responsive to exercise training. For instance, Dorfman and colleagues (2014) observed significant reductions in TMT B scores following 12 weeks of treadmill-based DT exercise training for older idiopathic fallers. Although the participants in both studies were of similar age, education, and cognitive status (i.e., MoCA scores), the participants did differ on their previous falls history. Cognition, especially EF, is highly associated with the control of gait, balance, and falls prevention (Amboni, Barone, & Hausdorff, 2013; Herman, Mirelman, Giladi, Schweiger, & Hausdorff, 2010); thus, when compared to those without a history of falls, older adults with a history of falls may have a greater degree of underlying executive dysfunction, which would be more sensitive and responsive to interventions directed towards mitigating falls risk. Differences in baseline TMT-B scores between the participants in the Dorfman study and the present study [mean (SD): 148.8 (65.3) vs. 69.9 (24.7) seconds] suggests greater executive deficit among the idiopathic fallers of the former study, which may have allowed for a more immediate EF response to training.

The observations presented herein are also aligned with previous work that investigated the additional cognitive benefit that is provided by including a DT training component to a standardized senior's fitness program (Gill et al., 2016). For instance, a previous study reported by our group (Gill et al., 2016) employed a 26-week randomized

controlled trial whereby participants performed a standardized senior's fitness program and mind-motor exercise (i.e., Square Stepping Exercise) in isolation, or with the addition of a cognitive task (i.e., verbal fluency or arithmetic). Following the intervention, improved global cognitive functioning was observed among those who performed the standardized fitness program and the DT mind-motor exercise when compared to those who performed the standardized fitness program and single-task mind-motor training. In contrast to the results of the present study, improvements in global cognition were driven by increased performance on verbal fluency and memory tasks, but not EF. The differences in the executive cognitive response between these interventions can be attributed in part to discrepancies in the DT requirements of the interventions. The DT component within the study by Gill and colleagues was a group-based Square Stepping Exercise with additional cognitive tasks. Briefly, the participants who performed the cognitive motor task were split into groups of six and were provided a demonstration of a foot-placement pattern that was to be memorized and replicated in order to progress across a gridded floor mat. While these participants were replicating the foot-placement pattern, they were also required to respond to verbal fluency and arithmetic tasks. In the present study, each individual participant was required to actively monitor and modify their gait while simultaneously answering verbal fluency and arithmetic tasks for the entire duration of the DT portion of the intervention. Participants in the HM2 study were subject to an intermittent DT training stimulus during 15 minutes of DT exercise rather than 15 minutes of consistent DT exercise training as was performed in the present study. Furthermore, individuals who quickly became proficient with the motor demands of the square stepping exercise could have moved across the mat more quickly than others,

which would have resulted in a reduced DT load than what was provided within the current study. Although DT training can benefit cognition, and specifically EF (Dorfman et al., 2014; Gill et al., 2016; Gregory et al., 2013), questions regarding which type of DT stimulus and the intensity of that stimulus are best suited to improve cognition, still remain. The relationship between EF and the control of gait may have allowed for the current intervention to more directly influence EF than those that employ an unrelated DT condition during training.

The longitudinal observation of the decay of the cognitive benefits that are obtained through exercise training has received little attention (Gregory et al., 2013). Recently, Rahe and colleagues (Rahe et al., 2015) observed the maintenance of improved attention up to after 1 year of follow-up, while the LIFE trial (Sink et al., 2015) did not detect any maintenance and suggest that the cognitive benefits of exercise training dissipate after 2 years of follow-up. Findings from the present study suggest that the cognitive benefits garnered through the participation in DAE training persist for up to 6 months following the cessation of the intervention. Taken together, it appears that mid to long duration (i.e., 12- to 26-weeks) exercise training interventions can provide cognitive benefits that persist for 6 to 12 months post-training; however, sustained participation in exercise training programs may be required to prevent the decay of any cognitive benefits that are achieved. Further work is required to determine the trajectory of the decay in the cognitive benefits that are garnered through exercise training.

The Effect of DAE Training on Usual and Dual-task Gait

Improvements in usual and DT gait speed and step length were observed following 26 weeks of DAE training, while stride time variability remained unchanged.

Despite the beneficial effect of training, the improvements in usual and DT gait speed and step length were not maintained after 26 weeks of no contact follow-up. Recent meta-analyses have identified increased gait speed as the primary mechanism by which exercise benefits gait performance (Howe, Rochester, Neil, Skelton, & Ballinger, 2011; Plummer, Zukowski, Giuliani, Hall, & Zurakowski, 2015). Indeed, these suggestions are aligned with the results of the current study and those from previous works, which observed increased usual and DT gait speed following 12 weeks of treadmill-based DT training (Dorfman et al., 2014) and DT gait speed following 26 weeks of standard senior's fitness training combined with single or DT mind-motor exercise training (Gregory et al., 2016). The influence of exercise training on usual and DT step length is less definitive, as improvements in step length have not been consistently found (Dorfman et al., 2014; Gregory et al., 2016). In contrast to results reported from Gregory and colleagues (Gregory et al., 2016), observations from treadmill-based training interventions suggest that these programs can increase usual and DT step length (Dorfman et al., 2014). Compared to other novel cognitive-motor interventions, treadmill-based interventions involve a repetitive stepping requirement that is readily comparable to the demands of usual gait, and thus provide benefits that are more readily translatable to daily locomotion. Differences in the motor requirements of the DT between these studies (i.e., treadmill-based versus Square Stepping Exercise) likely contributed to the discrepancies in the effect of the interventions on usual gait performance.

Stride time variability under usual and DT conditions was not influenced by the DAE intervention. Increased gait variability has been identified as a falls risk factor

(Hausdorff, Rios, & Edelberg, 2001; Springer et al., 2006) and is a common characteristic of mild cognitive impairment (Montero-Odasso et al., 2009; Verghese et al., 2008). Participants in the present study were, on average, cognitively healthy and functionally independent community-dwelling older adults. Furthermore, these individuals demonstrated relatively preserved stride time variability at baseline [stride time variability %, median (IQR): 1.8 (1.5 to 2.3) %]. Beauchet and colleagues (2013) determined that only those with the greatest variability at baseline (i.e., > 4.4%) experience reductions in stride time variability following exercise training. The relatively preserved cognitive and functional status of the participants in the current study likely contributed to the lack of observed change in the gait variability outcomes following the DAE intervention.

The Effect of DAE Training on Vascular Health

Following 26 weeks of DAE training, 24-hour ambulatory systolic and diastolic BP, and CAC remained unchanged, while cIMT increased. After 26 weeks of no-contact follow-up, 24-hour systolic and diastolic BP, CAC, and cIMT were not significantly different from baseline. CVD risk factors, specifically hypertension (Tsao et al., 2013) and the associated exacerbations in age-related arterial stiffening (Seals, Desouza, Donato, & Tanaka, 2008) have been implicated as mechanisms that drive neuropathological changes (i.e., reduced brain volume, white matter hyperintensities, and silent cerebral infarct) in the aging brain and the establishment of dementia (Akinyemi, Mukaetova-Ladinska, Attems, Ihara, & Kalaria, 2013). However, recent reductions in the incidence of cognitive impairment have been attributed in part to increased efforts to prevent and manage CVD risk factors (Langa KM, 2015; Shatenstein B, 2015). Exercise

training is a cornerstone lifestyle modification used for CVD risk factor management, and increasing evidence suggests that exercise can benefit cognition (Gregory et al., 2013). Although exercise-induced adaptations to vascular structure and function and improved neurovascular coupling have been suggested as primary mechanisms that drive improved cognition post-training (Barnes, 2015), the cognitive benefits that were observed within the current study emerged without concurrent changes in vascular health.

The lack of an observed change in ambulatory BP and CAC within the current study may be attributed to the level of baseline fitness of the study participants and the lack of change in predicted VO_{2max} following the intervention [mean (SD); V0: 29.2 (7.9); V2: 30.3 (8.1) mLO_2/kg/min]. There was no requirement for a history of recent sedentary living within the inclusion criteria, nor was habitual exercise participation quantified upon entry to the study; the blunted vascular response to training could have occurred as a result of participants substituting previously performed exercise training with the DAE intervention. In addition, although aerobically based exercise training has been shown to impart both cardiovascular and cognitive benefits, very little is known regarding whether these benefits occur alongside one another. Other mechanisms (i.e., elevations in circulating growth factors, cortical volume, neurogenesis, neural efficiency, or cerebral glucose metabolism, and reductions in oxidative stress, beta amyloid burden, etc.; Garcia-Mesa et al., 2015; Griffin et al., 2011; Lange-Asschenfeldt & Kojda, 2008; Lista & Sorrentino, 2010; Tsai, Wang, Pan, & Chen, 2015) that are able to act in a manner independent to changes in vascular physiology remain under investigated and may be equally as important to consider.

