# SEX AND GENDER DIFFERENCES IN PSYCHOSOCIAL AND PHYSIOLOGICAL DETERMINANTS OF HEALTH IN INDIVIDUALS WITH AND WITHOUT STROKE

**SEX AND GENDER DIFFERENCES IN PSYCHOSOCIAL FACTORS FOR EXERCISE AND RISK FACTORS FOR CARDIOVASCULAR DISEASE AND COGNITIVE IMPAIRMENT IN INDIVIDUALS WITH AND WITHOUT STROKE**

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## LAY ABSTRACT

The roles that an individual undertakes, and how they see themselves and are seen by others may be related to exercise participation. In addition, a person's biological makeup may impact their health and ability to think. In the first study of this thesis, we found that individuals with stroke seeing themselves as women had lower beliefs about their abilities to exercise, but their beliefs about the benefits of exercise or their motivation for exercise were similar to individuals who identify as men. There were no differences in beliefs about exercise abilities, outcomes, or motivation between individuals with stroke who took on masculine vs. feminine roles. In the second study, we found that walking distance, but not arterial health, was related to the ability to think in males and females. Overall, this work provides information of the importance of biological, social roles and behaviours on health.

# ABSTRACT

Sex and gender considerations are influential on psychosocial and physiological determinants of cardiovascular health in individuals with and without stroke. The first study of this thesis explored gender-based differences in exercise self-efficacy, outcome expectations for exercise and motivation for exercise post-stroke. Gender identity was assessed using the Bem Sex-Role Inventory-12 and a gender role index was created using established gender-related roles. The Self-Efficacy for Physical Activity Scale was used to assess self-efficacy for exercise, the Short Outcome Expectations for Exercise Scale assessed outcome expectations for exercise and a Relative Autonomy Index was calculated to assess motivation for exercise. We found that masculine gender identity was associated with highest ratings of exercise self-efficacy, whereas feminine gender identity was related to the lowest exercise self-efficacy [$F(3, 9)=5.36$, $p<0.05$]. Gender identity was not associated with outcome expectations [$F(3,8)=0.86$, $p=0.50$) nor motivation for exercise [$F(3,4)=0.67$, $p=0.61$)]. Additionally, there were no associations between gender roles and self-efficacy ($n=13$, $r=0.10$, $p=0.73$), outcome expectations ($n=13$, $r=-0.13$, $p=0.68$), or motivation for exercise ($n=8$, $r=0.09$, $p=0.83$).

The second study of this thesis examined the associations between global cognitive function (Montreal Cognitive Assessment, MoCA), arterial stiffness (carotid-femoral pulse wave velocity) and sex, and between global cognitive function, walking capacity (6-Minute Walk Test, 6MWT) and sex in older male and female adults with and without stroke. There was no association between global cognition and arterial stiffness, and sex did not moderate this association. However, cognitive function was positively associated with 6MWT, and with the addition of sex, Sex*6MWT, age and history of stroke, explained 21% of the variance of the MoCA score.

Our findings provide insight into the importance of sex-and gender-based considerations in clinical research and may inform future larger-scaled studies aiming to increase the generalizability of their findings to males and females and individuals of all gender identities.

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| | |
|---|---|
| BMI | Body Mass Index |
| BREQ-3 | Behavioral Regulations in Exercise Questionnaire-3 |
| BSRI-12 | Bem Sex-Role Inventory-12 |
| cfPWV | Carotid-Femoral Pulse Wave Velocity |
| IQR | Interquartile Range |
| MoCA | Montreal Cognitive Assessment |
| NO | Nitric Oxide |
| PWV | Pulse Wave Velocity |
| RAI | Relative Autonomy Index |
| SCT | Social Cognitive Theory |
| SBP | Systolic Blood Pressure |
| SEPA | Self-Efficacy for Physical Activity Scale |
| SOEE | Short Outcome Expectations for Exercise Scale |
| SD | Standard Deviation |
| 6MWT | 6-Minute Walk Test |

## DECLARATION OF ACHIEVEMENT

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# Chapter 1

# BACKGROUND

## 1.0 Introduction

Individuals with masculine gender roles and identities possess higher self-efficacy for exercise (Barrett et al., 2007; Chen et al., 2015; Chiu & Wray, 2011; Delahanty et al., 2006; Edwards & Sackett, 2016; Kim et al., 2008; Lee, 2005; McAuley et al., 1991; Nehl et al., 2012; Pauline, 2013; Rosenkranz et al., 2011; Scharff et al., 1999; Spence et al., 2010; Umstattd & Hallam, 2007; Wittig et al., 1987), outcome expectations for exercise (Craft et al., 2014; Daig et al., 2009; González-Cutre et al., 2011; Mao et al., 2020; Segar et al., 2002; Umstattd & Hallam, 2007), and motivation for exercise (Butt et al., 2011; Craft et al., 2014; Ednie & Stibor, 2017; Egli et al., 2011; Gao & Xiang, 2008; Gillison et al., 2006; González-Cutre et al., 2011; Sang Hyuk, 2012; Segar et al., 2002; Zervou et al., 2017) compared to individuals with feminine gender roles and identities. Individuals with stroke have low exercise self-efficacy (Nicholson et al., 2014; Shaughnessy et al., 2006; Simpson et al., 2011), outcome expectations for exercise (Barker & Brauer, 2005; Carin-Levy et al., 2009; Maher et al., 1999), and motivation for exercise (Nicholson et al., 2013; Simpson et al., 2011). Taken together, these psychosocial changes associated with stroke contribute to low exercise participation (Nicholson et al., 2013; Shaughnessy et al., 2006; Simpson et al., 2011).Whether there are gender-based differences in exercise self-efficacy, outcome expectations for exercise, and motivation for exercise in stroke has not been previously studied.

Additionally, sex differences in the associations between cognitive function, arterial stiffness and walking capacity may exist in older adults. Previous research has shown that older females tend to outperform older males in all domains cognition and measures of global cognition, with the exception of visuospatial abilities (Caskie et al., 1999; de Frias et al., 2006; McCarrey et al., 2016). In addition, older males experience greater rates of decline in markers of cardiovascular health, such as peak oxygen consumption (Buskirk & Hodgson, 1987; Fleg et al., 2005; Hossack & Bruce, 1982; Stathokostas et al., 2004; Toth et al., 1994; Weiss et al., 2006) in comparison to older females. Given that cardiac function is associated with cognitive decline (Oh et al., 2012), males may be more susceptible to subsequent cognitive decline and be at increased risk of earlier onset of cognitive impairment. Furthermore, negative associations between cognitive function and arterial stiffness have been established in males, but not in females (Kearney-Schwartz et al., 2009; Sabra et al., 2020; Singer et al., 2014; Waldstein et al., 2008). Individuals with stroke experience cognitive impairment (Renjen et al., 2015), elevated arterial stiffness (Tang et al., 2014; Tuttolomondo et al., 2010) and reduced walking capacity (Kelly et al., 2003) in comparison to the general population but the examination of sex differences in these associations have not been previously studied.

This thesis focused on examining sex-and gender-based differences in psychosocial and physiological outcomes of exercise and cardiovascular health in individuals with and without stroke. The overall objectives of this thesis were twofold. Firstly, we aimed to explore gender-based differences in psychosocial variables, namely exercise self-efficacy, outcome expectations for exercise and motivation for exercise post-stroke. Secondly, this thesis aimed to examine sex differences in the associations between global cognitive function and arterial stiffness and walking capacity in individuals with and without stroke.

## 1.1 Stroke

### 1.1.1 Characteristics of Stroke

With over 80 million individuals living with stroke globally, stroke is the second leading cause of death and leading cause of disability worldwide (Campbell et al., 2019). The burden of stroke is projected to continue to increase as the global population ages, with incidence expected to double by 2050 (Gorelick, 2019).

Stroke is defined as a neurological deficit attributed to an acute focal injury of the central nervous system by a vascular cause, which includes cerebral infarction, intracerebral hemorrhage and subarachnoid hemorrhage (Sacco et al., 2013). Ischemic stroke is responsible for the majority of stroke occurrences and occurs as a result of an interruption of cerebral blood supply (ie. arterial occlusion) (Campbell et al., 2019; Seitz & Donnan, 2015). A quarter of ischemic strokes are of lacunar type (Sudlow & Warlow, 1997), resulting from the occlusion of a single small perforating artery supplying the subcortical areas of the brain. Lacunar infarcts occur in the deep cerebral white matter, basal ganglia or pons (Bamford & Warlow, 1988). In contrast, hemorrhagic stroke is the most severe subtype of stroke, often resulting in severe disability or mortality (An et al., 2017), and is caused by a rupture of small penetrating cerebral arteries (Qureshi et al., 2009).

Many individuals with stroke live with a range of neurological sequelae, including physical (Aqueveque et al., 2017), cognitive (Al-Qazzaz et al., 2014) and communication impairment (González-Fernández et al., 2015). Furthermore, individuals with stroke are at increased risk for recurrent stroke and admission to an institution, where the risk of recurrent stroke is more than doubled within one year of stroke (Edwards et al., 2017). This population is often deconditioned and live a sedentary lifestyle, which in turn limits their abilities to perform activities of daily living, increases the risk of falls, and contributes to a greater risk for recurrent stroke and the progression of cardiovascular diseases (Billinger et al., 2014). Fortunately, physical inactivity and sedentary behaviours are modifiable behaviours, and engagement in regular exercise can lower risk for recurrent stroke and cardiovascular disease (Howard & McDonnell, 2015).

### 1.1.2 Benefits of Exercise Post-Stroke

The benefits of exercise following stroke are well-established in the literature. A recent synthesis of 75 studies (n=3617 participants) highlighted that exercise following stroke improved walking speed, balance and global indices of disability (Saunders et al., 2020). Specifically, aerobic exercise was effective in improving cardiovascular fitness, walking speed and capacity and balance parameters, mixed training (i.e. a combination of aerobic and strength training) improved walking function and balance, and strength training alone improved balance (Saunders et al., 2020). Of note, aerobic exercise training is the most common exercise modality following stroke with resistance-based training being less commonly studied (Tiozzo et al., 2015).

Meta-analyses have also shown that exercise and physical activity interventions are effective in reducing cholesterol and blood pressure (D'Isabella et al., 2017; Wang et al., 2019), improving cognitive function (Oberlin et al., 2017), improving upper and lower limb function, muscular force and motor function, and promoting greater quality of life and independence (Veldema & Jansen, 2020) in individuals with stroke. A combination of aerobic and strength training have demonstrated to produce the greatest gains in cognitive function following stroke (Oberlin et al., 2017), whereas strength training has been attributed to promote the greatest improvements in upper and lower limb function, muscular force and motor function, quality of life and independence in individuals with stroke (Veldema & Jansen, 2020). Exercise may also elicit psychological benefits after stroke, which include improved mood state and reductions in stress and anxiety (Simpson et al., 2011).

Despite the known benefits of exercise in individuals with stroke, psychosocial challenges have been shown to limit exercise participation and are often cited as the strongest barriers to the initiation of exercise (Pacheco et al., 2019; Rimmer et al., 2008; Simpson et al., 2011). Individuals with stroke often experience reduced energy levels, increased fatigue, reduced emotional tolerance, and often possess a negative outlook on what the future may hold (Perna & Le, 2018). In particular, women with stroke report increased stress and decreased quality of life, conflicted with prioritizing their own health and recovery with a self-perceived obligation to resume their roles and responsibilities (Heart and Stroke Foundation of Canada, 2018). Women are also twice as likely to be discharged to a long-term facility following a stroke, as a result of not having a caregiver at home and thus contributing to a loss of independence, diminished quality of life (Kapral et al., 2005) and reduced participation in stroke recovery programs (Heart and Stroke Foundation of Canada, 2018).

## 1.2 Sex and Gender

The integration of sex and gender considerations into clinical research has been of growing priority in the last two decades (Mazure & Jones, 2015), however, remains underresearched and misunderstood (Tannenbaum et al., 2016).

### 1.2.1 Definitions of Sex and Gender

It is important to define and distinguish between the terms *sex* and *gender* as these terms, while interrelated, are not interchangeable (Heidari et al., 2016).

*Sex* refers to a biological construct, whereby an individual is characterized as being a male or female according to genetics, anatomy, and physiology (Tannenbaum et al., 2016), which influence biological processes such as ageing and prevalence, diagnosis, severity, and outcomes of disease (Melloni et al., 2010). Sex-based differences are the primary drivers for longevity and health in many species due to the ever-changing biological processes occurring throughout the lifespan (Fischer & Riddle, 2018). For example, aging males experience mutations in DNA sequencing earlier in the lifespan and thus this among various biological factors lead to shorter lifespans in males compared to females (Fischer & Riddle, 2018).

*Gender* refers to the social, environmental, cultural, and behavioural factors and choices that impact a person, whereby an individual is characterized as being a man, woman, girl, boy, or gender diverse (Johnson et al., 2007). Gender is fluid, multifaceted, complex, and encompasses four different constructs: gender roles, gender identity, gender relations and institutionalized gender (Tannenbaum et al., 2016). Gender roles are often to subject to stereotypes, as they represent the behavioural norms applied to men and women in society, which influence an individual's everyday actions, expectations, and experiences (Tannenbaum et al., 2016). Gender identity refers to how an individual sees themselves and is seen by others (Tannenbaum et al., 2016). Of importance, an individual's gender identity may differ from their biological sex. In clinical research, best practices involve asking the individual their sex assigned at birth (male and female) and how they currently self-identify (man, woman, other, prefer not to answer) (Tannenbaum et al., 2016). Gender relations refers to how an individual interacts with others and how they are treated by people in society, based on the individual's gender (Tannenbaum et al., 2016). Finally, institutionalized gender refers to the distribution of power between men and women with regards to political, educational, and social institutions (Tannenbaum et al., 2016).

When incorporating sex and gender considerations into research, it is important to acknowledge that sex is a dichotomous variable (Clayton, 2018), whereas gender is a fluid and continuous variable that can be defined by a range of characteristics such as education, socioeconomic status, and occupation (Clayton, 2018; Mbuagbaw et al., 2017).

### 1.2.2 Incorporation of Sex and Gender into Health Research

Despite attention to health equity that is aimed at creating equal opportunities for men and women to partake in clinical research, women have been consistently underrepresented in all phases of the research process (Norris et al., 2020; Yakerson, 2019). Many researchers have intentionally excluded women, which is often rationalized as an attempt to minimize the effect of sex-based biological differences that would introduce variation into their data and thus complicating results and adding complexity to the analysis process (Giacomini & Baylis, 2003). Despite evidence of biological sex-based differences, historical studies have focused on male subjects, whereby researchers were guided by the belief that study results would also be transferable to females (Hayden, 2010). Underrepresentation of females is particularly evident with post-menopausal and pregnant women, attributed to additional hormonal considerations and the perceived legal liability issues that come along with these groups (e.g. fear of harming the embryo or fetus) (Yakerson, 2019). Gender-based factors, such as difficulties in recruitment and retention of women in research studies are also often used as rationale for underrepresentation or exclusion (Yakerson, 2019).

Positively, the representation of women in clinical trials has improved in recent years, as a result of the initiatives taken by a major Canadian funding agency aiming to address the inadequate incorporation of sex-and gender-based considerations into research (Johnson et al., 2014). In 2010, the Canadian Institutes of Health Research required all applicants to indicate whether, why, and how research designs accounted for sex and gender (Johnson et al., 2014). As a result of this initiative, the proportion of CIHR-funded research projects incorporating sex and gender considerations rose from 26% to 48% in a span of one year (Government of Canada, 2014). Additionally, the European Association of Sciences Editors established a sex and gender policy committee in 2012, which set to develop guidelines of reporting Sex and Gender Equity in Research (SAGER) (Heidari et al., 2016). The general principles of the SAGER guidelines state that authors should use the terms sex and gender carefully in order to avoid confusion between the two terms, research should be designed and conducted in manner that the results can be disaggregated by sex, and subjects should be differentiated by the social and cultural circumstances which encompass gender (Heidari et al., 2016).

In Canada, Sex-and Gender-Based Analysis has been labeled as the approach aiming to examine sex-based (biological) and gender-based (socio-cultural) differences, with a primary goal of promoting rigorous science that considers sex and gender and thus strengthening our understanding of health determinants for all members of society (Government of Canada, 2018). Moreover, incorporating sex and gender considerations allows researchers to better explain research findings (expands relevance and application of research findings), reduce the risk of harm (providing equal care for both sexes and all genders and not assuming that study results apply to everyone), enhance the opportunities to improve health outcomes (ensuring that research outcomes are relevant to both sexes and all genders), and improve the efficiency of research (being less likely to have inefficiencies in the research design, reporting, and knowledge translation) (Clayton, 2018). Thus, sex-and gender-based considerations increase study rigour and promote health equity (Clayton, 2018; Heidari et al., 2016). Sex and gender considerations may be particularly important in gaining a comprehensive understanding of psychosocial and physiological determinants of cardiovascular health in older adults without and without history of stroke.

### 1.3 Psychosocial Factors Influencing Exercise Behaviors

Psychosocial factors are known to influence exercise behaviours (Craft et al., 2014; Edwards & Sackett, 2016; Segar et al., 2002), and may be age-specific, or gender specific.

#### 1.3.1 Using the Social Cognitive Theory to Explain Behaviour

In 1986, Albert Bandura introduced the Social Cognitive Theory (SCT), which posits that human behaviour is determined by triadic reciprocal interactions between cognitive (i.e. personal factors), behavioural, and environmental factors (Bandura, 1989). Individual experiences, the actions of others, and other environmental factors determine whether or not the health behaviour is undertaken by the individual (Bandura, 1989). The SCT is made up of five distinct constructs, which include observational learning, reinforcements, behavioural capabilities, *self-efficacy* and *outcome expectations* (Bandura, 1989).

*Self-efficacy* is defined as internal and external factors that impact one's beliefs in their capabilities to organize and execute the courses of action required to manage prospective situations (Bandura, 1997). Self-efficacy is said to influence the activities that an individual chooses to pursue, the degree of effort they exert, and the level of persistence they demonstrate when faced with challenges and setbacks (Bandura, 1997). *Outcome expectations* involve beliefs that carrying out a specific behaviour will lead to a desired outcome (Bandura, 1997). Actions that produce positive outcomes are readily adopted, whereas those producing unfavourable outcomes are avoided (Bandura 1999). Self-efficacy and outcome expectations are interrelated, where individuals who possess strong beliefs about their abilities to succeed in a specific activity are more likely to find the activity to be worthwhile, whereas others may value the outcomes related to an activity, but do not possess strong beliefs in their abilities to execute the desired activity (Bandura 1999). The SCT has also been proposed to explain human *motivation* (Schunk

& DiBenedetto, 2020), where the presence of social support (external motivation) is the key environmental factor that shapes behaviour (Bandura, 1997).

### 1.3.2 Exercise Behaviours in Older Adults

With rising global rates of morbidity and mortality, physical inactivity has often been termed as a global pandemic (Kohl et al., 2012), where rates of exercise participation, particularly among older adults, remains low despite the known benefits of exercise (Thorp et al., 2011). Many factors have been thought to explain the high prevalence of physical inactivity in older adults, which often include, economic and environmental concerns (i.e. feeling unsafe), a lack of knowledge of the benefits of exercise, and lack of resources (Rimmer et al., 2004).

Low levels of exercise self-efficacy (McAuley et al., 2011), negative outcome expectations for exercise (Resnick, 2001) and low motivation for exercise (Yarmohammadi et al., 2019) have been proposed to be key barriers to the initiation and sustainment of exercise participation in older adults. Of note, psychological factors influencing exercise behaviour differ between younger and older adults (Lachman et al., 1997; Stephens et al., 1990; Trujillo et al., 2004). Older adults often face a greater fear of injury from engaging in exercise and thus demonstrate lower self-efficacy in comparison to younger adults (Stephens et al., 1990). Advancing age has also been associated with lower outcome expectations for exercise, which is primarily due to the perception that exercise will not improve health and may actually be harmful (Lachman et al., 1997). Finally, younger individuals are more likely to be motived to exercise for interpersonal reasons, such as maintaining or improving physical appearance, whereas older adults are more commonly motivated by the prevention of health-related concerns, which include exercising to avoid depression and possessing greater resistance to getting ill (Trujillo et al., 2004).

Factors of exercise self-efficacy, outcome expectations for exercise, and motivation for exercise, their influence on exercise participation in older adults and individuals with stroke, and potential gender-based differences in these factors will be discussed in the following sections.

### 1.3.3 Exercise Self-Efficacy

Exercise self-efficacy is the primary determinant of consistent exercise behaviour, whereby the belief that one can exercise given constraints and obstacles such as, feeling tired, being busy or alone, and exercising in undesirable weather is associated with a greater likelihood for exercise participation (Bandura, 1997; Marcus et al., 1992). It has been well-established that older adults possessing higher exercise self-efficacy were more likely to engage in exercise in comparison to those with low self-efficacy (Anderson et al., 2006; Castro et al., 1999; Chen et al., 2016; Cleland et al., 2010; Conn, 1998; Grembowski et al., 1993; Hwang & Chung, 2008; McAuley et al., 2011; Resnick & Jenkins, 2000; Rhodes et al., 1999; Schuster et al., 1995). Moreover, various studies have highlighted that high baseline exercise self-efficacy was predictive of sustained exercise behaviours at 2 (McAuley et al., 2003; Oman & King, 1998) and 5 years follow-up (McAuley et al., 2007) following initiation of exercise.

*Exercise Self-Efficacy Post-Stroke*

Exercise self-efficacy is reduced in individuals with stroke in comparison to older adults without stroke (Field et al., 2013; Prout et al., 2017). Qualitative studies have found that individuals living with stroke felt limited in their abilities to perform exercise as a result of stroke-related impairments (Damush et al., 2007; Nicholson et al., 2014; Reed et al., 2010; Simpson et al., 2011), and data of 312 individuals 21-91 years old with stroke found that lower levels of self-efficacy were associated with reduced physical activity, older age and increased fatigue, whereas receiving information regarding the benefits of exercise from a physician increased exercise self-efficacy (Shaughnessy et al., 2006).

A bidirectional relationship between exercise self-efficacy and levels of physical activity participation exists, where higher exercise self-efficacy is associated with increased physical activity participation (Bailey, 2019; Danks et al., 2016; Nosek et al., 2006) and maintenance of exercise behaviours (Caetano et al., 2020; Cardinal et al., 2004; Kinne et al., 1999; Patterson & Ross-Edwards, 2009), whereas low exercise self-efficacy is related to the avoidance of physical activity in individuals with stroke (Shaughnessy et al., 2006). Thus, interventions individualized to optimize adherence and aimed to enhance exercise self-efficacy may increase the likelihood of the initiation and adherence to an exercise program in individuals with stroke (Shaughnessy et al., 2006).

*Gender Roles Differences in Exercise Self-Efficacy*

There are known associations between gender roles and exercise self-efficacy. Older women engage in less physical activity, which may be a result of substantial household demands (Lee, 2005) and family characteristics (e.g. being a caregiver) (Scharff et al., 1999; Chen et al., 2015). This results in fewer opportunities for women to develop the necessary skills required to participate in physical activity (Chen et al., 2015; Verhoef et al., 1992). Women with diabetes commonly reported that the high volume of external demands, such as family obligations and the need to put others first, negatively influenced exercise self-efficacy and participation (Barrett et al., 2007). Of note, the individuals possessing masculine roles were characterized as being men (i.e. masculine identity), whereas the individuals possessing feminine gender roles were characterized as being women (i.e. feminine identity) in these previous studies (Barrett et al., 2007; Chen et al., 2015; Lee, 2005; Scharff et al., 1999).

*Gender Identity Differences in Exercise Self-Efficacy*

Previous studies in children and younger adults have shown that individuals identifying as boys and men possess higher self-efficacy and engage in increased physical activity compared to individuals identifying as girls and women (McAuley et al., 1991; Nehl et al., 2012; Pauline, 2013; Rosenkranz et al., 2011; Spence et al., 2010; Wittig et al., 1987). In a study of 270 undergraduate students, masculine identity was associated with the greatest exercise self-efficacy, whereas feminine identity was associated with the lowest exercise self-efficacy, as determined by the Bem Sex-Role Inventory (Wittig et al., 1987). This seminal research by Wittig et al. (1987) is particularly worth noting, as it is the only study to consider androgynous and undifferentiated gender identities, while also considering that one's identity may differ from their biological sex.

Gender-based differences in exercise self-efficacy have also been reported in older adults with and without health conditions. In a sample of 98 older adults (60-88 years old), high levels of self-efficacy and being a man were independently associated with regular exercise participation (Umstattd & Hallam, 2007). In 228 individuals identifying as women with history of gestational diabetes (age 34-38 years), participants reported low to moderate self-efficacy and suboptimal exercise performance (i.e. only performed light physical activity on a weekly bias) (Kim et al., 2008). In 1079 individuals enrolled in a diabetes prevention program (mean age 54 years), being a man and having higher exercise self-efficacy were independent correlates of sustained physical activity participation at 1 year and 3-year follow up (Delahanty et al., 2006). Finally, in a sample of 1619 older adults with type II diabetes (mean age 70 years), those self-identified as women reported lower self-efficacy and less favourable exercise behaviours compared to those self-identifying as men (Chiu & Wray, 2011). Taken together, the current body of evidence suggests that individuals identifying as men commonly possess higher self-efficacy for exercise and greater participation in physical activity compared to those identifying as women.

### 1.3.4 Outcome Expectations for Exercise

Positive outcome expectations for exercise (e.g. believing that exercise is enjoyable and will improve health) are predictive of positive exercise behaviours in older adults (Conn, 1998; Grembowski et al., 1993; Resnick & Spellbring, 2000; Resnick & Jenkins, 2000; Schneider, 1997; Schuster et al., 1995; Williams et al., 2005), whereas unpleasant sensations of exercise, the notion exercise may not improve or even worsen their current condition (Lachman et al., 1997; Resnick & Spellbring, 2000; Williams et al., 2005) or other personal barriers are known to contribute to negative outcome expectations (e.g. bad weather acting as barrier to exercise is based on the negative expectation of feeling cold or getting wet) (Williams et al., 2005).

Outcome expectations for exercise are more predictive of the initiation of an exercise behaviour more so than its sustainment as individuals may feel that, over time, the actual outcomes for exercise fell short of their initial expectations (Rothman, 2000), thus experiencing false hope violation (Polivy & Herman, 2002). Therefore, health care providers should strive to implement interventions aimed at strengthening the positive beliefs of exercise to ensure sustained exercise behaviours in older adults (Shaughnessy et al., 2006).

*Outcome Expectations for Exercise Post-Stroke*

Individuals with stroke often possess negative beliefs about the outcome of exercise and thus impacting physical activity participation (Barker & Brauer, 2005; Carin-Levy et al., 2009; Maher et al., 1999; Morris et al., 2012; Rimmer et al., 2008). A study of 83 individuals with stroke highlighted that 36% of participants did not believe that exercise would improve their current condition (Rimmer et al., 2008). Fear of pain or falling, failure, stroke recurrence and worries about unsatisfactory performance or being embarrassed were often regarded as negative outcomes of exercise and thus acting as barriers to exercise in individuals with stroke (Barker & Brauer, 2005; Carin-Levy et al., 2009; Jackson et al., 2018; Maher et al., 1999).

Positively, similar to older adults, when perceived outcomes of exercise outweighed the negative expectations, participants became increasingly active and maintained physical activity behaviours over a prolonged period of time (Bailey, 2019; Cardinal et al., 2004). Positive outcomes of exercise reported by individuals with stroke include improving health and fitness as well as the enjoyment factor of exercise (Barker & Brauer, 2005; Mansfield et al., 2016; Prout et al., 2017; Reed et al., 2010; Wiles et al., 2008).

*Gender Roles Differences in Outcome Expectations for Exercise*

There has been less focus to date examining gender role differences in outcome expectations for exercise in older adults, but there is preliminary evidence suggesting that individuals taking on feminine gender roles may also have lower outcome expectations for exercise. A recent study of 2147 adults found that men were more likely to report that enjoyment was an important outcome for exercise, which was hypothesized to be as a result of the more favourable masculine gender roles, such as higher education and less household responsibilities (Mao et al., 2020). In contrast, individuals taking on feminine gender roles were less likely to report satisfaction with their leisure activities (Daig et al., 2009) with gender roles typically undertaken by women hypothesized to interfere with leisure time and thus contributing to feeling less satisfied with their leisure activities in comparison to men (González-Cutre et al., 2011). Of note, the individuals in these studies possessing masculine roles were characterized as being men (i.e. masculine identity), whereas the individuals possessing feminine gender roles were characterized as being women (i.e. feminine identity), with no consideration of other potential identities.

*Gender Identity Differences in Outcome Expectations for Exercise*

The studies examining the influence of gender identity on outcome expectations for exercise have demonstrated that individuals identifying as men possess the most favourable outcome expectations for exercise and thus exhibit the most positive exercise behaviours. In a study of 98 older adults (60-88 years old), positive outcome expectations for exercise and being a man were independently associated with regular exercise participation (Umstattd & Hallam, 2007). In a sample of 180 younger adults between the ages of 18-25 years old, individuals identifying as men were more likely to report positive outcomes of exercise, including enjoyment and improved quality of life, whereas women reported exercising for outcome expectations related to weight loss (Craft et al., 2014). Such outcome expectations in women related to physical appearance are rooted in objectification (Segar et al., 2002), where girls and women are acculturated to internalize views of others as the primary view of their physical self, contributing to feelings of shame, obsessive compulsive exercise behaviours, and anxiety, which may in turn, diminish the enjoyment of exercise (Fredrickson & Roberts, 1997).

### 1.3.5 Motivation for Exercise

In the social cognitive model, intrinsic (self) and external influences independently impact motivational processes (Bandura 1986), whereby The Self-Determination Theory describes the manner in which these motivational processes influence behaviours (Ryan et al., 1997). Two distinct types of motivation have been described: *autonomous motivation* is regulated through internal processes and can be thought as a personal desire to engage in health behaviours, and *controlled motivation* is regulated through external factors that are contingent on rewards and punishments (Deci & Ryan, 2008). Higher autonomous motivation is more likely to contribute to the prolonged maintenance of a behaviour (Deci & Ryan, 2008).

The degree of autonomous or controlled motivation lays across a continuum of six types of regulatory styles, spanning non-regulation (i.e. *amotivation*, or lack of intention to act) to *intrinsic regulations* (i.e. autonomous motivation) (Ryan & Deci, 2000). Intervening regulatory styles of controlled regulations are *external regulations,* which involve behaviours that are undertaken to satisfy an external demand, *introjected regulations*, in which behaviours are solely undertaken to avoid feelings of guilt or anxiety, *identified regulation* which involves undertaking behaviours that are deemed as personally important, and *integrated regulations*, where behaviours are internalized as being congruent to one's needs and values (Ryan & Deci, 2000).

The influence of motivational processes on the execution of exercise behaviours are well-documented in older adults. In a recent systematic review involving 34 studies and 12,396 participants, a lack of motivation was deemed to be the primary intrapersonal factor acting as a barrier to the performance of physical activity, but interpersonal factors, such as a lack of companionship during exercise, were also reported as barriers (Yarmohammadi et al., 2019). The influence of external support, on the other hand, acted as a facilitator to exercise participation, where greater support systems resulted in higher motivation for exercise (Yarmohammadi et al., 2019). Moreover, in a study of 134 individuals (mean age 64 years) with heart disease and type 2 diabetes, low exercise self-efficacy was directly associated with low motivation for exercise (Alharbi et al., 2017).

*Motivation for Exercise Post-Stroke*

Both autonomous and controlled motivation play an important role in exercise participation in individuals with stroke, as increased introjected and intrinsic regulations are associated with exercise performance (Thilarajah et al., 2020) and external support from others is a key motivator for exercise (Jackson et al., 2018; Nicholson et al., 2013; Nicholson et al., 2014; Poltawski et al., 2015). However, a lack of both intrinsic and external motivational factors have been reported in this population. A systematic review of 6 studies (n=174 participants with stroke) highlighted that a lack of internal motivation was one of the strongest barriers to exercise participation, in addition to physical difficulties resulting from stroke, a shortage of external support, and lack of knowledge about what to do and how to access services (Nicholson et al., 2013).

*Gender Role Differences in Motivation for Exercise*

Gender role differences in motivational factors are influential on physical activity participation. In a study of younger and middle aged adults (n=449), it was hypothesized that the lower intrinsic motivation for women was attributed to the competing demands related to household duties, acting as a coordinator of the family, and fulfilling the roles of wife, mother and housekeeper (González-Cutre et al., 2011). Feminine gender roles may be drivers of low motivation for exercise, whereby individuals taking on feminine gender roles are often expected to prioritize the needs of others and thus making it increasingly difficult to focus on their own health (i.e. possess minimal time for exercise participation) (Segar et al., 2002).