Observational studies have identified cIMT as an index of vascular stiffness, and elevations in cIMT over time have been associated with adverse cardiovascular events (i.e., myocardial infarction; O'Leary et al., 1999), the development of white matter hyperintensities (Bots et al., 1993) and stroke (Bots, Hoes, Koudstaal, Hofman, & Grobbee, 1997). Although exercise training has consistently been shown to benefit traditional indices of vascular health (i.e., BP and arterial compliance), its influence on cIMT remains equivocal. Reductions in cIMT have been observed, but this response has only been found following high-intensity and long duration exercise training (Thijssen, Cable, & Green, 2012). In the current study, due to baseline fitness levels and lack of change in predicted VO_{2max} post-training, we did not expect to see significant changes in cIMT. The observed elevations in cIMT post-training are likely the result of normal age-related changes to vascular wall structure that occur in order to maintain intra-arterial pressure and flow homeostasis (Engelen et al., 2013). Furthermore, these observed elevations in cIMT are well within what is considered the "normal" range for older adults without established CVD (Engelen et al., 2013). Taken together, these observations suggest that the intensity of the DAE intervention was insufficient to prevent the natural progression of age-related elevations in cIMT.

Limitations

The majority of the participants in the current study were Caucasian (95%), nearly two-thirds female, and they were highly educated, all of which should be considered when interpreting and generalizing these findings. The current investigation followed a case study design, and there were no controls or comparison groups included. The omission of a comparison group does not allow for the determination of whether or not

the changes in cognition that were observed during the study occurred as a result of other extraneous factors (i.e., increased socialization). There were also limitations associated with the specific outcomes used in this study. Cognition was assessed using traditional pen and paper-based neuropsychological outcomes, which may have contributed to the occurrence of practice effects. However, as previous observations suggest, the likelihood of encountering practice effects on cognitive testing is significantly diminished if assessment sessions are spaced at least 12 weeks apart (Bartels, Wegrzyn, Wiedl, Ackermann, & Ehrenreich, 2010). Furthermore, environmental and contextual cues can also serve as a primer for cognitive performance. For instance, Hupbach and colleagues (2008) found that memories could be automatically reactivated when an individual returns to an original learning context. The participants in the current study performed the cognitive assessments in a small clinical room that was not used for any other study-related purposes, and this unique assessment environment may have served to subconsciously prime cognitive performance. The possibility for contextually cued cognitive performance during follow-up assessments and the absence of an inactive control group for appropriate comparisons of cognitive performance over time must be considered when interpreting these results. Furthermore, mechanistic outcomes that could allow for a more thorough interpretation of the mediators of the observed cognitive benefit (i.e., blood borne growth factors, cerebral spinal fluid, beta amyloid concentrations etc.] were not included in the study. Future work should aim to include a comprehensive battery of neuropsychological and neurophysiological outcomes. Several limitations related to the dual-task gait assessments must also be identified, including i) the task delivery was not randomized (i.e., usual gait followed by 3 DT conditions:

counting backwards from 100 by 1, semantic verbal fluency task, and serial 7's subtraction from 100), ii) the starting point for the serial subtraction DT was not modified between visits, and iii) performance on the secondary tasks within the DT gait assessment was not methodologically controlled (i.e., performance on serial 7's subtraction in isolation, without the walking task). Furthermore, this study contained a large number of outcome variables, which resulted in a large number of statistical analyses, and these analyses were not adjusted for any potential confounders. The large number of analyses may have increased the likelihood of committing Type I error. Finally, although ideal vascular testing conditions and the associated participant responsibilities were outlined and verbally communicated 24 hours prior to the vascular assessments (Pickering et al., 2005), adherence to these requirements was not evaluated or enforced.

Conclusions

Recent reductions in the age-specific prevalence and incidence of cognitive impairment can be attributed to a number of lifestyle factors, including attaining a higher level of formal education, leading a healthy lifestyle, and effective CVD risk factor management (Langa KM, 2015; Shatenstein B, 2015). These observations suggest that the risk of cognitive impairment and the progression of cognitive decline can be mitigated through interventions aimed at these and potentially other modifiable risk factors. Exercise training is regarded as a gold standard for CVD risk factor management, and increasing evidence supports the role of exercise alone, or in combination with cognitive training as a promising strategy to preserve brain health and functioning in aging. Numerous studies continue to support the use of cognitive and physical exercise training as an effective non-pharmacological intervention to mitigate CVD risk factor burden,

improve physical function, and benefit cognition (Bherer, 2015; Gregory et al., 2013). During pathological cognitive aging, EF and memory are often the first cognitive domains affected (Carlson, Xue, Zhou, & Fried, 2009); therefore, identifying interventions that aim to prevent incipient cognitive decline through the simultaneous targeting and training of these cognitive domains is of considerable importance. Treadmill-based DT gait training and AE may be an attractive choice, as the cognitive requirements of this exercise program (i.e., DT control of gait while providing responses to the verbal fluency task) targets and trains both EF and memory processes. Results from this study indicate that 26 weeks of DAE training can improve functioning within a number of diverse cognitive domains and benefit usual and DT gait performance, but not influence vascular health, in community-dwelling older adults without dementia. These observations support the notion that combined exercise training interventions impart diverse cognitive and motor benefits, and that DT gait training may be an effective method to directly target and train EF and memory. Future work is required to determine whether the cognitive benefits that are associated with DAE training are greater than what can be achieved following other exercise training modalities, and whether these observations can be replicated in a community-based setting.

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Chapter 5: Thesis Summary and Scientific Contributions

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Thesis Summary

The global purpose of this thesis was to explore the relationship between cognition, cardiovascular health, and gait, and to determine whether a novel dual-task gait training and aerobic exercise intervention could benefit cognition, cardiovascular health, and gait in community-dwelling older adults without dementia. In particular, the three studies included in ths thesis were conducted to:

i. Retrospectively investigate the relationship between: (i) global cognition, (ii) executive functioning (EF), (iii) cumulative cardiovascular disease (CVD) risk (i.e., QRISK2 score), and (iv) usual gait (UG) performance (i.e., UG composite score) (Chapter 2).

ii. Determine whether differences in: (i) cognition (i.e., global cognition, EF, information processing speed, verbal fluency, verbal learning and memory), (ii) gait (i.e., usual and dual-task gait speed, step length, and stride time variability), and (iii) vascular health [i.e., 24-hour systolic and diastolic blood pressure (BP), carotid intima-media thickness (cIMT), and carotid arterial compliance (CAC)] exist between older adults with normal BP dipping status and those with non-dipping status (Chapter 3).

iii. Examine the effect of a novel dual-task gait training and aerobic exercise (DAE) program on: (i) cognition (i.e., EF, information processing speed, verbal fluency, verbal learning and memory), (ii) gait (i.e., usual and dual-task gait speed, step length, and stride time variability), and (iii) vascular health

[i.e., 24-hour systolic and diastolic blood pressure (BP), carotid intima-media thickness (cIMT), and carotid arterial compliance (CAC)] (Chapter 3).

Scientific Contributions

Chapter 2 provided insight into the relationship between cumulative CVD risk, usual gait performance, and cognitive functioning. Further characterizing the relationship between these variables is of considerable clinical importance, as CVD risk factors (Dufouil et al., 2001; Hughes et al., 2014; Langbaum et al., 2012) and gait dysfunction (Mielke et al., 2013; Verghese et al., 2002) have been identified as two of the most promising dementia risk factors candidates. Although the relationship between brain health and specific CVD risk factors or gait parameters have been investigated and established, the association between cognition and cumulative CVD risk or overall gait performance has not been previously determined. The results from Chapter 2 suggest that addressing cumulative CVD risk would benefit cognition, specifically EF, to a greater degree than managing gait dysfunction. Furthermore, when considering these results with previous observations that have found associations between individual gait components (i.e., speed and variability) and cognitive impairment (Mielke et al., 2013; Watson et al., 2010) or pathological changes to the brain (Rosano, Brach, Studenski, Longstreth, & Newman, 2007; Rosano et al., 2008; Rosano et al., 2012), it appears that specific aspects of gait, rather than composite gait performance, may be most repflective of underlying cognitive dysfunction. Therefore, the management of cumulative CVD risk rather than gait dysfunction may provide the greatest benefit to cognitive functioning, specifically EF, in older adults who are at risk for future cognitive decline.