*Gender Identity Differences in Motivation for Exercise*

Gender identity differences in internal and external motivational factors for exercise have been well documented in young adults, whereby studies have demonstrated that individuals identifying as men were more likely to report internal motivators of challenge, enjoyment, strength and endurance gains as motives for exercise (Edwards & Sackett, 2016; Egli et al., 2011), whereas individuals identifying as women were more motivated by extrinsic factors driven by external appearance, such as weight loss and media-biased body image pressures (Butt et al., 2011; Craft et al., 2014; Gao & Xiang, 2008; Gillessen et al., 1995; Zervou et al., 2017). Externally-driven motivational factors may act as barriers to exercise participation, as exercise behaviours motivated by appearance were negatively associated with physical activity participation in women (n=812, mean age 19 years) (Ednie & Stibor, 2017). Moreover, a previous synthesis of the literature highlighted that younger men tended to report greater levels of social support, serving as a facilitator for exercise participation (Edwards & Sackett, 2016). In the one study to date encompassing masculine, feminine, androgynous, and undifferentiated identities in 170 college students, masculine identity was associated with the greatest exercise participation and intrinsic motivation (Sang Hyuk, 2012). Gender differences in motivational factors for exercise have recently been examined in older adults. In a study involving 1845 adults aged 60-67 years old, individuals identifying as women were more likely than men to report appearance and weight loss as motives for exercise (van Uffelen et al., 2017).

Thus, the current body of evidence suggests that individuals identifying as women are driven by external factors as motivators for exercise yet receive less external support from others to participate in exercise, than do individuals identifying as men (Chiu & Wray 2011).

#### 1.3.6 Gender Identity Differences in Overall Exercise Behaviours

There are also known associations between gender identity and exercise behaviours, where sex-typed individuals (i.e., masculine males and feminine females) have been shown to choose activities that conform to their sex more than non sex-typed individuals (i.e., androgynous and undifferentiated males and females) (Bem, 1981). In a sample of 80 younger adults, sex-typed individuals tended to associate more masculine traits to individuals participating in stereotypically termed masculine physical activities such as weightlifting, and more feminine traits to those participating in stereotypically termed feminine physical activities such as aerobic dance (Matteo, 1988). Conversely, individuals possessing androgynous and undifferentiated traits may not be affected by the gender-specific perceptions associated with various types of physical activity (Matteo, 1988). In a sample of 120 older Spanish adults, individuals with androgynous gender traits were more adaptable to various forms of physical activities compared to those possessing either masculine or feminine gender identities (Vafaei et al., 2014). Similarly, in a study of 120 older Canadian adults, individuals possessing androgynous gender identities possessed the greatest overall wellness (i.e. ability to perform activities of daily living, having strong morale and religiosity, and access to social resources) (Gale-Ross et al., 2009). Future studies are warranted to determine whether the adaptability and greater wellness of individuals with non-sex typed genders contribute to higher self-efficacy, outcome expectations and motivation for exercise than sex typed genders in older adults.

Gendered factors may contribute to differences in exercise self-efficacy, outcome expectations for exercise, and motivation for exercise in individuals with stroke, but this has yet to explored in this population. We may be able to gain some insights on possible gender differences in these factors based on previous research in older adults.

## 1.4 Physiological and Functional Outcomes of Cardiovascular Health

Sex is a key determinant of cardiovascular health, whereby the remaining sections will focus on discussing sex differences in novel, traditional and functional measures of cardiovascular health and cognition.

### 1.4.1 Cognitive Function in Older Adults

Cognition describes the internal and external mental processes which underlie how people perceive, retain information, speak, think, make decisions, and solve problems (Roy, 2013). Cognition encompasses five different domains of *attention* (ability to concentrate and focus on a specific stimulus, *memory* (ability to store and retrieve cognitive information) (Harada et al., 2013), e*xecutive function* (reasoning and problem solving) (Harvey, 2019), *visuospatial abilities* (understanding space in two and three dimensions) (Harada et al., 2013), and *language* (Harvey, 2019).

Validated cognitive tools with well-established reference values from a broad range of age and educational groups are used to identify individuals with cognitive impairment (Morley et al., 2015). Many domain-specific cognitive outcomes measures are available to evaluate performance in domains of cognition, but global measures of cognition, such as the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) and Mini-Mental State Examination (MMSE) (Folstein et al., 1975), that assess all five domains of cognition (Antony et al., 2017) are also widely used as screening tools for mild cognitive impairment (Nasreddine et al., 2005; Xu et al., 2002).

#### 1.4.1.1 Cognition and Aging

Age-associated changes in cognitive function can vary along a continuum ranging from mild cognitive impairment (i.e symptomatic pre-dementia stage) to Alzheimer’s dementia (Langa & Levine, 2014). The global prevalence of mild cognitive impairment has been reported in over 40% of the population aged over 60 years old (Hu et al., 2017). Mild cognitive impairment has been shown to affect performance of activities of daily living in older adults, where bathing, shopping and medication responsibilities have been shown to be the most discriminating activities to distinguish between individuals with and without cognitive impairment (Lee et al., 2019). Hypertension, diabetes, obesity, and smoking are potential risk factors for cognitive impairment (Baumgart et al., 2015; Ganguli et al., 2013), and cardiovascular diseases, such as stroke, heart failure, coronary heart disease, and atrial fibrillation have also been noted as important risk factors for mild cognitive impairment (de Bruijn & Ikram, 2014). Cognitive impairment is reported in up to 72% of individuals with stroke (Renjen et al., 2015), which is associated with lower quality of life, accelerated functional decline and a higher risk of dependence and mortality (Levine et al., 2015).

Structural brain changes have been implicated in age-associated cognitive decline, including decreases in grey matter volume, particularly in the prefrontal cortex, as a result of decreases in neuronal sizing and synaptic number, and decreased neuritic spines (Terry & Katzman, 2001) or complete neuronal death through beta-amyloid accumulation (Uttara et al., 2009). Beta-amyloid has been found in the cortex of 20-30% of healthy adults, however, is significantly elevated in cognitively impaired individuals (Pike et al., 2007; Rodrigue et al., 2009). Reductions in white matter volume (occurs as the result of damage to the myelin sheaths or axons) of up to 20% has also been reported in individuals over 70 years (Meier-Ruge et al., 1992), which have been attributed to reductions in cognition in adults 60 years and older (Breteler, van Swieten, et al., 1994; Lindgren et al., 1994).

#### 1.4.1.2 Sex Differences in Cognition in Older Adults

Sex differences across multiple domains of cognition are well-established. Females outperform males in language, executive function, memory, attention and global cognition tasks from the third decade until the eighth decade of life, whereas males tend to outperform females in tasks related to visuospatial abilities (Caskie et al., 1999; de Frias et al., 2006; McCarrey et al., 2016).

These sex differences may be attributed to greater gyrification in females, identified through neuroimaging, indicating less age-related brain atrophy and thus less risk of cognitive impairment (Luders et al., 2004), whereas older males have reduced white and grey matter parenchymal volume (Cowell et al., 1994). Additionally, the preservation of grey matter in brain areas known to control verbal function in older females (Kurth et al., 2017) may support better performance in the language domain in older females compared to males. It may be possible that hormonal influences, namely estrogen, may partially contribute to the gradual and linear cognitive decline observed throughout the lifespan in males, in contrast to the abrupt and steep decline observed at the onset of menopause in females (Petersen et al., 2010). Estrogen protects against apoptosis and inflammatory processes such as, beta amyloid accumulation, oxidative stress, and ischemia, while also stimulating the synthesis of neurotransmitters, such as acetylcholine, serotonin, noradrenalin, and glutamate (Henderson, 2008). Estrogen levels begin to decline 1 to 2 years before the onset of menopause (Henderson, 2008), which is followed by subsequent cognitive decline, but there is some evidence to support that long-term estrogen use throughout adulthood may be associated with reduced risk of the development of Alzheimer's in post-menopausal females (Baldereschi et al., 1998; Henderson et al., 2005; Paganini-Hill & Henderson, 1996; Tang et al., 1996).

### 1.4.2 Arterial Stiffness

#### 1.4.2.1 Physiology of Arterial Stiffness

Arteries are made up of three layers: the adventitia (outer layer composed of collagen fibrils interlaced with elastin that provide structural support and shape to the vessel), the tunica media (middle layer composed of smooth muscle cells, collagen, and elastic tissue which regulates the internal diameter of the vessel), and the tunic intima (inner layer consisting of endothelial cells which facilitates the movement of blood) (Kohn et al., 2015; Tucker & Mahajan, 2020).

Nitric oxide (NO) is the primary endothelium-derived relaxing factor and plays a critical role in the maintenance of vascular tone and reactivity (Zieman et al., 2005). Endothelial dysfunction, occurs when the enzyme NO synthase and other critical cofactors become uncoupled (Zieman et al., 2005), resulting in the production of potent oxidants (e.g. advanced glycation products), leading to oxidative stress and decreased net NO bioavailability (Anderson, 1999; Rojas et al., 2000; Zieman et al., 2005). Advanced glycation products increase inflammatory responses, resulting in the elevation of smooth muscle tone and atherosclerotic plaque formation (Zieman et al., 2005). Arterial stability and compliance are maintained through a balance of collagen and elastin at all three layers of the vessel, but inflammatory responses result in arterial stiffening through an overproduction of collagen and reduced quantities of elastin (Gillessen et al., 1995). Moreover, extrinsic factors such as sodium intake, hormonal and glucose levels are also known to induce structural changes that contribute to arterial stiffness (Zieman et al., 2005).

Arterial stiffness is accompanied by increases in pulse pressure (difference between systolic and diastolic blood pressure) and left ventricular load (Kohn et al., 2015). Augmented pulse pressure occurs when the outgoing (forward) arterial pressure waveform from the aorta is reflected more rapidly back to the aortic root during systolic ejection as a result of vascular stiffening, contributing to increased systolic pressure (Steppan et al., 2011). The augmented pulse pressure is a direct result of increased end-systolic stiffness, increased left ventricular workload, and reduced diastolic compliance, thus leading to increased left ventricular hypertrophy and increased oxygen consumption (Kass, 2002). The risk of subendocardial ischemia is elevated as a result of the oxygen consumption imbalance in the myocardia (Kohn et al., 2015).

With aging, central arteries (e.g aortic tree) are most susceptible to stiffening (Benetos et al., 2002). Arterial stiffness is an important marker for elevated cardiovascular risk factors including stroke (Lee et al., 2014) hypertension (Vaccarino et al., 2001), myocardial infarction (Mitchell et al., 1997), and heart failure (Chae et al., 1999; Kostis et al., 2001). Moreover, other risks factors such as hyperlipidemia, type II diabetes, smoking, and elevated body mass may be implicated in the process of accelerated arterial stiffening (Cecelja & Chowienczyk, 2012).

#### 1.4.2.2 Measurement of Arterial Stiffness

Arterial stiffness can be measured non-invasively using applanation tonometry, which involves measuring pulse waveforms at two separate points along the arterial tree to determine the speed of pulse waves, or pulse wave velocity (PWV) (Steppan et al., 2011). Measurement of PWV between the carotid and femoral arteries (i.e. carotid-femoral PWV, cfPWV) to represent central or aortic stiffness (elastic arteries) is the current criterion standard for the assessment of arterial stiffness (Millasseau et al., 2005). cfPWV measurements are highly correlated with arterial stiffness (Laurent et al., 1994), where higher PWV values are indicative of poor vascular health and may predict cardiovascular events in older adults (Sutton-Tyrrell et al., 2005). Other measures of PWV include heart-femoral PWV to assess central arterial stiffness (Phan et al., 2017), carotid-radial PWV (Ye et al., 2016) or femoral-dorsalis pedis PWV (Hickson et al., 2016) for peripheral stiffness (i.e. muscular arteries), and brachial-ankle PWV for an overall composite measurement of whole body stiffness (Tomiyama Hirofumi et al., 2019).

PWV is calculated as d (meters)/Δt (seconds), whereby d is the distance between the two points along the arterial tree and Δt is the transit time taken from the foot of the carotid waveform to the foot of the femoral waveform, and expressed in m/s (Millasseau et al., 2005). The true distance traveled between the two arterial sites is defined as the distance from the ascending aorta to the right common femoral artery, minus the distance from the ascending aorta to the right common carotid artery (Van Bortel et al., 2012). The most accurate estimate of this anatomical distance is determined by calculating 80% of the direct anthropometric carotid-femoral (i.e. common carotid artery-common femoral artery x 0.8) (Van Bortel et al., 2012).

#### 1.4.2.3 Sex Differences in Arterial Stiffness

The incidence of cardiovascular disease increases disproportionally in post-menopausal females, which may be partially explained by observed sex differences in arterial stiffness (Coutinho, 2014). Elevated arterial stiffness observed in post-menopausal females may be a result of higher systolic blood pressure and accelerated large artery stiffening (Berry et al., 2004; Franklin et al., 1997; Martins et al., 2001; Staessen et al., 1997). Shorter aortic lengths in females can also result in faster pulse waves (i.e. the reflected wave returns back to the aorta faster), leading to increased end-systolic stiffness, increased left ventricular workload, and reduced diastolic compliance (Coutinho et al., 2013; Goto et al., 2013; Kass, 2002; Shim et al., 2011).

Changes in sex hormones are also known to impact vascular ageing in older males and females (Coutinho, 2014). Positively, particularly for pre-menopausal females, estrogen has the ability to offset the excessive production of collagen that contributes to arterial stiffening through the increased production of elastin in the arteries (Natoli et al., 2005). As estrogen concentrations decrease throughout menopause, however, older females have less potential for arterial remodeling (Coutinho, 2014). Interestingly, post-menopausal females also have greater production of NO in endothelial cells (Forte et al., 1998), helping regulate endothelial function through its anti-inflammatory, antithrombotic, and antiplatelet properties (Jin & Loscalzo, 2010) and thus potentially offsetting the detrimental effects of estrogen loss.

#### 1.4.2.4 Association between Cognitive Function and Arterial Stiffness in Older Adults

Arterial stiffness has been established as an independent predictor of cognitive impairment and of subsequent cognitive decline (Li et al., 2017; Rabkin, 2012). A recent systematic review and meta-analysis of 38 studies (26 studies in general population and 12 studies in clinical population) of 43,115 participants (mean age of included studies 46-85 years old) found that elevated PWV was associated with greater cognitive impairment (Alvarez-Bueno et al., 2020). After adjusting for blood pressure, age, and BMI, elevated PWV was associated with lower scores on global cognition (ES:-0.21; 95%CI:-30,-0.11, p=0.000), executive function (ES:-0.08; 95%CI:-0.14,-0.03, p=0.0011), and memory (ES: -0.13;95%:-0.20,-0.05, p=0.000) (Alvarez-Bueno et al., 2020). Sensitivity analyses also found that the strength of the association between arterial stiffness and cognitive function was similar across general and clinical populations (Alvarez-Bueno et al., 2020).

Large artery stiffness has been postulated to be responsible for damage to smaller cerebral vessels that in turn contribute to cognitive impairment (O'Rourke & Safar, 2005). Furthermore, arterial stiffness is associated with reductions in white matter volume, resulting from excessive pulsatile pressure transmission and cerebral vascular damage (Mitchell, 2008) and hypoperfusion (Román, 2004). The presence of white matter lesions have been directly related to cognitive impairment (van Amerongen, et al., 1994), and is an independent risk factor for stroke (Vermeer et al., 2003).

A number of factors have been implicated in the negative association between arterial stiffness and cognitive function, such as education level, BMI, diet, antihypertensive medication use, race, smoking status, depression. However, systolic blood pressure, age, cardiovascular risk factors, and sex are most commonly known to influence this association (Alvarez-Bueno et al., 2020).

*Blood Pressure:* Hypertension is one of the most important predictors of both cognitive impairment (Iadecola et al., 2016) and cardiovascular disease (Karmali & Lloyd-Jones., 2017). Hypertension disrupts cerebral structures, thus contributing to white matter lesions (Harmsen et al., 2017; Iadecola et al., 2016), and increases pulsatile aortic wall stress leading to elastin degradation and collagen production thereby elevating arterial stiffness (Mitchell, 2014). In individuals in mid-late adulthood with hypertension cfPWV was found to be associated with impaired memory (Kearney-Schwartz et al., 2009; Muela et al., 2018), executive function, attention, visuospatial abilities (Muela et al., 2018) and global cognition (Muela et al., 2018; Triantafyllidi et al., 2009).