Building on previous work from Chapter 2, Chapter 3 retrospectively determined whether community-dwelling older adults who demonstrate reduced BP dipping (i.e., non-dippers, N-DS) was associated with worse performance on measures of cognition and gait and vascular health than those who demonstrate normal BP dipping. Specifically, baseline data from two exercise intervention studies were pooled, and N-DS participants were identified as those who demonstrated a > 10% reduction in 24-hour ambulatory systolic BP from daytime to nighttime. Despite having achieved a significantly higher level of formal education, N-DS participants performed worse on measures of EF, information processing speed, and memory, and demonstrated slower usual gait speed, shorter dual-task step length, and greater usual and dual-task stride time variability. Furthermore, although the participants were stratified by a known CVD risk factor and N-DS participants had previously experienced a significantly higher number of cardiovascular events, there were no between group differences for any of the measured vascular outcomes (i.e., 24-hour ambulatory systolic or diastolic BP, cIMT or CAC). Although these observations are aligned with previous work what have found associations between N-DS and cognitive function (Bellelli et al., 2004; Nagai, Hoshide, Ishikawa, Shimada, & Kario, 2008; Ohya et al., 2001; van Boxtel et al., 1998), this is the first study to investigate the relationship between N-DS, cognition, and gait in relatively healthy, functionally independent community-dwelling older adults. These results suggest that N-DS can influence the health and functioning of the brain regardless of an individual's hypertensive status and prior to the establishment of significant objective cognitive impairment, which highlights the potential impact that the restoration of the diurnal variation in BP could impart on cognitive functioning. Collectively, these

observations suggest that BP dipping status can provide additional prognostic utility for the development of cognitive impairment and neuropathological changes to the aging brain beyond what can be achieved using systolic BP alone, and implicates this independent vascular risk factor as a potential dementia risk factor candidate.

Chapter 4 explored the effect of a 26-week DAE training program on multiple domains of cognition (i.e., EF, information processing speed, verbal fluency, verbal learning and memory), usual and dual-task gait (i.e., speed, step length and stride time variability), and a number of traditional CVD risk factors (i.e., 24-hour ambulatory systolic and diastolic BP, cIMT, and CAC) in community-dwelling older adults without dementia. This novel DAE program was designed in an attempt to maximize the potential benefit to EF by combining two exercise modalities (i.e., dual-task and aerobic exercise training) that have been shown to preferentially benefit the functioning of this cognitive domain and the health of its associated brain structures (Colcombe & Kramer, 2003; Erickson et al., 2007). In line with previous work investigating the cognitive effects of 26 weeks exercise training interventions (Barnes et al., 2013; Dorfman et al., 2014; Gill et al., 2016), 26 weeks of DAE training was found to benefit EF, information processing, phonemic verbal fluency, and memory. Moreover, while the DAE program did not influence vascular health or cardiorespiratory fitness, improvements in usual and dual-task gait speed and step length were also observed. Previously Dorfman and colleagues (2014) observed improvements in EF and usual and dual-task gait speed following a similar, yet shorter-duration (i.e., 6 weeks) dual task and aerobic exercise training intervention in idiopathic fallers; however, improvements in EF failed to emerge prior to the completion of the full 26-week intervention in the current study. These discrepancies

suggest that certain patient populations may be more readily receptive to the cognitive benefits of exercise training interventions. For instance, a surmounting body of evidence suggests that intact cognitive functioning is required for the control of gait and falls prevention (Amboni, Barone, & Hausdorff, 2013); thus, a history of falls reflects underlying brain pathology and cognitive impairment. The presence of idiopathic fallers in Dorfman and colleagues (2014) work suggest that, despite having similar objective cognitive screening (i.e., MoCA) scores, these participants may have had a greater degree of underlying cognitive impairment at baseline when compared to the participants in the current study. An additional noteworthy contribution of this work was the inclusion of a longitudinal evaluation of the maintenance of cognitive change following the cessation of the DAE intervention. Previous studies have been limited by their omission of longitudinal follow-up, and the degree by which cognitive benefits are maintained following exercise training remains equivocal (Gregory, Gill, & Petrella, 2013). Results from this study suggest that the cognitive benefits provided by 26-weeks of DAE training can be maintained for at least 26-weeks following participation in the program. Despite the intrinsic gait requirements of the intervention and the observed benefit to cognition, the improvements in usual and dual-task gait that were observed following the intervention were not maintained at follow-up. These seemingly contradictory observations may be due to a number of factors: i) the possibility of having observed practice effects on the cognitive outcomes, ii) the requirements of the gait training portion of the DAE program did not effectively impact the cognitive control of gait during untrained tasks, and/or iii) the relationship between cognition and gait is dependent upon the degree of pre-existing cognitive impairment. Nevertheless, the observations from

Chapter 4 have helped to define the trajectory of cognitive change in older adults without dementia following exercise training interventions, as well provided preliminary evidence related to the maintenance of changes in cognition and gait following the cessation of training.

Future Directions

Higher cumulative CVD risk was associated with worse EF in a cohort of community-dwelling older adults without dementia. However, the relatively low total explained variance of the regression model in Chapter 2 (i.e., 28.4%, see Table 2.2)suggest that other CVD risk factors that are not captured by CVD risk composite scores may also contribute to cognitive impairment in aging. Future efforts should focus on the identification and characterization of novel CVD risk factors that are associated with neuropathological changes to the brain and cognitive impairment. Furthermore, the relationship between gait and EF becomes most pronounced while under dual-task conditions (Yogev-Seligmann, Hausdorff, & Giladi, 2008), and the control of gait is dependent upon not only EF, but also attention, memory, and visuospatial skills (Amboni et al., 2013). Thus, future work should investigate the relationship between cognition and dual-task gait, as well as the realtionship between gait performance and the functioning of a wide breadth of cognitive domains.

A number of exercise training modalities have been found to benefit the health and function of the aging brain. The results from Chapter 3 suggest that 26-weeks of DAE training can benefit ususal and dual task gait, and provide cognitive benefits that are maintained for at least 26-weeks followoing the cessation of training. Although there has recently been increasing attention paid to the evaluation of the maintenace of exercise-

induced cognitive benefits (Gill et al., 2016; Best, Chiu, Liang Hsu, Nagamatsu, & Liu-Ambrose, 2015; Rahe et al., 2015; Sink et al., 2015; Eggenberger, Schumacher, Angst, Theill, & de Bruin, 2015; Ngandu et al., 2015; Fiatarone Singh et al., 2014), future studies should include longitudinal follow-up periods with appropriately spaced assessment visits in order to definitively support these findings. The cognitive response to exercise training interventions is quite heterogeneous and appears to be dependent upon a number of factors, including: i) the specific exercise training modality employed, ii) the intensity of the training program (i.e., low, moderate, vigorous, progressive or static intensity), iii) the frequency of training, iv) the overall duration of the intervention, and v) the clinical characteristics of the study population (Gregory et al., 2013). Although the results from Chapter 3 suggest that DAE can benefit the functioning of a number of diverse cognitive outcomes, further work is required to determine the specific modality, training intensity, and overall duration of training that will provide the greatest beneit to the health and functioning of the aging brain. Furthermore, despite the intrinsic gait requirements of the intervention the observed benefit to cognition, the improvements in usual and dual-task gait that were observed following the intervention were not maintained at follow-up. These seemingly contradictory observations may be due to a number of factors, including: i) the possibility of having observed practice effects on the cognitive outcomes, ii) the requirements of the gait training portion of the DAE program did not effectively impact the cognitive control of gait during untrained tasks, and/or iii) the relationship between cognition and gait is dependent upon the degree of pre-existing cognitive impairment. Future efforts aimed at developing interventions to benefit cognition and mobility in aging should strive to further delineate the relationship between

cognition, gait, and vascular health in preclinical populations, and develop exercise interventions that are of sufficient intensity to stimulate the maintenance of improvements in gait outcomes following the cessation of the program. Last, although the results from Chapter 4 implicate BP dipping status as a potential vascular-related dementia risk factor, further research is required to define the relationship between N-DS as well as other BP dipping phenotypes and brain health and functioning in those with and without pre-existing CVD and cognitive impairment.

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Appendices

Appendix A

Western University Research Ethics Board Approval

Research Western

Use of Human Participants - Ethics Approval Notice

Principal Investigator: Dr. Robert Petrella
File Number:102434
Review Level: Full Board
Approved Local Adult Participants:126
Approved Local Minor Participants:0
Protocol Title:HM2: Healthy Mind, Healthy Mobility â€" Dual-task Aerobic Exercise for Older Adults with Cognitive Impairment. (REB# 18858)
Department & Institution: Schulich School of Medicine and Dentistry\Family Medicine,Western University
Sponsor: Canadian Institutes of Health Research

Ethics Approval Date: May 31, 2012
Ethics Expiry Date: March 31, 2014

Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
Western University Protocol	(including instruments noted in section 8.1)	
Letter of Information & Consent		2012/03/05
Letter of Information & Consent	Informant	2012/05/04
Advertisement		
Other	Telephone Script	

This is to notify you that the University of Western Ontario Health Sciences Research Ethics Board (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced study on the approval date noted above. The membership of this HSREB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the University of Western Ontario Updated Approval Request form.

Member of the HSREB that are named as investigators in research studies, or declare a conflict of interest, do not participate in discussions related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Appendix B

Lawson Health Research Institute Research Ethics Board Approval

LAWSON HEALTH RESEARCH INSTITUTE

FINAL APPROVAL NOTICE

RESEARCH OFFICE REVIEW NO.: R-12-265

PROJECT TITLE: HM2: Healthy Mind, Healthy Mobility - Dual-task Aerobic Exercise for Older Adults with Cognitive Impairment

PRINCIPAL INVESTIGATOR: Dr. Robert Petrella

DATE OF REVIEW BY CRIC: June 12, 2012

Health Sciences REB#: 18858

Please be advised that the above project was reviewed by the Clinical Research Impact Committee and the project:

Was Approved

PLEASE INFORM THE APPROPRIATE NURSING UNITS, LABORATORIES, ETC. BEFORE STARTING THIS PROTOCOL. THE RESEARCH OFFICE NUMBER MUST BE USED WHEN COMMUNICATING WITH THESE AREAS.

Dr. David Hill
V.P. Research
Lawson Health Research Institute

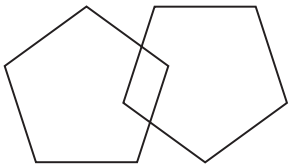
All future correspondence concerning this study should include the Research Office Review Number and should be directed to Sherry Paiva, CRIC Liaison, LHSC, Rm. C210, Nurses Residence, South Street Hospital.

Appendix C
Mini-Mental State Examination (MMSE)

The Mini-Mental State Exam

Patient_____ Examiner _____ Date_____

Maximum	Score	
		Orientation
5	( )	What is the (year) (season) (date) (day) (month)?
5	( )	Where are we (state) (country) (town) (hospital) (floor)?
		Registration
3	( )	Name 3 objects: 1 second to say each. Then ask the patient all 3 after you have said them. Give 1 point for each correct answer. Then repeat them until he/she learns all 3. Count trials and record. Trials _____
		Attention and Calculation
5	( )	Serial 7's. 1 point for each correct answer. Stop after 5 answers. Alternatively spell "world" backward.
		Recall
3	( )	Ask for the 3 objects repeated above. Give 1 point for each correct answer.
		Language
2	( )	Name a pencil and watch.
1	( )	Repeat the following "No ifs, ands, or buts"
3	( )	Follow a 3-stage command: "Take a paper in your hand, fold it in half, and put it on the floor."
1	( )	Read and obey the following: CLOSE YOUR EYES
1	( )	Write a sentence.
1	( )	Copy the design shown.



_____ Total Score

ASSESS level of consciousness along a continuum _____

Alert Drowsy Stupor Coma

"MINI-MENTAL STATE." A PRACTICAL METHOD FOR GRADING THE COGNITIVE STATE OF PATIENTS FOR THE CLINICIAN. *Journal of Psychiatric Research*, 12(3): 189-198, 1975. Used by permission.

Appendix D

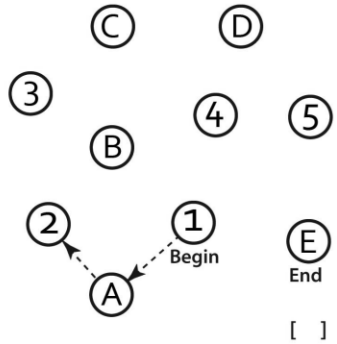
Montreal Cognitive Assessment (MoCA)

MONTREAL COGNITIVE ASSESSMENT (MOCA®)
Version 7.2 Alternative Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS

Copy rectangle



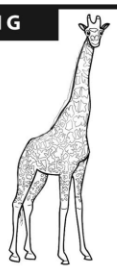
[ ] [ ]

Draw CLOCK (Five past four)
(3 points)

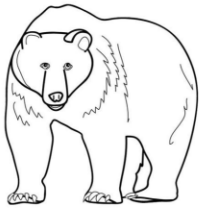
[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING



[ ]



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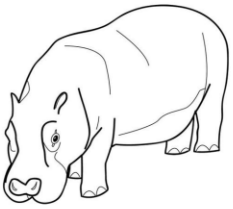

[ ]

__/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	TRUCK	BANANA	VIOLIN	DESK	GREEN
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).
Subject has to repeat them in the forward order [ ] 3 2 9 6 5
Subject has to repeat them in the backward order [ ] 8 5 2
__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B
__/1

Serial 7 subtraction starting at 90 [ ] 83 [ ] 76 [ ] 69 [ ] 62 [ ] 55
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**
__/3

LANGUAGE Repeat : A bird can fly into closed windows when it's dark and windy. [ ]
The caring grandmother sent groceries over a week ago. [ ]
__/2

Fluency / Name maximum number of words in one minute that begin with the letter S [ ] _____ (N ≥ 11 words)
__/1

ABSTRACTION Similarity between e.g. carrot - potato = vegetable. [ ] diamond - ruby [ ] cannon - rifle
__/2

DELAYED RECALL

	TRUCK	BANANA	VIOLIN	DESK	GREEN	Points for UNCUED recall only
Has to recall words WITH NO CUE	[ ]	[ ]	[ ]	[ ]	[ ]	
Optional Category cue						
Optional Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City
__/6

Adapted by : Z. Nasreddine MD, N. Phillips PhD, H. Chertkow MD
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Administered by: _____

Normal ≥ 26 / 30

TOTAL __/30
Add 1 point if ≤ 12 yr edu

Appendix E

Centre for Epidemiological Studies-Depression Scale (CES-D)

Center for Epidemiologic Studies Depression Scale (CES-D), NIMH

Below is a list of the ways you might have felt or behaved. Please tell me how often you have felt this way during the past week.

	During the Past Week			
	Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	Most or all of the time (5-7 days)
1. I was bothered by things that usually don't bother me.	☐	☐	☐	☐
2. I did not feel like eating; my appetite was poor.	☐	☐	☐	☐
3. I felt that I could not shake off the blues even with help from my family or friends.	☐	☐	☐	☐
4. I felt I was just as good as other people.	☐	☐	☐	☐
5. I had trouble keeping my mind on what I was doing.	☐	☐	☐	☐
6. I felt depressed.	☐	☐	☐	☐
7. I felt that everything I did was an effort.	☐	☐	☐	☐
8. I felt hopeful about the future.	☐	☐	☐	☐
9. I thought my life had been a failure.	☐	☐	☐	☐
10. I felt fearful.	☐	☐	☐	☐
11. My sleep was restless.	☐	☐	☐	☐
12. I was happy.	☐	☐	☐	☐
13. I talked less than usual.	☐	☐	☐	☐
14. I felt lonely.	☐	☐	☐	☐
15. People were unfriendly.	☐	☐	☐	☐
16. I enjoyed life.	☐	☐	☐	☐
17. I had crying spells.	☐	☐	☐	☐
18. I felt sad.	☐	☐	☐	☐
19. I felt that people dislike me.	☐	☐	☐	☐
20. I could not get "going."	☐	☐	☐	☐

SCORING: zero for answers in the first column, 1 for answers in the second column, 2 for answers in the third column, 3 for answers in the fourth column. The scoring of positive items is reversed. Possible range of scores is zero to 60, with the higher scores indicating the presence of more symptomatology.

Appendix F

Lawton-Brody Instrumental Activities of Daily Living (IADL) Scale

Instrumental Activities of Daily Living (IADL)

Instructions: Circle the scoring point for the statement that most closely corresponds to the patient's current functional ability for each task. The examiner should complete the scale based on information about the patient from the patient him-/herself, informants (such as the patient's family member or other caregiver), and recent records.