*Age:* Arterial stiffness has been associated with both poorer performance on tasks related to executive function and with greater white matter lesions in 1260 adults 45-65 years old, which was not seen in younger adults 30-45 years of age (Pase et al., 2016). Similarly, older adults (n=27, mean age 78 years) demonstrated greater arterial stiffness and poorer performance on the Cambridge Neuropsychological Test Automated Battery compared to younger adults (n=31, mean age 35 years) (Csipo et al., 2019). A recent review of 38 studies examining the association between arterial stiffness and cognitive impairment confirm that the body of research in this area has focused throughout mid-late adulthood (mean age range 45-86 years old) (Alvarez-Bueno et al., 2020), highlighting the importance of age as a critical factor to consider when examining the relationship between vascular dysfunction and cognitive impairment.

*History of Stroke:* Individuals with stroke may experience both elevated arterial stiffness (Chen et al., 2017; Tang et al., 2014; Tuttolomondo et al., 2010) and impaired cognitive function

(Levine et al., 2015; Renjen et al., 2015). To date, one study has examined the association between arterial stiffness and cognitive function in individuals with chronic stroke (n=102, mean age 61 years), where arterial stiffness was negatively associated with global cognition (r=-0.45, p<0.001) (Lee et al., 2014).

#### 1.4.2.5 Sex Differences in the Association between Cognitive Function and Arterial Stiffness

To date, of four studies that have examined sex-based differences in the association between arterial stiffness and cognitive function, it appears that male sex has a moderating effect on the association between arterial stiffness and memory and executive function. Adult males were reported to score lower on measures of memory at higher values of cfPWV (Kearney-Schwartz et al., 2009; Singer et al., 2013) and pulse pressure (Waldstein et al., 2008), and a negative association was reported between arterial stiffness and executive function in males but not females (Sabra et al., 2020).

### 1.4.3 Walking Capacity

Walking capacity is often clinically used as an indication of aerobic capacity in older (Rikli & Jones, 1998) and clinical populations, such as individuals with cardiovascular conditions and stroke (Ross et al., 2010; Salbach et al., 2014). Decreases in walking capacity in older adults are associated with reduced aerobic capacity (Fiser et al., 2010; Richardson et al., 2015), increased energy expenditure and fatigue (Richardson et al., 2015; Wert et al., 2013), of which contribute to reductions in the ability to perform activities of daily living and greater risk for subsequent disability (Avlund et al., 2002; Paterson & Warburton, 2010).

Low walking capacity has also been shown to be a predictor of cardiovascular events, including heart failure, myocardial infarction and mortality in a sample of 556 individuals with coronary heart disease (Beatty et al., 2012) and all-cause mortality in a cohort of 1,665 community-dwelling adults (Yazdanyar et al., 2014). Hence, walking capacity is an important determinant of cardiovascular health (Beatty et al., 2012; Yazdanyar et al., 2014) and maintaining walking capacity is often a priority of clinicians and older adults (Wert et al., 2013).

#### 1.4.3.1 Measurement of Walking Capacity

The 6-minute walk test (6MWT) (Butland et al., 1982) is the most commonly used method to assess walking capacity in older adults (Dunning, 2011). Published guidelines for conducting the 6MWT are available, which include scripted instructions and standardized phrases of encouragement (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories, 2002). Maximum distance walked is the primary outcome of this assessment, whereby reference values for older adults between 60-89 years old are between 345-623m (Steffen et al., 2002).

The 6MWT has shown to be highly related with $VO_{2peak}$ assessed using a modified Balke treadmill protocol in older adults (r=0.71 in males and 0.82 in females) (Rikli & Jones, 1998), while also providing an accurate estimation of peak oxygen uptake ($VO_2$peak) ($r=0.68$, $p<0.001$) in individuals with cardiovascular conditions (Ross et al., 2010). In community-dwelling adults with stroke, the 6MWT elicits high intensities of aerobic challenge, with $HR_{peak}$ higher than those achieved on a cycle ergometer test, thus allowing clinicians to use results to prescribe aerobic exercise in individuals with stroke (Salbach et al., 2014).

#### 1.4.3.2 Sex Differences in Walking Capacity in Older Adults

Less is known about sex-based differences in walking capacity in both middle-aged and older adults. Studies in community dwelling older adults have reported that males achieved further distances on the 6MWT (Hill et al., 2011; Ramnath et al., 2018; Troosters et al., 1999), but arguably, confounding factors such as height, lower limb length, weight, and body composition were not controlled in these analyses and make it difficult to interpret if sex differences in 6MWT distance exist. One study in older adults found that greater distances walked by males were no longer significant following the adjustment of height (Lord & Menz, 2002).

Research into sex-specific physiological mechanisms have shown that greater walking capacity may be achieved by females. For example, females may have more efficient peripheral and pulmonary oxygen extraction and thus faster uptake during moderate-intensity walking bouts than males (Beltrame et al., 2017), contrasting conventional physiological beliefs that male physiology contributes to superior cardiovascular fitness (de Simone Giovanni et al., 1995; Goodrich et al., 2018; Gulati et al., 2010; Harms, 2006; Lewis et al., 1986; Schwartz et al., 1988). Of note, this study was conducted in middle aged-adults (Beltrame et al., 2017), thus future studies are warranted to determine if these sex differences in walking capacity transpire into late-adulthood.

Females also appear to experience slower decline in aerobic capacities with age compared to males (Buskirk & Hodgson, 1987; Fleg et al., 2005; Hossack & Bruce, 1982; Stathokostas et al., 2004; Toth et al., 1994; Weiss et al., 2006). Males experience greater age-associated reductions in inotropic sensitivity to beta-adrenergic agonist, resulting in reduced relaxation rate, reduced contractility, reduced heart rate, and decreased vasodilation in smooth muscle cells (Weiss et al., 2006), thereby compromising cardiovascular fitness and walking capacity. Thus, there is evidence to support that biological mechanisms, which include greater oxygen uptake and greater preservation of beta-adrenergic agonists throughout the lifespan may contribute to greater walking capacity in older females than males.

#### 1.4.3.3 Association between Cognitive Function and Walking Capacity in Older Adults

Higher walking capacity in older adults with and without chronic conditions, quantified by greater distance walked on the 6MWT, has been shown to be associated with greater grey matter density (Makizako et al., 2013), greater global cognition (Baldasseroni et al., 2010; Cavalcante et al., 2018; Ferreira et al., 2015; Hayashi et al., 2018; Lord & Menz, 2002; Matthé et al., 2015), memory function (Cavalcante et al., 2018; Ferreira et al., 2015; Makizako et al., 2013), attention (Ferreira et al., 2015; Schure et al., 2016; Sherwood et al., 2019), verbal fluency (Ferreira et al., 2015; Sherwood et al., 2019), and executive function (Ferreira et al., 2015; Loprinzi, 2016; Sherwood et al., 2019).

Blood pressure, age, history of stroke, and sex may be influential in the relationship between cognitive function and walking capacity (i.e. aerobic capacity) in older adults.

*Blood Pressure:* Greater aerobic capacity is inversely associated with risk (Blair et al., 1984; Chase et al., 2009), progression and incidence (Faselis Charles et al., 2012; Juraschek et al., 2014) of hypertension in adults, independent of other risk factors such as age, race, obesity, and diabetes. In a study of individuals with peripheral artery disease, 85% of whom presented with hypertension, lower 6MWT distance was related to worse performance on tests of memory and global cognition (Cavalcante et al., 2018). There also appears to be a less favourable association between attention, memory, verbal fluency, executive function, and global cognition and 6MWT in individuals with low brachial-ankle index (used for detecting peripheral artery disease) and hypertension (mean systolic blood pressure 147 mmHg) in comparison to healthy older adults (Ferreira et al., 2015).

*Age:* Aging is known to be associated with the development of walking impairments typically caused by reduced strength, flexibility and aerobic capacity (Brach & VanSwearingen, 2013). A study involving 155 individuals demonstrated that 6MWT distance decreased from 756m to 468m between 40 and 80 years of age, representing a 38% decrease in capacity (Masmoudi et al., 2008). There is also evidence to suggest that as aerobic capacity declines with age, the exertion associated with habitual walking also increases and thus walking speed is reduced (Fiser et al., 2010). Indeed, previous studies in community dwelling older adults have shown a relationship between cognition and walking capacity, whereby greater 6MWT distance was associated with better global cognitive function (Lord & Menz, 2002; Matthé et al., 2015; Sherwood et al., 2019), executive function (Sherwood et al., 2019) and attention (Sherwood et al., 2019).

*History of Stroke:* Walking capacity and cardiorespiratory fitness are reduced by approximately 50% in individuals with stroke compared with age-matched non-stroke counterparts (Kelly et al., 2003). Stroke-related impairments including limited cardiovascular fitness, muscle weakness and loss of coordination (Kelly et al., 2003) are said to be the major limitations to 6MWT distance (Eng et al., 2002). Furthermore, the added effect of post-stroke cognitive impairment may contribute to accelerated functional decline (Barker-Collo et al., 2010). A study examining the relationship between global cognitive function and 6MWT in individuals with stroke demonstrated that higher 6MWT distance was related to better performance on the Mini-Mental State Examination ($r=0.37$, $p<0.001$) (Lee et al., 2014).

#### 1.4.3.4 Sex Differences in the Association between Cognitive Function and Walking Capacity

Interestingly, of all the studies examining the association between cognitive function and walking capacity, no study to date has disaggregated findings by sex. However, there is evidence to suggest that physiological differences may favour female sex in the relationship between cognitive function and walking capacity. Older males have demonstrated greater rate of decline in peak oxygen consumption (Buskirk & Hodgson, 1987; Fleg et al., 2005; Hossack & Bruce, 1982; Stathokostas et al., 2004; Toth et al., 1994; Weiss et al., 2006), cardiac output, and arteriovenous difference (Weiss et al., 2006) in comparison to older females. Thus, given that cardiac function is associated with cognitive decline (Oh et al., 2012), males may be more susceptible to subsequent cognitive decline and be at increased risk of earlier onset of cognitive impairment.

### 1.5 Overall Thesis Objectives

To date, no study has examined the associations between gender roles and identities and exercise self-efficacy, outcome expectations for exercise, and motivation for exercise in individuals with stroke, and whether gender roles and identities are related. In addition, no study to has examined whether the associations between global cognitive function, arterial stiffness and walking capacity differ between older males and females with and without stroke, and if the addition of age, blood pressure, and history of stroke, of which are common risk factors for cognitive impairment, arterial stiffness and reduced walking capacity, mediate these associations. Thus, this thesis is comprised of two studies which aim to fill this gap in knowledge.

#### 1.5.1 Study #1. Exploring the Associations Between Gender Roles and Identity with Psychosocial Factors for Exercise Post-Stroke

This was a cross-sectional study trial with the purpose of exploring gender role and gender identity differences in exercise self-efficacy, outcome expectations for exercise, and motivation for exercise in individuals with stroke.

The objective of this study was three-fold:

- Objective #1 (Primary Objective): Determine the associations between gender roles (masculine to feminine) and gender identities (masculine, feminine, androgynous and undifferentiated) with exercise self-efficacy in individuals with stroke.

*Specific hypothesis:* Individuals possessing masculine gender roles and identities would have the highest exercise self-efficacy whereas individuals possessing feminine gender roles and identities would have the lowest exercise self-efficacy. We expected a negative and a moderate to strong association ($r \geq -0.4$) between masculine gender role and identity scores and exercise self-efficacy.

- Objective #2 (Secondary Objective): Determine the associations between gender roles (masculine to feminine) and gender identities (masculine, feminine, androgynous and undifferentiated) with outcome expectations for exercise and motivation for exercise in individuals with stroke.

  *Specific hypothesis:* Individuals possessing masculine gender roles and identities would have the highest outcome expectations and motivation for exercise, whereas individuals possessing feminine gender roles and identities would have the lowest outcome expectations for exercise and motivation for exercise. We expected a negative and a moderate to strong association ($r \geq -0.4$) between masculine gender role and identity scores and outcome expectations for exercise and motivation for exercise in individuals with stroke.

- Objective #3 (Tertiary Objective): Determine whether gender roles and gender identity constructs are related in individuals with stroke.

  *Specific hypothesis:* Gender roles and gender identity constructs would be related in individuals with stroke, where masculine gender roles would be associated with masculine gender identities, feminine roles would be associated with feminine gender identities and neutral gender roles would be associated with androgynous or undifferentiated gender identities.

### 1.5.2 Study #2. Is Cognitive Function Associated with Arterial Stiffness and Walking Capacity and Sex in Older Males and Females with and without Stroke?

The objective of this cross-sectional study was two-fold:

- Study Objective #1 (Primary Objective): Examine the associations between global cognitive function, arterial stiffness and sex, and between global cognitive function, walking capacity and sex in older male and female adults with and without stroke.

  *Specific hypothesis:* Global cognitive function would be associated with arterial stiffness and with walking capacity with an additional interaction of sex

- Objective #2: Determine if the addition of age, systolic blood pressure and history of stroke explains a portion of variance in the relationships between global cognitive function, arterial stiffness or walking function, and sex.

*Specific hypothesis:* The addition of age, systolic blood pressure and history of stroke would explain an additional portion of the variance in the relationships between global cognitive function, arterial stiffness or walking function, and sex.

# Chapter 2

## Study 1- Exploring the Associations Between Gender Roles and Identity with Psychosocial Factors for Exercise Post-Stroke

**Abstract**

**Introduction:** In the general population, men often have more support and opportunity for exercise engagement than women, contributing to higher exercise self-efficacy, outcome expectations for exercise, and motivation for exercise and thus greater participation in exercise. Whether these associations are observed in individuals with stroke has not been previously studied. The purpose of this study was to explore gender role and gender identity differences in exercise self-efficacy, outcome expectations for exercise and motivation for exercise in individuals with stroke. In addition, we aimed to determine if gender roles and gender identity constructs were interrelated in the participants with stroke. We hypothesized that masculine roles and identities would be associated with higher exercise self-efficacy, outcome expectations for exercise and motivation for exercise compared to feminine roles in individuals with stroke. We also hypothesized that feminine roles would be associated with feminine identities, masculine roles with masculine identities, and neutral roles with androgynous or undifferentiated identities in individuals with stroke.

**Methods:** Gender identity was assessed as masculine, feminine, androgynous, or as undifferentiated using the Bem Sex-Role Inventory-12 (BSRI-12) and a gender index was created using established gender-related roles (feminine roles: light and heavy housework, caregiving; masculine roles: yard work, home repairs, education). The Self-Efficacy for Physical Activity Scale was used to assess self-efficacy for exercise, the Short Outcome Expectations for Exercise Scale assessed outcome expectations for exercise and a Relative Autonomy Index was calculated to assess motivation for exercise. Bivariate correlation analyses were conducted to determine the associations between gender role scores and exercise self-efficacy, outcome expectations for exercise, and motivation for exercise, and one-way ANOVAs were conducted to determine the associations between gender identity and each psychosocial factor for exercise and to determine the relationships between gender roles and identities.

**Results:** Data were collected and analyzed from 13 individuals with stroke. There were no correlations between gender role scores and exercise self-efficacy ($n=13$, $r=0.10$, $p=0.73$), outcome expectations for exercise ($n=13$, $r=-0.13$, $p=0.68$) and motivation for exercise ($n=8$, $r=0.09$, $p=0.83$). There were differences in exercise self-efficacy across the four gender identities of the BSRI-12 [$F(3, 9)=5.36$, $p<0.05$], where a post-hoc multiple-comparison test revealed that individuals possessing masculine gender identities had higher self-efficacy than individuals possessing feminine gender identities ($p<0.05$). There were no differences in outcome expectations for exercise [$F(3,8)=0.86$, $p=0.50$] or motivation for exercise [$F(3,4)=0.67$, $p=0.61$] between gender identities from the BSRI-12. Gender roles and gender identity constructs were not related in individuals with stroke [$F(3,9)=0.25$, $p=0.85$].

**Conclusion:** Masculine gender identity appeared to be related to possessing the highest exercise self-efficacy, whereas feminine gender identity was related to possessing the lowest exercise self-efficacy in individuals with stroke. However, there were no associations between gender roles and exercise self-efficacy, outcome expectations for exercise, and motivation for exercise, nor for gender identity and outcome expectations and motivation for exercise. Findings suggest that the stereotypical gender roles observed in older adults may not be relevant in stroke.

## 2.1 Background

Exercise is known to have many benefits following stroke, with multiple systematic reviews reporting improved cardiovascular fitness, walking function, balance (Saunders et al., 2020), cognitive function (Oberlin et al., 2017), upper and lower limb function (Veldema & Jansen, 2020), and reductions in vascular risk factors, including cholesterol and blood pressure levels (D'Isabella et al., 2017; Wang et al., 2019).

### 2.1.1 Psychological Barriers to Exercise Post-Stroke

Despite the known benefits of exercise after stroke, stroke survivors are often sedentary, where physical activity levels are substantially lower than those observed in older adults (Field et al., 2013). Individuals with stroke have reported low levels of exercise self-efficacy (Damush et al., 2007; Nicholson et al., 2014; Reed et al., 2010; Simpson et al., 2011), lower expectations on the benefits of exercise (Barker & Brauer, 2005; Carin-Levy et al., 2009; Maher et al., 1999; Rimmer et al., 2008), and low intrinsic motivation for exercise (Nicholson et al., 2013), which can each influence the initiation and adherence of exercise (Resnick & Spellbring, 2000). In contrast, support from sources, such as family, friends, and healthcare personnel are essential forms of external motives for exercise participation in individuals with stroke (Damush et al., 2007; Poltawski et al., 2015; Simpson et al., 2011).

### 2.1.2 Gender Roles and Gender Identity and Exercise Behaviours

Gender may be an important factor associated with exercise self-efficacy, outcome expectations for exercise and motivation for exercise. Gender refers to the social, environmental, cultural and behavioural factors and choices that impact a person's self-identity and health, where gender roles, gender identity, institutionalized gender and gender relations are the four constructs that comprise of an individual's gender (Tannenbaum et al., 2016).

*Gender roles* represent the societal behavioural norms applied to men and women that influence an individual's everyday actions (Pelletier et al., 2015). Socially constructed feminine gender roles include household tasks (shopping, cooking, cleaning, dish washing, cleaning, etc) (Cunningham, 2007), caregiving responsibilities (Sharma, Chakrabarti & Grover, 2016), and working less paid hours (Smith & Koehoorn, 2016). Conversely, socially constructed gender roles typically assigned to men include responsibilities that do not involve daily commitment, such as home repairs or yard maintenance (Cerrato & Cifre, 2018).

Of note, historical gender roles may shift over time. For example, education is a gender role that experienced a shift in recent decades from traditionally a masculine role to currently a feminine role (Severiens & ten Dam, 2012). Universities and college settings were historically dominated by men until the late 1960s, as women primarily engaged in housekeeping and caregiving roles rather than pursuing higher education (*Women, Marriage, Education, and Occupation in the United States from 1940-2000 | History 90.01: Topics in Digital History*, 2016). The imbalance progressively equalized over time such that in 1991, there was an equal distribution of men and women attending university in Canada (Frenette & Zeman, 2007). By 2001, women accounted for 58% of university graduates (Frenette & Zeman, 2007).

Previous research has shown that masculine gender roles are positively associated with higher exercise self-efficacy and greater exercise participation in older adults (Barrett et al., 2007; Chen et al., 2015; Lee, 2005; Scharff et al., 1999). In contrast, women have had less opportunity to participate in exercise, which may be as a result of feminine gender roles (Chen et al., 2015; Segar et al., 2002; Verhoef et al., 1992). Additionally, men were more likely to consider enjoyment associated with exercise as an important outcome and motivator for exercise (Mao et al., 2020), whereas women were reported to have low intrinsic motivation for exercise as a result of the competing demands related to household and caregiving activities (González-Cutre et al., 2011). Notably, the association between gender roles and perceptions of exercise have been observed in both younger and older adults, suggesting that these differences are established in early adulthood and continue throughout the lifespan (Mao et al., 2020).

*Gender identity* refers to an individual's innermost concept of self as man, woman, or other, which can be the same or different from one's biological sex (Roselli, 2018; Tannenbaum et al., 2016). Differences in exercise behaviours across gender identities are reported early in life and transpire into adulthood. Individuals with masculine gender identities (boys, younger and older men) were more likely to possess higher exercise self-efficacy and thus more likely to participate in exercise compared to girls and women (Barrett et al., 2007; Chen et al., 2015; Chiu & Wray, 2011; Delahanty et al., 2006; Lee, 2005; Kim et al., 2009; McAuley et al., 1991; Nehl et al., 2012; Pauline, 2013; Rosenkranz et al., 2011; Scharff et al., 1999; Spence et al., 2010; Umstattd & Hallam, 2007; Wittig et al., 1987). Moreover, men were more likely to report challenge, enjoyment, and gains in strength and fitness as exercise motives (i.e. intrinsic motivation), while women were extrinsically motivated to exercise by less sustainable motives of stress or physical appearance (e.g. weight management) (Butt et al., 2011; Craft et al., 2014; Ednie & Stibor, 2017; Gao & Xiang, 2008; Gillessen et al., 1995; Sang Hyuk, 2012; Van Uffelen et al., 2017; Zervou et al., 2017). Women have also reported to receive less family support than men for exercise (Chiu & Wray 2011), while men were also more likely than women to report positive outcome expectations for exercise, which included greater enjoyment and improved quality of life from participation in exercise (Craft et al., 2014; Daig et al., 2009; González-Cutre et al., 2011; Mao et al., 2020; Umstattd & Hallam, 2007).

**2.2 Objectives and Hypotheses**

Taken together, the body of evidence suggests that differences in gender roles and gender identities are associated with exercise self-efficacy, outcome expectations and motivation for exercise in adults across the lifespan. However, whether theses gender-based differences are observed in individuals with stroke has yet to be examined. Thus, the objectives of this study were three-fold:

- Objective #1 (Primary Objective): Determine the associations between gender roles (masculine to feminine) and gender identities (masculine, feminine, androgynous and undifferentiated) with exercise self-efficacy in individuals with stroke.

  *Specific hypothesis:* Individuals possessing masculine gender roles and identities would have the highest exercise self-efficacy whereas individuals possessing feminine gender roles and identities would have the lowest exercise self-efficacy. We expected a negative and a moderate to strong association ($r \geq -0.4$) between masculine gender role and identity scores and exercise self-efficacy.

- Objective #2 (Secondary Objective): Determine the associations between gender roles (masculine to feminine) and gender identities (masculine, feminine, androgynous and undifferentiated) with outcome expectations for exercise and motivation for exercise in individuals with stroke.

*Specific hypothesis:* Individuals possessing masculine gender roles and identities would have the highest outcome expectations and motivation for exercise, whereas individuals possessing feminine gender roles and identities would have the lowest outcome expectations for exercise and motivation for exercise. We expected a negative and a moderate to strong association ($r \geq -0.4$) between masculine gender role and identity scores and outcome expectations for exercise and motivation for exercise in individuals with stroke.

- Objective #3 (Tertiary Objective): Determine whether gender roles and gender identity constructs are related in individuals with stroke.

*Specific hypothesis:* Gender roles and gender identity constructs would be related in individuals with stroke, where masculine gender roles would be associated with masculine gender identities, feminine roles would be associated with feminine gender identities and neutral gender roles would be associated with androgynous or undifferentiated gender identities.

## 2.3 Methodology

### 2.3.1 Study Design

This study was a cross-sectional analysis of data collected from two studies: a multi-site randomized controlled trial (McMaster University Hamilton Integrated Research Ethics Board (HIREB) 4713, McGill University Centre de Recherche Interdisciplinaire en Réadaptation du Montréal Métropolitain (CRIR-1310-0218) and a prospective single-group study (McMaster University HIREB 3113). All study procedures were followed in accordance to guidelines outlines by each institution's research ethic committees. Informed written consent was obtained from all participants.

### 2.3.2 Participants

Participants for both studies were recruited from the community, through local community stroke groups and from a database of former research participants who consented to be contacted for future research studies. Eligibility criteria for individuals with stroke for both studies were similar. Individuals were eligible to participate in the randomized controlled trial if they were 40-80 years old, 6-60 months following their first-ever stroke (confirmed by neuroimaging scan), living in the community and able to walk at least 10 meters independently (gait aids permitted). Participants were excluded if they had a stroke of non-cardiogenic origin or tumor, were actively engaged in stroke rehabilitation or a structured exercise program within the past 6 months, presented with a score $<2$ on the Modified Rankin Scale, any contraindications to exercise testing or training outlined by the American College of Sports Medicine Guidelines of Exercise Testing and Prescription (*ACSMs Guidelines for Exercise Testing and Prescription, 2017)*, presented any class C or D American Heart Association Risk Criteria, presented with other neurological or musculoskeletal comorbidities, pain that worsened with exercise, or cognitive, communication, or behavioural issues that could limit their ability to provide consent or follow instructions.

The same eligibility criteria were followed in the prospective single-group study, with the exception that there was no upper limit on time post-stroke (≥ 6 months).

### 2.3.3 Assessments

*Participant Characteristics*

Participant demographic information, stroke lesion type and location, time post-stroke, degree of disability and neurologic deficit using the Modified Rankin Scale (Rankin, 1957), and National Institutes of Health Stroke Scale (Brott et al., 1989) were collected. The Modified Rankin Scale is a tool used to evaluate global stroke disability using a Likert scale ranging between 0 (no symptoms at all) to 6 (death) (Rankin, 1957; van Swieten et al., 1988). The National Institutes of Health Stroke Scale is a 11-item scale that gives a sampling of level of alertness, motor and sensory function, and language to provide an overall indication of severity of stroke (maximum score 42, where higher scores indicate greater severity) (Brott et al., 1989).

*Psychosocial Outcomes for Exercise*

Case report forms for psychosocial outcomes for exercise are provided in Appendix 1.

**Self-Efficacy for Exercise:** With the 5-item Self-Efficacy for Physical Activity Scale (SEPA) (Marcus et al., 1992), participants were asked to rate their levels of confidence in their abilities to exercise using a 5-point Likert scale ranging from 1 (not confident at all) to 5 (extremely confident). Scores for all items were averaged to determine a summary score (Marcus et al., 1992). The SEPA has demonstrated strong internal consistency (Cronbach's alpha 0.76-0.85) and test-retest reliability (r=0.90) in adults (Marcus et al., 1992), and predictive validity for participation in physical activity guidelines in adults (Mendoza-Vasconez et al., 2018).

**Outcome Expectations for Exercise:** The Short Outcome Expectations for Exercise Scale (SOEE) (Resnick et al., 2000; Shaughnessy et al., 2004) is a 5-item questionnaire that is used to evaluate the outcome expectations related to exercise that are relevant to older adults. Participants were asked to rate their expectation of positive outcomes for exercise on a 5-point

Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree), and scores on all items were averaged to determine a summary score (Shaughnessy et al., 2004). In individuals with stroke, the SOEE demonstrated both high internal consistency (Cronbach's alpha 0.90) and construct validity with common outcome expectations related to exercise, which include exercising to improve mood, alertness, endurance and believing that exercise is enjoyable ($\lambda$= 0.67-0.88) (Shaughnessy et al., 2004).

**Motivation for Exercise:** For the subset of participants enrolled in the randomized controlled trial, motivation for exercise was measured using the Relative Autonomy Index (RAI) (Ryan et al., 1997; Vaz et al., 2016).

The RAI was calculated based on responses to the 24-item Behavioral Regulation in Exercise Questionnaire-3 (BREQ-3) (Markland et al., 2004; Wilson et al., 2006), which measures 6 types of motivational regulations which include amotivation, external regulations, introjected regulations, identified regulation, integrated regulation, and intrinsic motivation (Sweet et al., 2014; Wilson et al., 2012). External and introjected regulation are typically viewed as externally driven forms of motivation, whereas identified regulation, integrated regulation and intrinsic motivation are driven internally (Verloigne et al., 2011). Statements on the BREQ-3 were rated on a 5-point Likert scale ranging from 0 (not true for me) to 4 (very true for me). The BREQ-3 was administered one week into the 12-week exercise intervention.

The BREQ-3 was summed and weighted scores were determined as follows: ([amotivation x -3] + [external x -2] + [introjected x -1] + [identified x 1] + [integrated x 2] + [intrinsic x 3]) (Ryan & Deci, 2000; Wilson et al., 2006). Higher positive scores for the RAI indicate more autonomous motivation, whereas lower negative scores indicate more controlled motivation (introjected or external) (Verloigne et al., 2011). The RAI has demonstrated to predict up to 40% of exercise leisure-time in younger adults ($F_{1,1175}$=284.29, p<0.01;R=0.44), and higher RAI scores have been consistently related to more frequent exercise behavior in younger adults (Wilson et al., 2012).

*Gender Identity and Gender Roles Measurement Tools*

Case report forms for all gender identity and gender role tools are provided in Appendix 2.

**Gender Identity:** The Bem Sex-Role Inventory-12 (BSRI-12), a 12-item questionnaire (Mateo & Fernández, 1991) derived from the original 60-item BSRI questionnaire (Bem, 1974), was used to assess gender identity. The BSRI-12 consists of two scales with 6 stereotypical feminine gender traits (warm, gentle, affectionate, sympathetic, sensitive to other's needs, tender) and 6 stereotypical masculine gender traits (has leadership abilities, strong personality, acts as leader, dominant, defends own beliefs, makes decisions easily) (Mateo & Fernández, 1991). Participants rated the extent to which each trait reflected themselves on a 7-point Likert scale (1=never or almost never true, 7=always or almost always true) (Mateo & Fernández, 1991).

The BSRI-12 is scored by determining the overall median value for both feminine and masculine scales, which is then compared to the mean scores for each scale separately. Feminine gender identity was classified if the mean score on the feminine scale was higher than the overall median and mean score on the masculine scale was lower, masculine gender identity classified if mean score on the masculine scale was higher than the overall median and mean score on the feminine scale was lower, undifferentiated if mean scores for both the feminine and masculine scales fell below the median, and androgynous if mean scores on both scales were equal to or above the median (Carver et al., 2013).

The BSRI-12 has high internal consistency in older adults (feminine scale Cronbach's alpha 0.76, masculine scale Cronbach's alpha 0.75) and discriminant validity between the two separate masculine and feminine scales (chi square test $\chi^2 - \chi^2 = 33$; $df_1 - df_2 = 1$, $p<0.001$) (Ahmed et al., 2016).

**Gender Role Index:** A gender index was constructed using specific gender-related responses to questions from the Physical Activity for Individuals with Physical Disabilities (Washburn et al., 2002) related to housework (light, heavy), home repairs, lawn repairs, caregiving and education. Highest level of education completed was included in the construction of the gender index using demographic data. Education was deemed to be a masculine gender role based on the age range of the individuals in our sample. Each measure of the index is described in Table 1.

An overall gender index score was determined as the sum of all scores from the gender index. Scores ranged from 0-18, where higher scores were indicative of possessing more feminine gender roles and lower scores indicated more masculine gender roles.

**Table 1.** Items and scoring used in the constructed gender index

| **Item** | **Gender Role** | **Scoring** |
|---|---|---|
| **Light Housework**<br><br>*"During the past 7 days, how often have you done any light housework, such as dusting, sweeping floors or washing dishes?"* | Feminine | 0= Never<br>1= Seldom (1-2 days)<br>2= Sometimes (3-4 days)<br>3= Often (5-7 days) |
| **Heavy Housework**<br><br>*"During the past 7 days, how often have you done any heavy housework or chores such as vacuuming, scrubbing floors, washing windows, or walls, etc?"* | Feminine | 0= Never<br>1= Seldom (1-2 days)<br>2= Sometimes (3-4 days)<br>3= Often (5-7 days) |

| | | |
|---|---|---|
| **Home Repairs**<br><br>*"During the past 7 days, how often have you done home repairs such as carpentry, painting, furniture refinishing, electrical work, etc?"* | Masculine | 3= Never<br>2= Seldom (1-2 days)<br>1= Sometimes (3-4 days)<br>0= Often (5-7 days) |
| **Lawn Repairs**<br><br>*"During the past 7 days, how often have you done lawn work or yard care, including mowing, leaf or snow removal, tree of bush trimming, or wood chopping, etc?"* | Masculine | 3= Never<br>2= Seldom (1-2 days)<br>1= Sometimes (3-4 days)<br>0= Often (5-7 days) |
| **Caregiving**<br><br>*"During the past 7 days, how often did you care for another person, such as children, a dependent spouse, or another adult?"* | Feminine | 0= Never<br>1= Seldom (1-2 days)<br>2= Sometimes (3-4 days)<br>3= Often (5-7 days) |
| **Education**<br><br>Highest level of education by self-report | Masculine (based on age of our cohort) | 0= College diploma or University degree<br>1= Some post-secondary education<br>2=Some secondary education or high-school diploma<br>3=0-8 years of education |

### 2.3.4 Statistical Analyses

Participant demographics were described using descriptive mean and standard deviations for normally distributed continuous variables. Categorical variables were described using frequency (percentage), and non-normal distributed data were summarized using median and interquartile range. All data was analyzed using StataIC Version 15 (College Station TX, USA) and a two-tailed significance test with an alpha of 0.05 was set.