A. Ability to use telephone	Score
1. Operates telephone on own initiative; looks up and dials numbers, etc.	1
2. Dials a few well-known numbers	1
3. Answers telephone but does not dial	1
4. Does not use telephone at all	0

B. Shopping	
1. Takes care of all shopping needs independently	1
2. Shops independently for small purchases	0
3. Needs to be accompanied on any shopping trip	0
4. Completely unable to shop	0

C. Food preparation	
1. Plans, prepares, and serves adequate meals independently	1
2. Prepares adequate meals if supplied with ingredients	0
3. Heats and serves prepared meals, or prepares meals but does not maintain adequate diet	0
4. Needs to have meals prepared and served	0

D. Housekeeping	
1. Maintains house alone or with occasional assistance (e.g., "heavy work domestic help")	1
2. Performs light daily tasks such as dishwashing, bed making	1
3. Performs light daily tasks but cannot maintain acceptable level of cleanliness	1
4. Needs help with all home maintenance tasks	1
5. Does not participate in any housekeeping tasks	0

E. Laundry	Score
1. Does personal laundry completely	1
2. Launders small items; rinses stockings, etc.	1
3. All laundry must be done by others	0

F. Mode of transportation	
1. Travels independently on public transportation or drives own car	1
2. Arranges own travel via taxi, but does not otherwise use public transportation	1
3. Travels on public transportation when assisted or accompanied by another	1
4. Travel limited to taxi or automobile with assistance of another	0
5. Does not travel at all	0

G. Responsibility for own medications	
1. Is responsible for taking medication in correct dosages at correct time	1
2. Takes responsibility if medication is prepared in advance in separate dosages	0
3. Is not capable of dispensing own medication	0

H. Ability to handle finances	
1. Manages financial matters independently (budgets, writes checks, pays rent and bills, goes to bank), collects and keeps track of income	1
2. Manages day-to-day purchases, but needs help with banking, major purchases, etc.	1
3. Incapable of handling money	0

(Lawton & Brody, 1969)

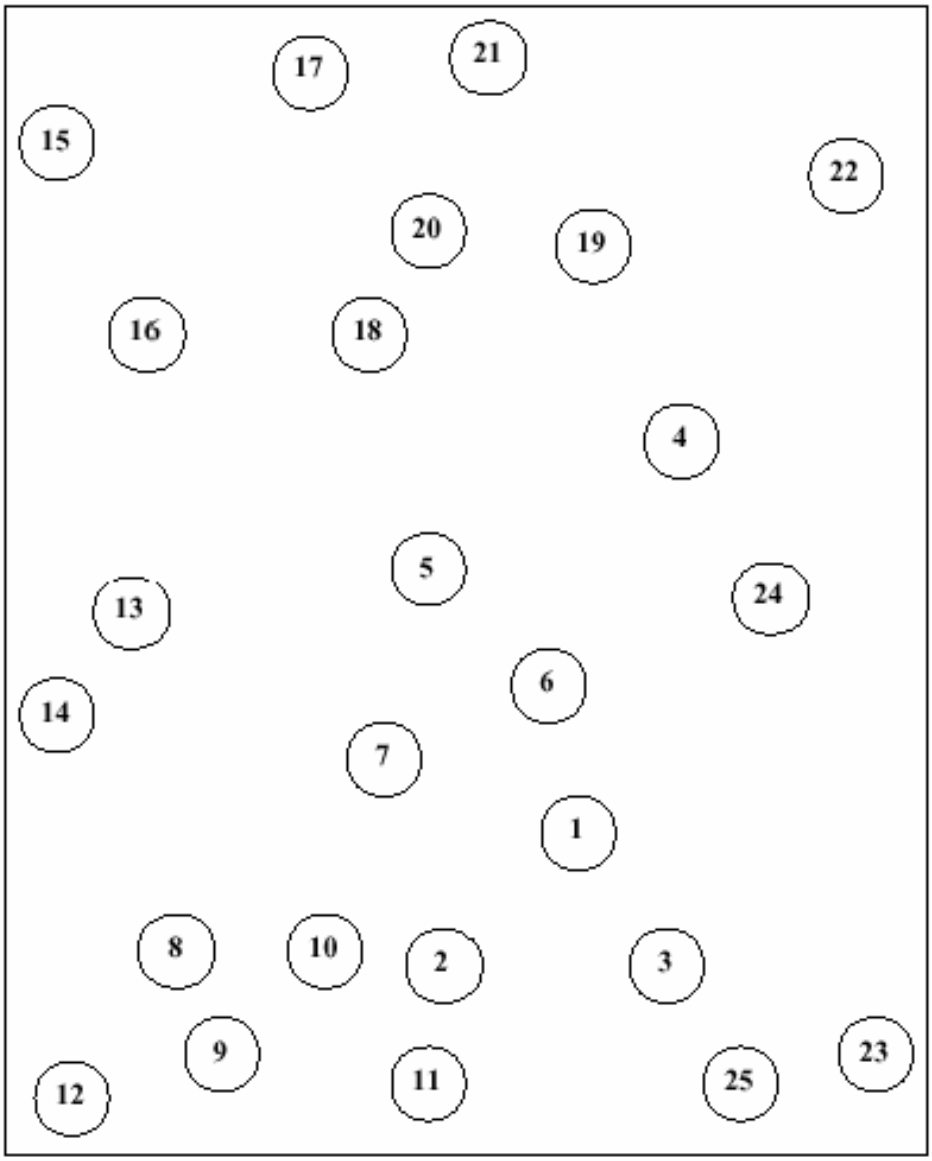
Scoring: The patient receives a score of 1 for each item labeled A – H if his or her competence is rated at some minimal level or higher. Add the total points circled for A – H. The total score may range from 0 – 8. A lower score indicates a higher level of dependence.

Appendix G

Trail Making Test Part A

Trail Making Test Part A

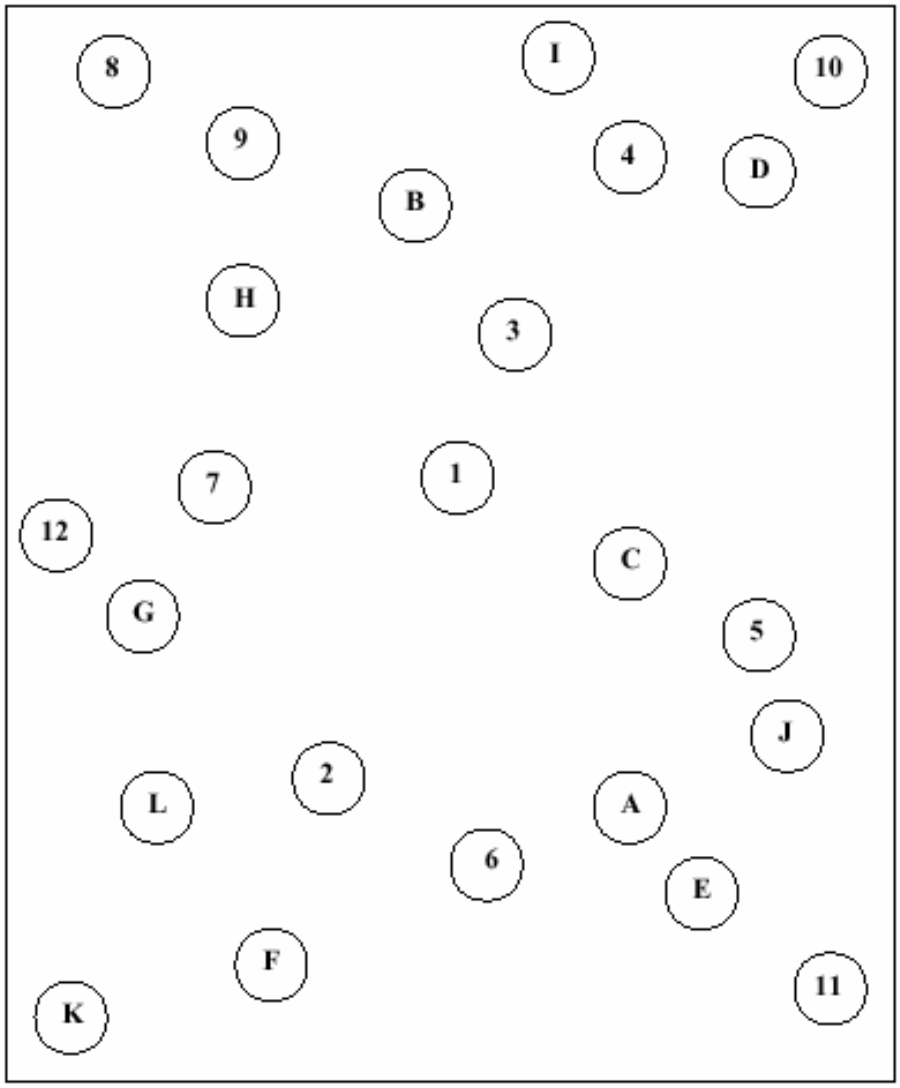
Patient's Name: _____ Date: _____



Appendix H
Trail Making Test Part B

Trail Making Test Part B

Patient's Name: _____ Date: _____



Appendix I

Auditory Verbal Learning and Memory Test

Auditory Verbal Learning Test (A.V.L.T.) Version A

Baseline Visit

START TIME: ☐☐☐☐ (24-hour clock)

Trial 1 Instruction:

Say, **"I am going to read a list of words. Listen carefully, for when I stop you are to repeat back as many words as you can remember. It doesn't matter in what order you repeat them, just try to remember as many as you can."**

Trial 2-5 Instructions:

Say, **"Now I am going to read the same words again, and once again when I stop I want you to tell me as many words as you can remember, including words you said the first time. It doesn't matter in what order you say them, just as many words as you can remember, whether or not you said them before."**

List B Instructions:

Say, **"Now I'm going to read a second list of words. Listen carefully, for when I stop you are to repeat back as many words as you can remember. It doesn't matter in what order you repeat them, just try to remember as many as you can."**

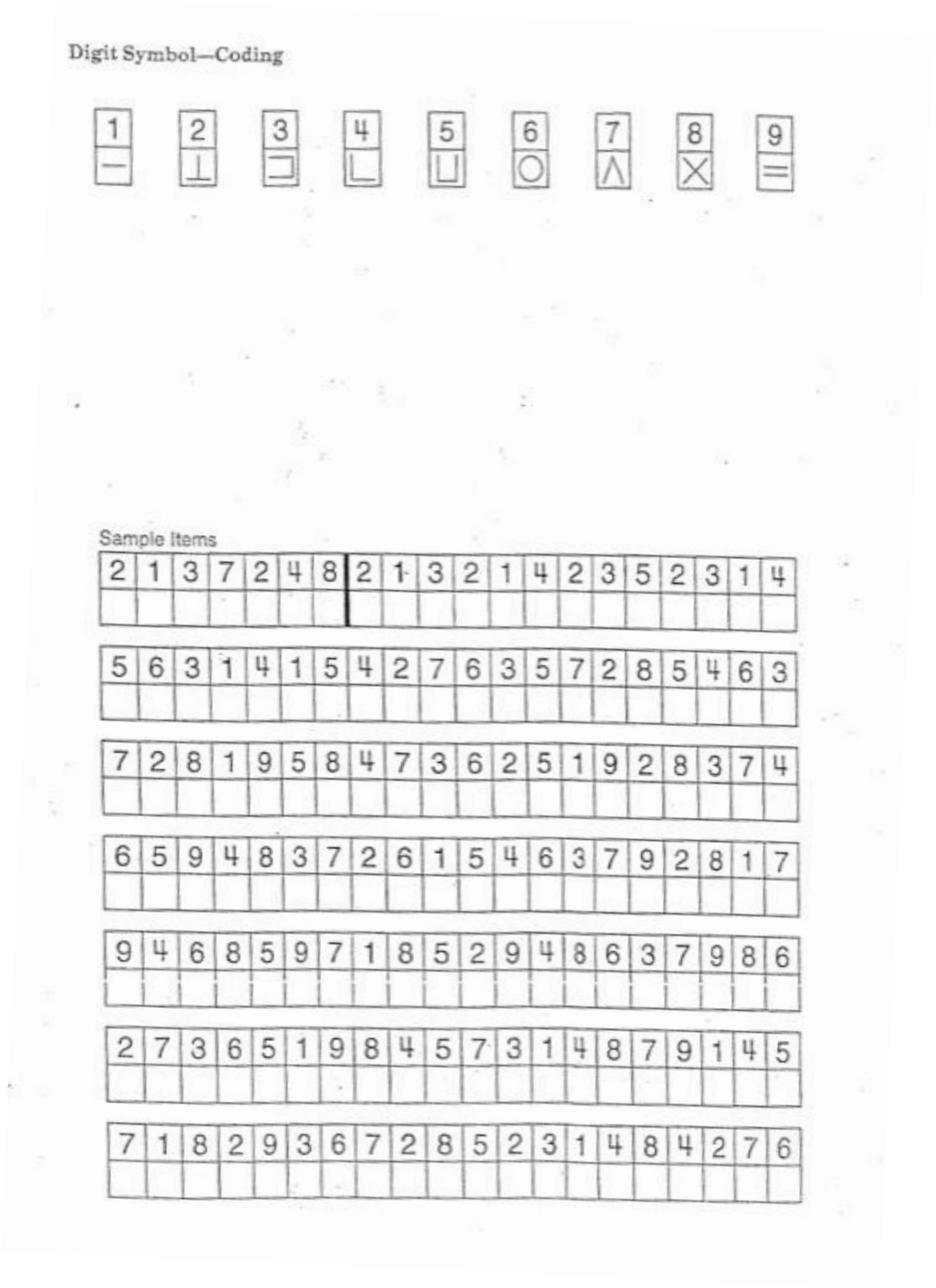
Trial 6 Instructions:

Say, **"Now tell me all the words you can remember from the first list, the list I repeated a number of times."**

List A	1	2	3	4	5	AFTER B-RECALL 6	List B	List B Recall
Drum							Desk	
Curtain							Ranger	
Bell							Bird	
Coffee							Shoe	
School							Stove	
Parent							Mountain	
Moon							Glasses	
Garden							Towel	
Hat							Cloud	
Farmer							Boat	
Nose							Lamb	
Turkey							Gun	
Color							Pencil	
House							Church	
River							Fish	
Totals								

Appendix J

Digit-Symbol Substitution Test



Appendix K
Semantic Verbal Fluency Test

Semantic Fluency (Animal Naming):

Instructions: I am going to give you one minute to name to me as many animals as you can think of. They can be animals from the farm, the zoo, the jungle, underwater animals, house pets, or any kind of animal that you can think of. Any Questions? (Pause) "Now, name for me as many animals as you can think of. (Time for 60 seconds) "Stop".

Record exact responses
Responses within the first 15 seconds

Responses within the last 45 seconds

Total number of correct responses:

Number of correct responses in the first 15 seconds:

Number of correct responses in the last 45 seconds:

Appendix L

Phonemic Verbal Fluency Test – Controlled Oral Word Association (COWA) Test

Phonemic Fluency [Controlled Oral Word Association (COWA) Test]:

Instructions: The examiner gives the following instructions" Tell me as many words as you can think of that begin with a certain letter of the alphabet that I will tell you in a moment. You can say any kind of word you want, except for proper nouns (like Bob or Boston), numbers, or words that begin with the same sound but have a different suffix, for example, love, lover, loving, etc. I will tell you to stop after one minute. Are you ready? (Pause) Now, tell me as many words as you can think of that begin with the letter "C". (Time for 60 seconds) "Stop".

Record exact responses
Responses within the first 15 seconds

Responses within the last 45 seconds

Total number of correct responses:

Number of correct responses in the first 15 seconds:

Number of correct responses in the last 45 seconds:

Appendix M

Step Test for Exercise Prescription (STEP) Stepping Unit and Predicted VO_2max Equation

pVO2max = 3.9 + (1511/time)*((weight/HR)*0.124) – (age*0.032) – (sex*0.633)

Where pVO2max is the predicted maximal oxygen uptake (L/min); time is the time to complete the stepping test; weight is body mass (kg); heart rate is beats per minute palpated immediately upon completion of the stepping test; age is the participant's age (years); and sex is 1 for males and 2 for females. The predicted VO2max (mL/kg/min) is used to determine fitness classification for the prescription of individualized and appropriate aerobic exercise intensity during the intervention.

Curriculum Vitae

CURRENT POSITION

Doctor of Philosophy Candidate (PhD), Rehabilitation Sciences (RS) Sept. 2012 – present
London ,ON
- *with distinction in collaborative musculoskeletal health research (CMHR)*

Health & Rehabilitation Sciences, University of Western Ontario
Thesis title: "Dual-task gait training and aerobic exercise for community-dwelling older adults without dementia"

Thesis committee: Dawn P. Gill, Kevin Shoemaker, Jeff Holmes, Cheri L. McGowan, Robert J. Petrella (advisor)

EDUCATION

Master's of Human Kinetics (M.H.K.), Cardiovascular Physiology September 2012
Windsor, ON
Department of Kinesiology, University of Windsor
Thesis title: "The effects of isometric handgrip training in carotid arterial compliance and resting blood pressure in postmenopausal women"
Thesis committee: Kevin Milne, Huimung Zhang, Cheri McGowan (advisor)

Bachelor's of Science (B.Sc.) Honour's, Biological Sciences (BIOS) February 2010
Guelph, ON
College of Biological Sciences, University of Guelph

RESEARCH EXPERIENCE

Graduate Research Assistant Sept. 2012 – Current
London, ON
Parkwood Research Institute
Parkwood Institute, in affiliation with Lawson Health Research Institute
(Primary Affiliation)

Multi-site Study Coordinator, Isometric handgrip training and the neurovascular control of blood pressure Oct. 2011 – Aug. 2012
Physical Activity and Cardiovascular Research Lab (PACR), University of Windsor
Vascular Dynamics Laboratory, McMaster University
Principle Investigator: Michael Gregory (with Cheri McGowan, Philip Millar, and Maureen MacDoanald)

Research Assistant, Biological Mass Spectrometry Facility Dec. 2009 – Dec. 2010
Advanced Analysis Centre, University of Guelph
Supervisor: Dyanne Brewer and Armen Charchoglyan
Training time: 550 hours