*Objective #1: Determine the associations between gender roles (masculine to feminine) and gender identities (masculine, feminine, androgynous and undifferentiated) with exercise self-efficacy*

To address Objective #1, scatterplots were first visually inspected for outliers and tests for normality were conducted. A bivariate correlation analysis was then conducted to determine the associations between gender role scores and exercise self-efficacy. To determine if there were any differences between the four constructs of gender identity and exercise self-efficacy scores, we performed a one-way analysis of variance (ANOVA) followed by a post-hoc Bonferroni comparison to access where the differences were between the four constructs of the BSRI-12.

*Objective #2: Determine the associations between gender roles (masculine to feminine) and gender identities (masculine, feminine, androgynous and undifferentiated) outcome expectations for exercise and motivation for exercise.*

To address Objective #2, scatterplots were visually inspected for outliers and tests for normality were conducted. Bivariate correlation analyses were then conducted to determine the associations between gender role scores and exercise-related outcome expectations and motivation for exercise. To determine if there were any differences between the four constructs of gender identity and outcome expectations for exercise and motivation for exercise scores, we performed one-way ANOVA tests. A post-hoc comparison was not performed, as there were no differences between group means in gender identity constructs.

*Objective #3: Determine whether gender role scores and identities differ between individuals with stroke.*

To address Objective #3, data were visually inspected and a test for normality was performed prior to running any analysis of variance test. We then performed a one-way ANOVA to determine if gender roles and gender identity constructs were related in the individuals with stroke.

**2.4 Results**

Figure 1 depicts the flow of participants through the study. Thirteen individuals were enrolled and completed this current study (n=9 males, 4 females). Participant characteristics for the 13 participants are shown in Table 2. Data for SOEE was missing for one participant (declined to answer), thus data from 12 participants were included in the analyses for outcome expectations for exercise. RAI were determined for the subset of n=8 participants who were enrolled in the randomized controlled trial.

National Institute of Health Stroke Scale and Modified Rankin Scale values suggested that participants had strokes of mild to moderate severity. Gender role scores suggested that our sample took on primarily neutral gender roles (combination of masculine and feminine roles) and the highest percentage of individuals (46.2%) were categorized as possessing feminine gender identities.

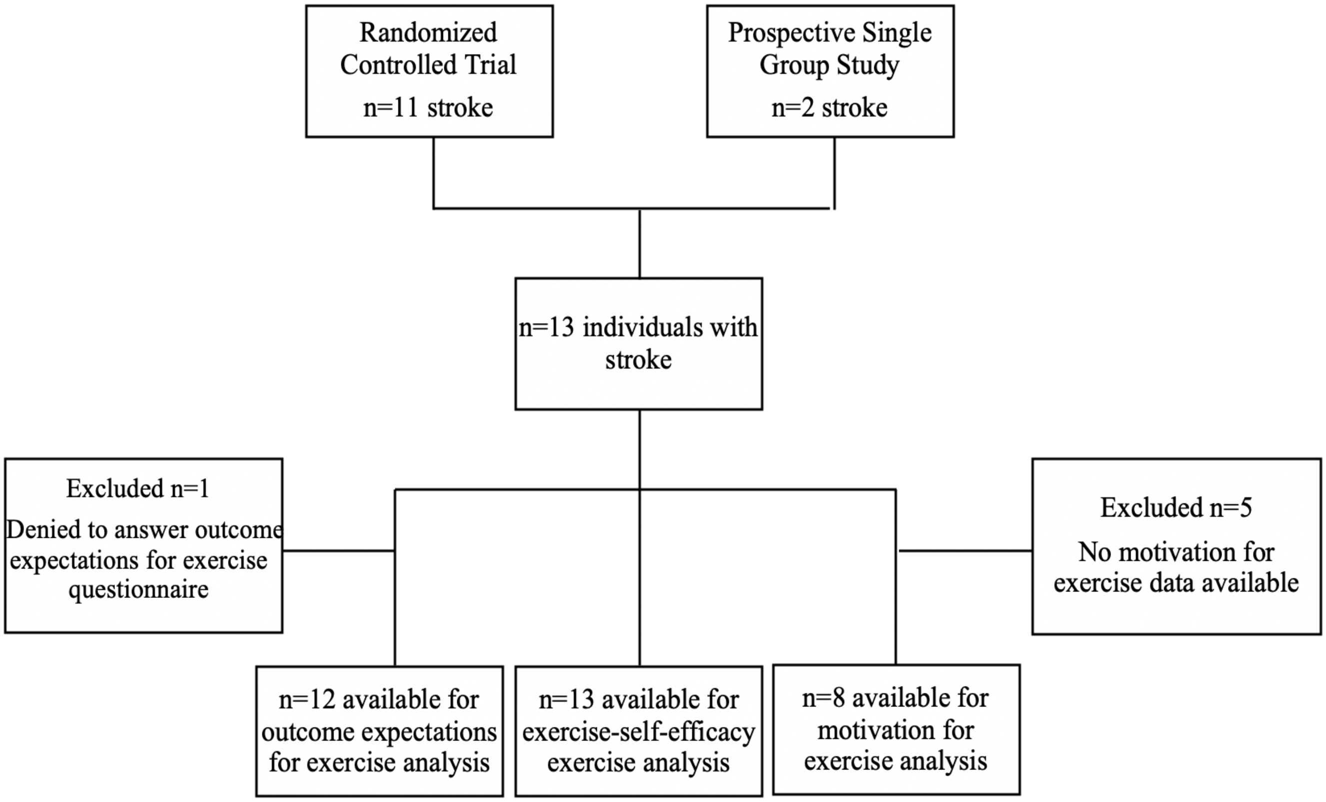



**Figure 1. Flow chart of participants through the study**

**Table 2. Participant Characteristics (n=13)**

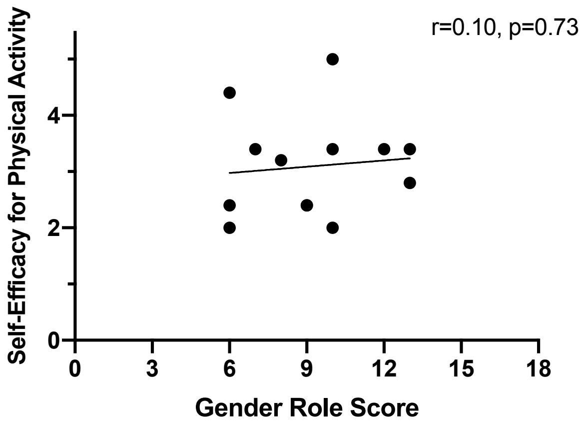
| | |
|---|---|
| Sex, n (%) | |
| Females | 4 (30.8) |
| Males | 9 (69.2) |
| Age (years), Mean (SD) | 60.5 (13.1) |
| Years post-stroke, Median (IQR) | 2.9 (0.9) |
| Limb Affected, n (%) | |
| Right | 4 (30.8) |
| Left | 8 (61.5) |
| Bilateral | 1 (7.7) |
| Stroke type, n (%) | |
| Ischaemic | 7 (53.8) |
| Haemorrhage | 4 (30.8) |
| Unknown | 2 (15.4) |
| Montreal Cognitive Assessment, Mean (SD) | 25.8 (3.0) |
| National Institutes of Health Stroke Scale, Mean (SD) | 3 (1.4) |
| Modified Rankin Scale, Median (IQR) | 2 (1.0) |
| Chedoke-McMaster Stroke Assessment, Mean (SD) | |
| Arm | 5.8 (1.4) |
| Hand | 5.3 (0.8) |
| Gender Role Scores, Mean (SD) | 9.2 (2.5) |
| Bem Sex-Role Inventory-12, n (%) | |
| Feminine | 6 (46.2) |
| Masculine | 4 (30.8) |
| Androgynous | 2 (15.4) |
| Undifferentiated | 1 (7.7) |
| Self-Efficacy for Physical Activity, Mean (SD) | 3.1 (0.9) |
| Short Outcome Expectations for Exercise, Mean (SD) | 3.9 (0.8) |
| Relative Autonomy Index, Median (IQR) | 15.4 (8.8) |

**Note.** IQR= Interquartile Range, SD= Standard Deviation

*Objective #1: Associations between gender variables and exercise self-efficacy*

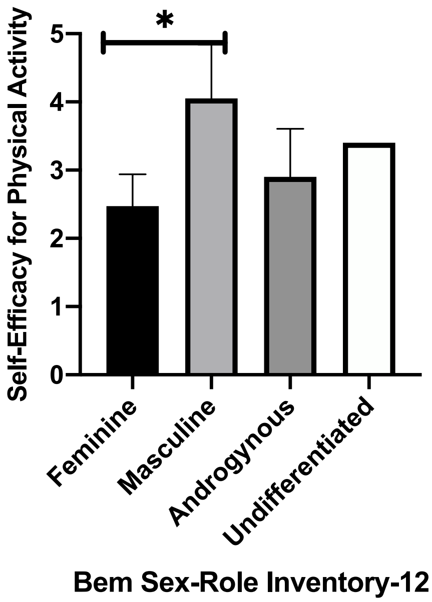
There was no correlation observed between gender role scores and exercise self-efficacy (r=0.10, p=0.73) (Figure 2).

**Figure 2. Scatterplot depicting the associations between gender role scores and exercise self-efficacy as measured by the Self-Efficacy for Physical Activity Scale**




A one-way ANOVA demonstrated differences between the four gender identity constructs of the BSRI-12 [$F(3, 9)=5.36$, $p<0.05$]. A post-hoc multiple-comparison test using the Bonferroni correction revealed that individuals possessing masculine gender identities had higher exercise self-efficacy than individuals possessing feminine gender identities (p=0.02) (Figure 3). There were no other differences in exercise self-efficacy among the four constructs of the BSRI-12.

**Figure 3. Self-Efficacy for Physical Activity scores for feminine, masculine, androgynous and undifferentiated gender identities assessed by the Bem Sex-Role Inventory-12. Error bars represent standard deviation values. * p<0.05.**

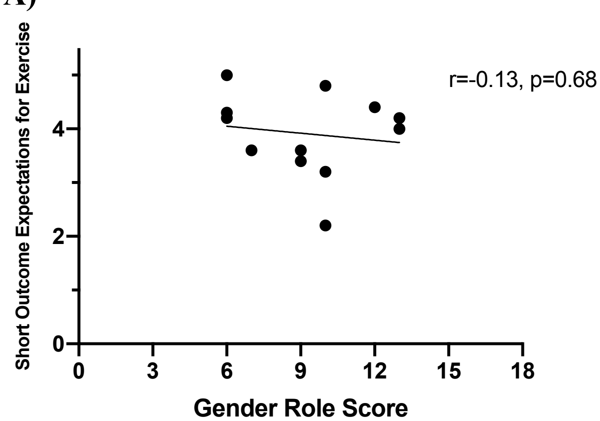



*Objective #2: Associations between gender variables and outcome expectations for exercise and motivation for exercise*

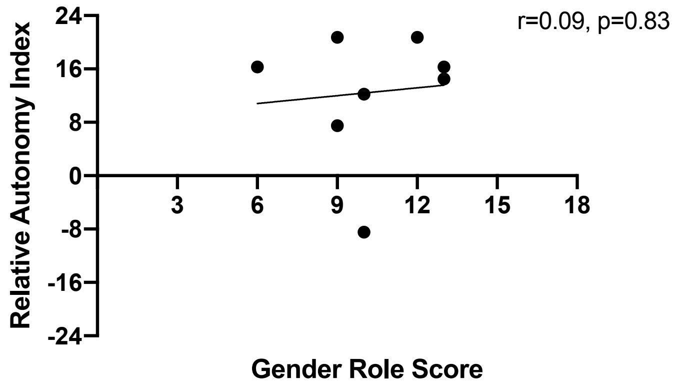
Scatterplots for the associations between gender roles and outcome expectations for exercise and motivation for exercise are presented in Figure 4.

**Figure 4. Scatterplots depicting the associations between gender role scores and A) Outcome Expectations for Exercise, and B) Relative Autonomy Index**

**A)**



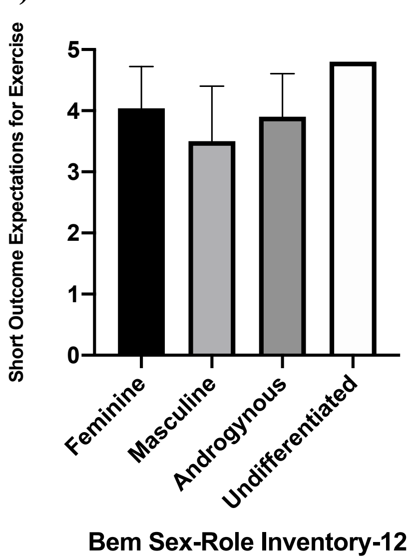
**B)**



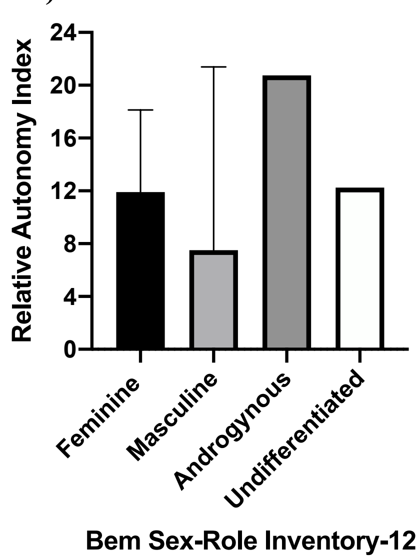

With regards to gender identity, one-way ANOVAs revealed no differences in SOEE scores between the four constructs of the BSRI-12 [F(3,8)=0.86, p=0.50] (Figure 5 Panel A), nor with RAI scores across BSRI-12 constructs [F(3,4)=0.67, p=0.61] (Figure 5, Panel B).

**Figure 5. A) Short Outcome Expectations for Exercise scores and B) Relative Autonomy Index scores for feminine, masculine, androgynous and undifferentiated gender identities assessed by the Bem Sex-Role Inventory-12. Error bars represent standard deviation**

**A)**



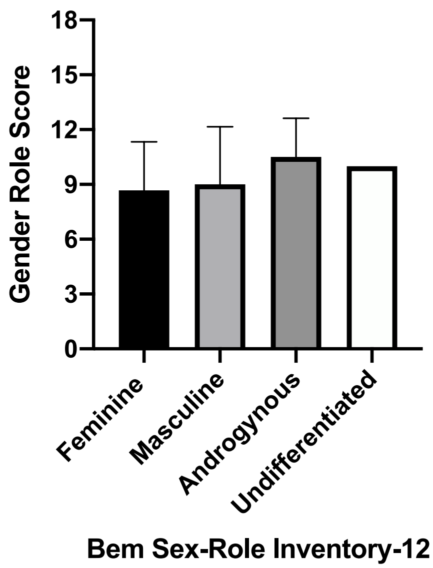

**B)**



*Objective #3: Associations between gender roles and gender identity constructs*

In a one-way ANOVA, we found that gender roles and gender identity constructs were not related in the individuals with stroke [F(3,9)=0.25,p=0.85] (Figure 6).

**Figure 6. Gender scores for feminine, masculine, androgynous and undifferentiated gender identities assessed by the Bem Sex-Role Inventory-12. Error bars represent standard deviation**




**2.5 Discussion**

The results from this study are the first to contribute to the literature surrounding gender differences in exercise self-efficacy, outcome expectations for exercise and motivation for exercise in individuals with stroke. Although preliminary, our findings suggest that individuals possessing masculine gender identities had the highest exercise self-efficacy, whereas individuals possessing feminine gender identities had the lowest exercise self-efficacy. We did not observe any associations between gender roles, exercise self-efficacy, outcome expectations and motivation for exercise in individuals with stroke, nor any differences between gender identity constructs and outcome expectations and motivation for exercise. Finally, there were no associations between gender roles scores and gender identity constructs.

It may be that the lack of association between gender roles and exercise self-efficacy in individuals with stroke is attributable to factors that are specific to this population, whereby stroke-related psychological challenges may have contributed to lower self-efficacy for exercise to a greater extent than gender role differences. Feelings of vulnerability and anxiety towards exercise (Carin-Levy et al., 2009), in addition to a loss of purpose and willingness to participate in exercise (Reed et al., 2010), may have contributed to lower exercise self-efficacy across individuals taking on a range of masculine and feminine gender roles. Interestingly, however, our findings suggested that gender identity was associated with exercise self-efficacy in individuals with stroke. Indeed, these findings were consistent with previous literature in young (McAuley et al., 1991; Nehl et al., 2012; Pauline, 2013; Rosenkranz et al., 2011; Spence et al., 2010; Wittig et al., 1987) and older adults (Chen et al., 2015; Lee, 2005; Scharff et al., 1999), and in individuals with type II diabetes (Barrett et al., 2007; Chiu & Wray, 2011; Delahanty et al., 2006).