SCHOLARSHIPS, AWARDS, & DISTINCTIONS

1. **Registration Fellowship ($989)**, Alzheimer's Association International Conference (2014)
2. **Early Researcher Award ($400)**, Ontario Long-Term Care Association (2014)
3. **Travel Grant ($170)**, Canadian Association on Gerontology (2013)

4. **Neuroscience Conference Poster Award ($300)**, Baycrest 23rd Annual Conference (2013)

SCHOLARSHIPS, AWARDS, & DISTINCTIONS (cont'd)

5. **Graduate Research Scholarship ($14,268)**, Western University (2012-2013, 2013-2014)
6. **Verdecchia Family Scholarship in Health Sciences ($1500)**, University of Windsor (2012)
7. **Department of Human Kinetics Master's Honour Roll**, University of Windsor (2012)
8. **Graduate Student Society Scholarship ($500)**, University of Windsor (2011)

PROFESSIONAL SERVICES & AFFILIATIONS

Professional Memberships

- Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART) Member 2015 – 2016
- American College of Sports Medicine (ACSM) Student Member 2014 – 2015
- Canadian Association on Gerontology (CAG) Student Member 2013 – 2015
- Canadian Society for Exercise Physiology (CSEP) Student Member 2012 – 2013

Editorial Services

- Response to the World Health Organization's request for comments on the document: *How to Use the ICF: A Practical Manual for using the International Classification of Functioning, Disability and Health, October 2013.* Contributors: Bartlett D, Sharakis-Doyle E and members of the RS Journal Club at Western University

Ad-Hoc Reviewer

- Manuscript for Experimental Gerontology Apr. 2016
- Manuscript for Frontiers in Neuroscience Jan. 2016
- Manuscript for the Journal of Aging and Physical Activity Apr. 2015
- Abstracts for the Canadian Association on Gerontology Annual Meeting June 2013
- Manuscripts for Applied Physiology, Nutrition, and Metabolism Mar. 2013

Professional Services

- Member, 2013 & 2014 FHS-ARGC Symposium Planning Committee 2012 – 2014
- Volunteer, MacSenior's Health and Wellness Program, McMaster University 2011 – 2012
- Volunteer, Windsor-Essex Community Active Aging Program 2010 – 2012
- Judge, Windsor Regional Science, Technology & Engineering Fair 2010 – 2012

RESEARCH FUNDING - CURRENT

Healthy Mind, Healthy Mobility: Combined Dual-task Gait Training and Aerobic Exercise for Older Adults with Cognitive Impairment
Operating Grant: 2012-2013 (CIHR Open Operating Grant)
Canadian Institutes of Health Research
Principal Investigator: Robert J. Petrella
Role: Co-Investigator
$356,547 CAD total (Oct. 2013 – Sept. 2016)

RESEARCH FUNDING - HISTORY

Healthy Mind, Healthy Mobility (HM^2): Dual-task and aerobic gait-training for community-dwelling older adults with and without cognitive impairment, but not dementia (CIND)
Mary Elizabeth Horney Fellowship in Rehabilitation Research
St. Joseph's Health Care Foundation
Role: Principal Applicant, Co-Investigator
$33,692 CAD total (Sept. 2014 – Aug. 2015)

Healthy Mind, Healthy Mobility (HM^2): Dual-task exercise for older adults
Fellowship in Care of the Elderly Research Endowment
St. Joseph's Health Care Foundation
Role: Principal Applicant, Co-Investigator
$30,000 CAD total (Sept. 2012 – Aug. 2013)

BIBLIOGRAPHY

Published Refereed Papers (6 Total)

1. Silva NBS, **Gregory MA**, Gill DP, Petrella RJ. Multiple-modality exercise and mind-motor training to improve cardiovascular health and fitness in older adults at risk for cognitive impairment: a randomized controlled trial. Accepted for publication: Arch Gerontol Geriatr, Oct 20th, 2016.

2. Heath M, Weiler J, **Gregory MA**, Gill DP, Petrella RJ. A six-month aerobic exercise intervention improves executive control in persons with objective cognitive impairment: evidence from the antisaccade task. Accepted for publication in *Journal of the Alzheimer's Disease,* Aug. 2016.

3. **Gregory MA**, Gill DP, Shellington EM, Liu-Ambrose T, Shigematsu R, Zou G, Shoemaker K, Owen AM, Hachinski V, Stuckey M, Petrella RJ. Group-based exercise and cognitive-physical training in older adults with self-reported cognitive complaints: The multiple-Modality, Mind-Motor (M4) study protocol (2016). *BMC Geriatr*; 16(1):17.

4. **Gregory MA**, Gill DP, Zou G, Liu-Ambrose T, Shigematsu R, Fitzgerald C, Hachinski V, Shoemaker K, Petrella RJ. Group-based exercise combined with dual-task training improves gait but not vascular health in active older adults without dementia (2016). *Arch Gerontol Geriatr*; 63:18-27.

5. Gill DP, **Gregory MA**, Zou GY, Liu-Ambrose T, Shigematsu R, Hachinski V, Fitzgerald C, Petrella RJ. The Healthy Mind, Healthy Mobility (HM2) Trial: A Proof-of-Concept Randomized Controlled Trial of a Novel Exercise Program to Improve Cognition in Older Adults (2015). *Med Sci Sports Exerc*; 48(2):297-306.

6. **Gregory MA**, Gill DP, Petrella RJ. Brain health and exercise for older adults (2013). *Current Reviews in Sports Medicine*, 2013 12(4):256-271.

Submitted Refereed Papers (5 total: 1 under review; 4 in progress)

1. **Gregory MA**, Felfeli T, Holmes J, Johnson A, and Petrella RJ. The impact of cognitive impairment on psychosocial functioning in community-dwelling older adults: a scoping review. In preparation for submission to: *Journal of Alz Dis.*

2. **Gregory MA**, Gill DP, Petrella RJ. Vascular risk, mobility, and brain health in aging: a targeted review. In preparation for submission to: *Med Sci Sports Exerc.*

3. **Gregory MA**, Gill DP, Liu-Ambrose T, Shigematsu R, Hachinski V, Shoemaker K, Holmes J, Petrella RJ. Cardiovascular risk contributes to the prediction of executive function but not global cognition in community-dwelling older adults at risk for future cognitive decline. In preparation for submission to: *J Alz Dis*.

4. **Gregory MA**, Gill DP, Liu-Ambrose T, Shoemaker K, Holmes J, Hachinski V, Petrella RJ. The effect of combined dual-task gait training and aerobic exercise on cognition, mobility, and vascular health in community-dwelling older adults at risk for future cognitive decline. In preparation for submission to: *Arch Phys Med Rehabil.*

5. **Gregory MA,** Gill DP, McGowan CL, Petrella RJ. Diurnal blood pressure dipping status as a novel risk factor for cognitive and mobility impairments in older adults without dementia. In preparation for submission to: *Journ Hypertens.*

Refereed Oral Presentations (6 Total; Presenting author is underlined)

1. **Gregory MA**, Gill DP, McGowan CL, Petrella RJ. Diurnal blood pressure dipping status as a novel risk factor for cognitive and mobility impairments in community-dwelling older adults without dementia. Abstract submitted to: European Council for Cardiovascular Research Annual Meeting (Lake Garda, ITY, October 14-16, 2016). To be published in: *High Blood Pressure & Cardiovascular Prevention.*

2. Silva NCBS, Gill DP, **Gregory MA**, De Cruz A, Petrella RJ. The effects of a multi-modality exercise program combined with mind-motor task training for older adults at risk of cognitive impairment on usual gait and balance: a randomized trial. Bodies of Knowledge Graduate Conference 2016, University of Toronto (Toronto, ON, CAN. May 5-6, 2016). *Note: also delivered as a poster presentation at London Health Research Day 2016, Schulich School of Medicine and Dentistry and Lawson Health Research Institute (London, ON, CAN).*

3. Shellington EM, **Gregory MA**, Gill D, and Petrella RJ. Dual-task gait training and aerobic exercise improves information processing, memory, and gait in older adults with cognitive impairment. Canadian Society for Exercise Physiology (CSEP) Annual Meeting (Hamilton, ON, Oct 2015). Published in: *Appl Phys, Nutr, & Metab* 2015, 40(S1):S57.

4. **Gregory MA**, Gill DP, Petrella RJ. Investigating the effects of dual-task gait training and aerobic exercise on cognition and vascular health in older adults with cognitive impairment, no dementia (CIND). Canadian Society for Exercise Physiology (CSEP) Annual General Meeting (St. John's, Newfoundland; October 22-25, 2014). Published in *Appl Phys, Nutr, & Metab* 2014, 39(S1):S20.

5. Gill DP, **Gregory MA**, Liu-Ambrose T, Hachinski V, Zou GY, Fitzgerald C, Shigematsu R, De Cruz A, Petrella RJ. A randomized controlled trial to examine combined multiple-modality and mind-motor exercise on cognitive functioning in community-dwelling older adults: A Pilot Study. Submitted to: Alzheimer's Association International Conference (Copenhagen, Denmark; July 12-17, 2014). Published in: Alz & Dem 2014, 10;(4 Suppl):P210.

6. Gill DP, **Gregory MA**, Koblinsky N, Morton H, De Cruz A, Gonzalez L, Fitzgerald C, Shigematsu R, Petrella RJ. Effects of an Aerobic Exercise and Dual-Tasking Intervention on Cognition and Balance In Older Adults. 2014 American College of Sports Medicine Annual Meeting (Orlando, FL. May 27-31, 2014). Published in: Med Sci Sports Exercise 2014, 46;(5 Suppl).

Refereed Poster Presentations (14 Total; Presenting author is underlined)

1. Silva NCBS, Gill DP, De Cruz A**, Gregory MA**, Petrella RJ. Multi-Modality Exercise Training May Decrease Risk for Dementia and Improve Mobility in Older Adults with Subjective Cognitive Complaints. Abstract submitted to: Canadian Association on Gerontology 45th Annual Meeting (Montreal, QC, CAN, Oct 20-22, 2016).

2. **Gregory MA**, Gill DP, McGowan CL, Petrella RJ. Cardiovascular risk contributes to the prediction of executive function, but not global cognition in older adults at risk for future cognitive decline. Abstract submitted to: Alzheimer's Association International Conference (Toronto, ON, CAN, July 24-28, 2016). To be published in: *Alz & Dem* 2016.

3. **Gregory MA**, Gill DP, De Cruz A, Petrella RJ. Dual-task gait training and aerobic exercise improves cognition in older adults with early indications of cognitive impairment. Abstract submitted to: Alzheimer's Association International Conference (Toronto, ON, CAN, July 24-28, 2016). To be published in: *Alz & Dem* 2016.

4. Silva NCBS, Gill DP, **Gregory MA**, De Cruz A, Petrella RJ. The efficacy of a multi-modality exercise program combined with mind-motor task training for older adults at risk of cognitive impairment on gait parameters: a randomized controlled trial. Abstract submitted to: Alzheimer's Association International Conference (Toronto, ON, CAN, July 24-28, 2016). To be published in: *Alz & Dem* 2016.

5. Heath M, **Gregory MA**, Gillen C, Gill DP, Petrella RJ. A six-month exercise-training program improves cognitive-motor control in persons with an identified cognitive complaint: Evidence from the antisaccade task. Abstract presented at: Society for Neuroscience Annual Meeting. Chicago, IL. October 17-21, 2015.

6. **Gregory MA**, Gill DP, De Cruz A, Shigematsu R, Petrella RJ. A multiple-modality exercise program plus dual-task training improved mobility but did not impact vascular health in active older adults without dementia. Alzheimer' Association International Conference

(Washington, DC, USA, July 18-23, 2015). Published in: *Alz & Dem* 2015, 1(7, Suppl):P742. *Note: also presented at the Western University Annual Bone and Joint Research Retreat (May. 6th, 2015)*

7. **Gregory MA**, Gill DP, Morton H, De Cruz A, Gonzalez L, Petrella RJ. The effects of mind-motor and aerobic exercise on cognition and mobility in older adults with cognitive impairment but not dementia. Alzheimer's Association International Conference (Copenhagen, DN, July 12-17, 2014). Published in: *Alz & Dem* 2014, 10;(4 Suppl):P448-449.

8. **Gregory MA**, Koblinsky N, Morton H, Gonzalez L, DeCruz A, Fitzgerald C, Shigematsu R, Liu-Ambrose T, Gill DP, Petrella RJ. HM2: Healthy Mind, Healthy Mobility - Dual-task Aerobic Gait-Training for Older Adults with Cognitive Impairment but Not Dementia (CIND). American College of Sports Medicine's (ACSM) 61st Annual Meeting, 5th World Congress on Exercise is Medicine®, Orlando, FL, May 25-30, 2014. Published in: *Med Sci Sports Exercise* 2014, 46;(5 Suppl).

9. **Gregory MA**, Koblinsky N, Morton H, Gonzalez L, Gill DP, Petrella RJ. HM2: Healthy Mind, Healthy Mobility: Dual-task aerobic exercise for older adults with cognitive impairment. Canadian Association of Gerontology 23rd Annual Meeting, Halifax, NS, Oct-17-19th, 2013.

10. Deosaran A, **Gregory MA**, Gill DP, Koblinsky N, Morton H, De Cruz A, Gonzalez L, Fitzgerald C, Shigematsu R, Petrella RJ. Effects of combined aerobic exercise and dual-task training on vascular health in older adults. American College of Sports Medicine's (ACSM) 61st Annual Meeting, 5th World Congress on Exercise is Medicine®, Orlando, FL, May 25-30, 2014. Published in *Med Sci Sports Exerc* 2014, 46;(5 Suppl). *Note: also presented at the 2014 FHS-ARGC Symposium at Western University (Feb. 7th, 2014)*

11. De Cruz ARL, **Gregory MA**, Gonzalez L, Gill DP, Petrella RJ. The effects of a combined program of mind-motor and aerobic exercise on gait performance in older adults with cognitive impairment, but not dementia (CIND). Baycrest/Rotman Research Institute 24th Annual Conference. Toronto, ON, Mar 11th, 2014. *Note: this presentation won the annual poster award competition, and was also presented at the 2014 FHS-ARGC Symposium at Western University (Feb. 7th, 2014).*

12. Gill DP, Koblinsky N, **Gregory M**, Morton H, Fitzgerald C, Petrella RA. Preliminary findings from a 6-month randomized controlled trial of combined dual-task gait training and aerobic exercise in older adults with cognitive impairment but no dementia. Alzheimer's Association International Conference 2013. Boston, MA, USA. July 13-18, 2013. Published in: *Alz & Dem* 2013;9(4, Suppl): P480. *Note: also presented at Dementia Care @ AAIC 2013: Translating Research to Practice – with the Alzheimer's Association Massachusetts/New Hampshire Chapter. Boston, MA, USA. July 17, 2013. [Invited Poster Presentation]*

13. **Gregory MA**, Koblinsky N, Morton H, Gonzalez L, Gill DP, Petrella RJ. Dual-task aerobic exercise for older adults with cognitive impairment. Baycrest 23rd Annual Rotman Research Institute Conference, Toronto, ON, March 4-6th, 2013.

14. **Gregory M**, Kovecavic M, Millar PJ, McGowan CL. Isometric leg training delays time to claudication in patients with type II diabetes and peripheral arterial disease: a pilot study. Canadian Society for Exercise Physiology Annual Meeting, Quebec City, QC, October 2011. Published in: *Appl Phys, Nutr & Metabol* 2011;36(S2): S323.

Other Presentations (5 Total; Presenting author is underlined)

1. Bocti JP, **Gregory MA**, Gill DP, De Cruz A, Gonzalez L, Koblinsky N, Petrella RJ. Effects of combined aerobic exercise and dual-task training on gait variability in community-dwelling older adults. 2014 FHS-ARGC Symposium at Western University. Feb. 7th, 2014.

2. **Gregory MA**, Koblinsky N, Morton H, Gonzalez L, Gill DP, Petrella RJ. Healthy Minds, Healthy Mobility: Dual-task aerobic exercise for older adults with cognitive impairment. 2013 FHS-ARGC Symposium at Western University. Feb. 1st, 2013. *Note: this was also presented at the Faculty of Health Sciences Graduate Research Forum, Western University, Feb 6th, 2013.*

3. **Gregory M**, Kovecavic M, Millar PJ, McGowan CL. Isometric leg training increases claudication distance without improvements in local blood flow in a diabetic patient with peripheral arterial disease: a case study. Department of Kinesiology Research Day, University of Windsor, ON, 2012.

4. Hanik S, **Gregory MA**, Seifarth J, Clarke D, MacDonald M, Millar P, Petrella R, Zinszer K, Milne K, McGowan CL. Effects of isometric handgrip training on ambulatory blood pressure and muscle sympathetic nerve activity in post-menopausal women: a proposal. Department of Kinesiology Research Day, University of Windsor, ON, 2012.

5. **Gregory MA**, Seifarth J, Clarke D, MacDonald M, McCartney N, Millar P, Zinszer K, Milne K, McGowan CL. The Effect of Isometric Handgrip Training on Ambulatory Blood Pressure and Neurovascular Function in Post-Menopausal Women: A Thesis Proposal. Department of Kinesiology Research Day, University of Windsor, ON, 2011.