Lower exercise self-efficacy observed in individuals identifying as women may in part be attributed to health pressures, such as the influence of others to achieve a perceived ideal body image (van Uffelen et al., 2017), experienced even prior to stroke. Low exercise self-efficacy and low exercise participation in individuals identifying as women may also have been a result of little opportunity for exercise over the lifetime due to competing gender roles, contributing to few exercise-related mastery experiences in older women. Thus, low self-efficacy observed in individuals identifying as women with stroke may have been established earlier in the lifecourse.

Contrary to our hypothesis, we did not observe any associations for either gender roles or gender identity with outcome expectations for exercise. Previous literature in other populations have reported that masculine gender roles and identities contribute to higher enjoyment for exercise (Craft et al., 2014; Daig et al., 2009; González-Cutre et al., 2011; Mao et al., 2020). The lack of associations observed in the current study may have been in part because individuals with stroke, independent of gender roles or gender identities, often do not perceive outcomes of exercise as being beneficial for stroke recovery (Rimmer et al., 2008). Healthcare professionals should consider various ways to provide education to caregivers and stroke survivors on the importance of exercise on physical and psychosocial domains (Billinger et al., 2014), which have been shown to directly influence exercise behaviour (Shaughnessy et al., 2006) and thus may increase outcome expectations for exercise. Interestingly, the perception that exercise training may have limited value during rehabilitation may be reinforced by stroke physiotherapists, who have reported that they do not prioritize exercise in their management plans nor establish exercise as a rehabilitation goal for their patients (Moncion et al., 2020). Limited access to resources such as equipment, space, and educational opportunities to support the routine implementation of exercise within clinical practice may contribute, but may be addressed with implementation strategies (Moncion et al., 2020). Strategies to support stroke rehabilitation professionals in integrating exercise programming within current practice can help facilitate positive exercise experiences for individuals with stroke and thus enhancing outcome expectations.

While previous literature in older adults have suggested that men are more motivated by intrinsic factors for exercise, and that, women tend to be motivated by extrinsic factors for exercise (van Uffelen et al., 2017), we found no associations between gender roles and identities and motivation for exercise. Post-stroke disability is highly prevalent, affecting independence in basic and instrumental activities of daily living (Hachisuka et al., 1998; Ullberg et al., 2015).

This can lead to changes in responsibilities and daily activities previously undertaken prior to stroke, potentially shifting roles away from stereotypical gender roles. Indeed, previous studies have shown that individuals with stroke report symptoms of depression as a result of a loss of social roles in the community (Trigg et al., 1999). Thus, the lack of association between the gender roles and psychosocial factors for exercise in individuals with stroke may in fact reflect role changes as a result of disability from stroke. Future studies should aim to identify both pre- and post-stroke gender roles and whether these differ, and their associations with exercise factors.

Additionally, the absence of association between gender identities and motivation for exercise in stroke could potentially be explained by depressive and apathy symptoms often experienced by stroke survivors (Towfighi Amytis et al., 2017; van Dalen Jan Willem et al., 2013) that are independent of gender. Indeed, depression is experienced in both men and women with stroke, with a systematic review highlighting the prevalence only being marginally higher in women (Poynter et al., 2009), and apathy is similarly prevalent in both men and women (Caeiro et al., 2013). Both may result in low internal motivation and decreased goal-oriented behaviour (Marin, 1990; Towfighi Amytis et al., 2017) for exercise participation (Rochette et al., 2007; Mayo et al., 2009). Individuals experiencing depression beyond three months of stroke onset are less likely to have favourable outcomes and will spend more time in inpatient care or rehabilitation, contributing to further reductions in motivation (Aaron et al., 2016). Apathy and depression are correlated within stroke survivors (Marin et al., 1994), and are commonly known to decrease interest and increase fatigue, thus resulting in lower motivation to perform any activities in life (Ishizaki & Mimura, 2011), including exercise (Rochette et al., 2007). Thus, the similar prevalence of post-stroke apathy and depression between men and women may explain the lack of associations between gender roles and identities and exercise motivation observed in our study.

We did not observe any associations between gender role scores and gender identity constructs, and in fact noted that the majority of the participants in the current study reported neutral rather than differentiated gender role scores. These findings underscore the complexity of gender as a multifaceted and fluid concept that encompasses gender relations and institutionalized gender, in addition to the constructs of gender roles and gender identity that were examined in the current study (Tannenbaum et al., 2016). *Gender relations* describes how individuals interact with one another, but has been far less studied and understood, particularly in terms of its assessment and how it could interact with other variables (Tannenbaum et al., 2016). *Institutionalized gender* reflects the distributions of power between men and women, which may be assessed through qualitative methods (e.g. case studies, descriptive or narrative approaches) (Tannenbaum et al., 2016). Of note, no study to date has confirmed if these constructs are interrelated or are indeed independent of one another. While this study was limited in scope by examining gender roles and gender identities only due to the quantitative study design, our findings suggest that gender roles and gender identity are independent constructs in the stroke population (e.g. an individual with stroke identifying as a woman may not necessarily take on gender roles typically assigned to women). Future research including further quantitative work and structured interviews are warranted to better understand gender-related factors in health outcomes after stroke. A gender role index may be constructed based on findings from larger cohort studies and themes arising from qualitative work.

**Limitations**

We acknowledge that this study has limitations. Firstly, the construction of the gender index was based on gender roles that we believed were relevant to our study participants. No official gender role index exists, therefore the construction of the index was extrapolated from available evidence in other populations. Additionally, given that there is no current criterion standard or consensus for the ideal measure to capture gender identity, we acknowledge that we selected the BSRI-12 as it the most commonly used questionnaire. Future research may focus on developing population-specific gender role indices and universally validated tools to assess gender identity. Moreover, ongoing work in this area should place a greater focus on examining exercise behaviours in non-sex typed individuals (i.e. androgynous and undifferentiated), especially across the lifespan and across health conditions.

Our study did not take into account other psychological variables such as apathy and depression that may potentially be associated with exercise behaviours, and we also acknowledge that the sample size for this preliminary analysis was small. Future research should consider implementing questionnaires assessing other post-stroke psychological changes which may be influential on exercise self-efficacy, outcome expectations and exercise motivation in individuals with stroke.

## 2.6 Conclusions

Results from this study are the first to provide insight into the associations between gender roles and gender identities with psychosocial variables related to exercise in stroke. We demonstrated that there are gender identity differences in exercise self-efficacy, where individuals possessing masculine gender identities had the highest exercise self-efficacy and, individuals possessing feminine gender identities had the least favorable outcomes. Our findings also suggest that although psychosocial changes are common after stroke, gender roles and identities may not influence these variables to the extent that we may have expected.

Our study also provides an important framework for the assessment of gender constructs in individuals with stroke. We provided preliminary evidence that gender roles can be captured through the construction of gender role index and that gender identity can be assessed through well-known tools, such as the BSRI-12. There remains a need for validated gender indices to evaluate gender roles and identities that are specific to the population of interest.

# Chapter 3

## Study 2- Is Cognitive Function Associated with Arterial Stiffness and Walking Capacity and Sex in Older Males and Females with and without Stroke?

## Abstract

**Introduction:** Cognitive impairment is reported in approximately 40% of older adults worldwide. Vascular health and functional capacity, namely arterial stiffness and low walking capacity, are associated with cognitive impairment. Preliminary evidence suggests that sex differences may exist in these associations, where males have stronger negative association between vascular and walking outcomes and cognitive impairment than females. The relationships between sex and cognitive impairment with vascular health and walking capacity have not been examined in older adults with and without stroke. Thus, the purpose of this study was to examine the associations between global cognitive function, arterial stiffness and sex, and between global cognitive function, walking capacity and sex in older male and female adults with and without stroke. We also wanted to determine if the addition of age, systolic blood pressure and history of stroke explained a portion of variance in these relationships. We hypothesized that global cognitive function would be associated with arterial stiffness and with walking capacity with an additional interaction of sex. We also hypothesized that age, systolic blood pressure and history of stroke would explain an additional portion of the variance in these relationships

**Methods:** Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA), arterial stiffness was assessed using the criterion standard of carotid-femoral pulse wave velocity (cfPWV), and walking capacity was assessed using the 6-minute walk test (6MWT). Stepwise multivariable regression analyses were performed to determine the influence of arterial stiffness and walking capacity on global cognitive function. Sex (male), along with sex*cfPWV or Sex*6MWT distance, were then added to the model and if appropriate age, systolic blood

pressure, and history of stroke. Candidate variables were added in a stepwise fashion until the models were no longer significant and the highest coefficient of determination was achieved.

**Results:** Sixty-two (24 females, 38 males) participants with (n=28) and without stroke (n=34) were included in this study. There was no association between global cognitive function and arterial stiffness, and no moderating effect of sex (Sex*cfPWV) was observed. Global cognitive function was associated with walking capacity, and the addition of sex and sex*6MWT together explained 19% of the variance of the MoCA score. Additional candidate variables of history of stroke and age provided the best model fit, together explaining 21% of the variance of the MoCA score.

**Conclusion:** While we did not find an association between cognitive function and arterial stiffness and no moderating effect of sex, we did observe that cognitive function was associated with walking capacity, with potential sex differences favouring female sex in this association. The addition of history of stroke and age added modestly to the proportion of explained variance in global cognitive function. The results from this study are important first steps for examining sex-based differences in the associations between various risk factors for cardiovascular disease.

### 3.1 Background

Cognitive impairment is reported in approximately 40% of older adults worldwide (Hu et al., 2017). Individuals with cognitive impairment experience greater difficulty with activities of daily living (Tabert et al., 2002), experience higher prevalence of depression, apathy, irritability, report lower quality of life (Lyketsos et al., 2002), and are at higher risk of cardiovascular disease and mortality (Hussin et al., 2019; Leritz et al., 2011).

Well-established, traditional risk factors for cardiovascular disease, such as hypertension, type II diabetes and hyperlipemia, have also been shown to be risk factors for cognitive impairment (Novak & Hajjar, 2010). Arterial stiffness, which reflects gradual fragmentation and loss of elastin and accumulation of collagen fibers in the arterial wall (Wagenseil & Mecham, 2012) has gained attention as a novel risk marker of both cardiovascular disease (Mitchell et al., 2010) and cognitive impairment (Alvarez-Bueno et al., 2020). A recent systematic review (38 studies, n=43,115) of older adults with and without a range of health conditions such as stroke, hypertension, Parkinson's disease, and impaired glucose tolerance reported a negative relationship between arterial stiffness and cognition (Alvarez-Bueno et al., 2020). The relationships with arterial stiffness were observed specifically in cognitive domains of executive function, memory, and global cognition (Alvarez-Bueno et al., 2020).

The criterion method for assessing arterial stiffness is carotid-femoral pulse wave velocity (cfPWV). cfPWV is measured by determining the travel time of an arterial pulse wave between the carotid and femoral arteries providing a measure of overall velocity (Van Bortel et al., 2012). Faster velocities indicate greater stiffness, whereby higher stiffness is associated with a greater risk for cardiovascular events including stroke (Lee et al., 2014), myocardial infarction (Mitchell et al., 1997), and heart failure (Chae et al., 1999; Kostis et al., 2001).

The inverse association between cognition and arterial stiffness is influenced by many factors, most commonly blood pressure, age, cardiovascular risk factors, and sex.

Individuals with hypertension exhibit elevated cfPWV and reduced cognitive function (Kearney-Schwartz et al., 2009; Muela et al., 2018; Triantafyllidi et al., 2009). Aging affects both vascular systems and cognitive function (Hazzouri & Yaffe, 2014), whereby adults over the age of 45 exhibited greater arterial stiffness and reduced function in all five domains of cognition and global cognition, in comparison to younger adults 30-45 years old (Csipo et al., 2019; Pase et al., 2016). Stroke is also known to result in vascular dysfunction (Chen et al., 2017; Tuttolomondo et al., 2010), with reports of cognitive impairment being highly prevalent in these individuals (Cumming et al., 2013). To date, only one study has reported a negative association between global cognition and arterial stiffness in individuals with stroke ($r=-0.45$, $p<0.001$) (Lee et al., 2014).

Very few studies have implemented sex-and gender-based considerations into research that examines the association between cognitive function and arterial stiffness. In four studies that incorporated sex-based analysis into the research design, higher arterial stiffness was associated with lower cognitive function in males in comparison to females, specifically in executive function and memory domains (Kearney-Schwartz et al., 2009; Sabra et al., 2020; Singer et al., 2013; Waldstein et al., 2008).

Aerobic capacity is also known to influence cognitive function in older adults, where higher levels of aerobic capacity have been associated with the preservation of cognitive function in older adults and reduced risk of developing dementia (Gomez-Pinilla & Hillman, 2013). Aerobic capacity can be assessed using more clinically feasible measures such as functional tests of walking capacity, often expressed as the maximum distance walked within a specified duration of time (Wert et al., 2013). The 6-Minute Walk Test (6MWT) (Butland et al., 1982) is a well-established functional assessment of walking capacity (Dunning, 2011) that has been used in studies to examine the relationship between walking capacity and cognitive function. Higher walking capacity in older adults with and without chronic conditions, quantified by greater distance walked on the 6MWT, has been shown to be associated with greater global cognition (Baldasseroni et al., 2010; Cavalcante et al., 2018; Ferreira et al., 2015; Hayashi et al., 2018; Lord & Menz, 2002; Matthé et al., 2015), memory function (Cavalcante et al., 2018; Ferreira et al., 2015; Makizako et al., 2013), attention (Ferreira et al., 2015; Schure et al., 2016; Sherwood et al., 2019), verbal fluency (Ferreira et al., 2015; Sherwood et al., 2019), and executive function (Ferreira et al., 2015; Loprinzi, 2016;  Sherwood et al., 2019).

Blood pressure, age, history of stroke, and sex may also be influential in the relationship between cognitive function and walking capacity (i.e. aerobic capacity) in older adults.

High blood pressure is independently and negatively related to both cognitive function (Iadecola et al., 2016; Reitz & Luchsinger, 2007) and aerobic capacity (Juraschek et al., 2014). In a study of individuals with peripheral artery disease, 85% of whom presented with hypertension, lower 6MWT distance was related to worse performance on tests of memory and global cognition (Cavalcante et al., 2018). There also appears to be a stronger negative association between cognitive function and 6MWT in individuals with low brachial-ankle index (used for detecting peripheral artery disease) and hypertension (mean systolic blood pressure 147 mmHg) in comparison to healthy older adults (Ferreira et al., 2015).

Aging is associated with both declines in cognition (Murman, 2015), and walking capacity (Cunningham et al., 1982), where individuals with stroke are known to present with lower walking capacity, as assessed using the 6MWT (Carvalho et al., 2013; Danielsson et al., 2011; Enright et al., 2003; Fulk et al., 2010; Kubo et al., 2018; Muren et al., 2008; Patterson et al., 2007; Polese et al., 2013). Individuals with stroke may have difficulties engaging in sustained levels of physical activity (Törnbom et al., 2017), thus potentially contributing to declines in aerobic capacity and further cognitive impairment (Wendell et al., 2014). A study examining the relationship between global cognitive function and 6MWT in individuals with stroke demonstrated that higher 6MWT distance was related to better performance on the Mini-Mental State Examination ($r=0.37$, $p<0.001$) (Lee et al., 2014).

To date, no study has investigated sex differences in the relationship between cognitive function and walking capacity, but there is evidence to suggest that physiological mechanisms may favour female sex in this relationship. Older males have demonstrated greater rate of decline in peak oxygen consumption (Buskirk & Hodgson, 1987; Fleg et al., 2005; Hossack & Bruce, 1982; Stathokostas et al., 2004; Toth et al., 1994; Weiss et al., 2006), cardiac output, and arteriovenous difference (Weiss et al., 2006) in comparison to older females. Given that cardiac function is associated with cognitive decline (Oh et al., 2012), males may be more susceptible to subsequent cognitive decline and be at increased risk of earlier onset of cognitive impairment. Taken together, these sex-specific physiological differences may suggest a more favourable association between cognitive function and walking capacity in females.

### 3.2 Objectives and Hypotheses

While the associations between cognitive function and arterial stiffness and cognitive function and aerobic fitness (walking capacity) are well established in many populations, no study to date has examined whether these associations differ between older male and female adults with and without stroke. Furthermore, it is currently unknown whether demographic (i.e. age) and clinical (i.e. blood pressure and history of stroke) variables mediate the associations between global cognitive function, arterial stiffness, and sex and global cognitive function, walking capacity, and sex. Thus, the objectives of this study were two-fold:

- Study Objective #1 (Primary Objective): Examine the associations between global cognitive function, arterial stiffness and sex, and between global cognitive function, walking capacity and sex in older male and female adults with and without stroke.

  *Specific hypothesis:* Cognitive function would be associated with arterial stiffness and with walking capacity with an additional interaction of sex

- Objective #2: Determine if the addition of age, systolic blood pressure and history of stroke explains a portion of variance in the relationships between global cognitive function, arterial stiffness or walking function, and sex.

  *Specific hypothesis:* The addition of age, systolic blood pressure and history of stroke would explain an additional portion of the variance in the relationships between global cognitive function, arterial stiffness or walking function, and sex.

## 3.3 Methodology

### 3.3.1 Study Design

This study was a secondary cross-sectional analysis of data collected from 3 studies of individuals living in the community with stroke: a multi-site randomized controlled trial in individuals with stroke (McMaster University Hamilton Integrated Research Ethics Board (HIREB 4713; McGill University Centre de Recherche Interdisciplinaire en Réadaptation du Montréal Métropolitain (CRIR-1310-0218)), a prospective single-group study in individuals with stroke (HIREB 3113) and an observational cohort study in individuals with and without stroke (HIREB 13-348). The study procedures were followed in accordance to guidelines outlined by each institution's research ethic committees. Informed written consent was obtained from all participants.

### 3.3.2 Participants

The eligibility criteria for individuals with stroke for all three studies were similar. Participants with stroke were recruited from the community, through local community stroke groups and from a database of former research participants who consented to be contacted for future research studies. Community dwelling adults without stroke were also recruited through databases of former research participants who consented to be contacted for future studies.

Individuals with stroke were eligible to participate in the randomized controlled trial if they were 40-80 years old, 6-60 months following their first-ever stroke (confirmed by neuroimaging scan), living in the community and able to walk at least 10-meters independently. Participants were excluded if they had a stroke of non-cardiogenic origin or tumor, were actively engaged in stroke rehabilitation or a structured exercise program within the past 6 months, scored <2 on the Modified Rankin Scale, any contraindications to exercise testing or training as set forth by the American College of Sports Medicine Guidelines of Exercise Testing and Prescription (*ACSMs Guidelines for Exercise Testing and Prescription, 2017)*, presented any class C or D American Heart Association Risk Criteria, presented with other neurological or musculoskeletal comorbidities, pain worsened with exercise, or cognitive, communication, or behavioural issues that could limit their ability to provide consent or follow instructions.

The same eligibility criteria were followed in the prospective single-group and cohort studies, with the exception that there was no upper limit on time post-stroke (≥ 6 months) nor Modified Rankin Scale criterion for the individuals with stroke in the cohort study.

### 3.3.3 Assessments

Study assessments took place within a one-week period. Participants demographic information, including age, biological sex and medical history were obtained in all participants. All cardiovascular-related data were collected in the Vascular Dynamics Lab at McMaster University and the Memory Lab at McGill University, where participants were asked to refrain from the ingestion of food or drink 4 hours prior to testing. Furthermore, participants were also asked to refrain from physical activity 24 hours prior to their visit.

In the participants with stroke, stroke lesion type and location, time post-stroke, and degree of neurologic deficit using the National Institutes of Health Stroke Scale (Brott et al., 1989) were collected. The National Institutes of Health Stroke Scale is a 11-item scale that gives a sampling of level of alertness, motor and sensory function, and language to provide an overall indication of severity of stroke (maximum score 42, where higher scores indicate greater severity) (Brott et al., 1989).

**Cognitive Function:** Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA) (Appendix 3), which was developed for the purpose of detecting cognitive impairment (Nasreddine et al., 2005). The MoCA assesses specific domains of cognition, which include attention, memory, visuospatial abilities, language, abstraction, concentration and orientation (Nasreddine et al., 2005). A cumulative score is calculated to provide an indication global cognition, where the maximum possible score is 30, with higher scores indicative of better cognitive function and a score <26 implies mild cognitive impairment (Nasreddine et al., 2005).

The MoCA has excellent sensitivity (90%) and specificity (87%) in its abilities to detect mild cognitive impairment in older adults (Nasreddine et al., 2005), excellent internal consistency (Cronbach's Alpha=0.83) and concurrent validity with the Mini-Mental State Examination (r=0.87) (Nasreddine et al., 2005). Furthermore, the MoCA has high sensitivity and specificity in a cardiovascular population (McLennan et al., 2011) and is a feasible tool for cognitive screening in individuals with stroke (Cumming et al., 2013).

**Resting Blood Pressure***:* Participants rested comfortably supine in a quiet, temperature-controlled laboratory for ten minutes prior to measurement of supine brachial artery systolic and diastolic blood pressure using an automated blood pressure machine (DINAMAP, V100 vital signs monitor, Critikon Inc). Blood pressure was assessed in the dominant arm in individuals without stroke, and in the unaffected arm of individuals with stroke. The average of two readings were recorded, but if values differed by more than 5 mmHg, two additional measures were performed and averaged across 4 readings (Pickering et al., 2005). Systolic blood pressure values (mmHg) were used for analysis, as it is a better predictor of cardiovascular risk factors than diastolic blood pressure (Mourad, 2008).

**Arterial Stiffness:** Following ten minutes of supine rest, central arterial stiffness was measured non-invasively using applanation tonometry (Millar SPT-301, Millar Inc Houston, TX, USA) to collect arterial pressure waveforms at the carotid and femoral arteries on dominant side for individuals without stroke, and on the unaffected side for individuals with stroke. Twenty continuous waveforms were collected by two trained assessors (hardware PowerLab model ML870, AD instruments, Colorado Springs, USA; software LabChart 7 and 8, AD instruments, Colorado Springs, USA) to determine cfPWV. An anthropometric tape measure was used to determine the distance between the carotid and femoral artery pulse sites, and 80% of the direct measure between the two arteries was calculated to reflect the true distance travelled in the arterial tree (Distance, $D$ = common carotid artery - common femoral artery x 0.8, in meters) (Van Bortel et al., 2012). cfPWV was calculated as $D$(m)/Δ$t$ (sec), where $D$(m) represents the distance between the two points along the arterial tree and $\Delta t$ is the transit time of pulse waves between the carotid and femoral arteries.

**Walking Capacity**: The 6MWT (Butland et al., 1982) was used to assess walking capacity. Per standardized guidelines (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories, 2002), participants were instructed to walk as far as possible over the course of 6 minutes. The total distance covered was recorded. In order to ensure participant safety, resting and peak blood pressure and heart rate were recorded, and rate of perceived exertion was determined at the end of the test. Participants were permitted to use gait aids and were allowed a rest period throughout the test if needed. Assessors refrained from providing encouragement throughout the test.

In older adults, the 6MWT has high test-retest reliability, high convergent validity with maximal treadmill testing (r=0.71 in males and 0.82 in females) and construct validity in its ability to distinguish between older (60-69 years) and elderly adults (80-89) ($F(2,74)=10.7$, $p<0.001$) and low-active and high-active individuals ($F(1,74)=37.5$, $p<0.001$) (Rikli & Jones, 1998). In individuals with stroke, 6MWT distance has excellent test-retest reliability (ICC=0.99)

(Eng et al., 2004), and concurrent validity with the Functional Independence Measure – locomotion (Spearman rho=0.69) and motor subscales (Pearson r=0.52) (Fulk et al., 2008), $VO_2$ peak (r=0.66-0.72) (Eng et al., 2004;Tseng & Kluding, 2009), and Five Meter Walk velocity for preferred (r=0.79) and fast speed (r=0.82) (Tang et al., 2006).

### 3.3.4 Statistical Analyses

Participant demographics were described using descriptive mean and standard deviations for normally distributed continuous variables. Categorical variables were described using frequency (percentage) and skewed data were summarized using median and interquartile range. All data was analyzed using StataIC Version 15 (College Station TX, USA) and a two-tailed significance test with an alpha of 0.05 was set.

*Objective #1: Examine the associations between global cognitive function, arterial stiffness and sex, and between global cognitive function, walking capacity and sex in older male and female adults with and without stroke.*

To address Objective #1, bivariate correlation analyses were conducted, data were visually inspected for outliers and distribution, and assumptions for normality were tested using the Shapiro-Wilk test, while assumptions for heteroskedasticity were tested using the Cook-Weisberg test. Stepwise multivariable regression analyses were then performed to determine the influence of arterial stiffness and walking capacity (independent variables) on global cognitive function (dependent variable). Separate models for arterial stiffness and walking capacity were performed. To determine if there was an interaction of sex on the associations between cognitive function arterial stiffness, and walking capacity; variables of sex (male), along with sex*cfPWV or sex*6MWT distance, were included in the models.

*Objective #2: Determine if the addition of age, systolic blood pressure and history of stroke explains a portion of variance in the relationships between global cognitive function, arterial stiffness or walking function, and sex.*

To address Objective #2, bivariate correlations between all variables were conducted, as well as stepwise multivariable regression analyses with additional candidate variables to determine the best model of fit. Given the sample size of 62 participants, up to 6 variables were included in our regression models (Vittinghoff et al., 2012). Systolic blood pressure, age, and history of stroke are known to be influential on arterial stiffness and walking capacity and thus were explored as additional potential correlates with global cognitive function, along with arterial stiffness, walking capacity, and sex. Candidate variables were added in a stepwise fashion until the models were no longer significant and the highest coefficient of determination was achieved. Separate models for arterial stiffness and walking capacity were performed.

### 3.4 Results

In total, 64 participants were enrolled in the three trials. The MoCA was not administered for two individuals with stroke due to aphasia and a language barrier. Therefore, 62 (24 females and 38 males) participants were included in the analysis. A flow chart of participants through the study is provided in Figure 7.

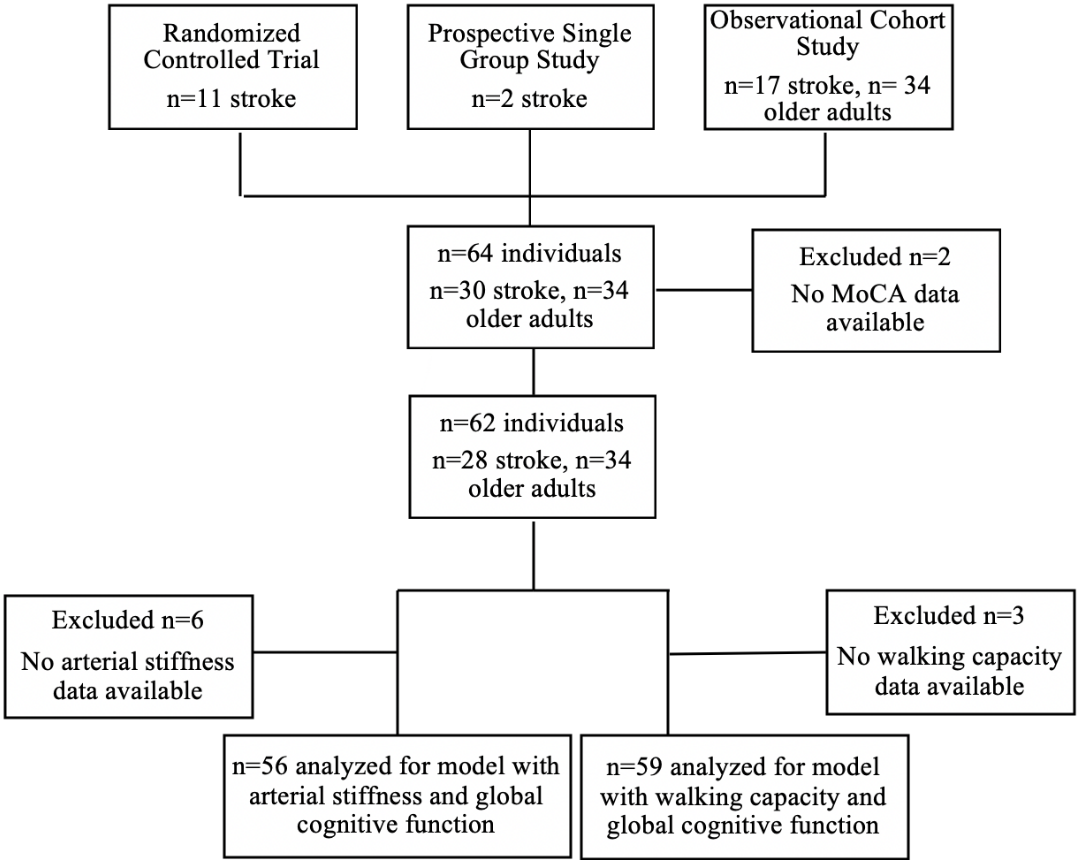



**Figure 7. Flow chart of participants through the study**

Participant characteristics are described in Table 3. The median MoCA score was 25, which was below the threshold of 26 and thus suggesting mild cognitive impairment (Nasreddine et al., 2005). Distances walked for the 6MWT fell within the range of reference values for older adults between 60 and 69 years (497-623m) (Steffen et al., 2002) and similarly, cfPWV values were within reference ranges for older adults 60-69 years of age (mean 10.3 m/s, range 5.5-15.0 m/s) (Reference Values for Arterial Stiffness' Collaboration, 2010). Systolic blood pressure values suggested that participants were in Stage 1 Hypertension (>130 mmHg) (Pickering et al., 2005).

**Table 3. Participant Characteristics (n=62)**

| Characteristics | n | Values |
|---|---|---|
| **Sex** | 62 | |
| Females, n (%) | | 24 (38.7) |
| Males, n (%) | | 38 (61.3) |
| Age (years), median (IQR), min-max | 62 | 68 (10.0), 42-80 |
| Montreal Cognitive Assessment, median (IQR), min-max | 62 | 25 (4.0), 13-30 |
| Carotid-femoral pulse wave velocity (m/s), median (IQR), min-max | 56 | 9.6 (2.5), 5.5-18.7 |
| 6-Minute Walk Test distance (meters), mean (SD), min-max | 59 | 473.1 (115.2), 203-750 |
| **Gait Aid, n (%)** | 62 | |
| None | | 57 (92.0) |
| Single Point Cane | | 3 (4.8) |
| Quad Cane | | 1 (1.6) |
| Rollator | | 1 (1.6) |
| Resting Systolic Blood Pressure (mmHg) mean (SD), min-max | 61 | 129.7 (13.8),101-159 |
| Resting Diastolic Blood Pressure (mmHg), mean (SD), min-max | 61 | 73.9 (9.6), 53-100 |
| Antihypertensive and lipid lowering agents (No), n (%) | 62 | 28 (45.2%) |

Abbreviations. IQR=Interquartile Range, SD=Standard Deviation, mmHg= Millimetres of Mercury

Furthermore, there were no sex differences in any variables of interest, with the exception of blood pressure, whereby males demonstrated higher values for both systolic and diastolic pressure. See Table 4 for participant demographics disaggregated by sex.

**Table 4. Participant Characteristics Disaggregated by Sex (n=62)**

| | Males | | Females | | p-value |
|---|---|---|---|---|---|
| | n | Values | n | Values | |
| Age (years), median (IQR), min-max | 38 | 70 (12.0), 42-80 | 24 | 68.0 (5.0), 47-76 | 0.40 |
| Montreal Cognitive Assessment, median (IQR), min-max | 38 | 24 (5.0), 13-30 | 24 | 26 (4.0), 17-29 | 0.06 |
| Carotid-femoral pulse wave velocity, m/s, median (IQR), min-max | 36 | 9.9 (3.8), 5.5-18.7 | 20 | 9.5 (2.1), 7.3-13.8 | 0.37 |
| 6-Minute Walk Test distance (meters), mean (SD), min-max | 36 | 474.8 (130.9), 203-749 | 23 | 470.4 (87.7), 253-601 | 0.89 |
| Resting Systolic Blood Pressure (mmHg), mean (SD), min-max | 38 | 133.5 (13.8), 104-159 | 23 | 123.3 (11.4), 101-145 | <0.01* |
| Resting Diastolic Blood Pressure (mmHg), mean (SD), min-max | 38 | 77.8 (9.2), 60-100 | 23 | 67.6 (6.4), 53-79 | <0.01* |

*P<0.05
Abbreviations. IQR=Interquartile Range, SD=Standard Deviation, mmHg= Millimetres of Mercury

Of the 28 individuals with stroke, the median time post-stroke was 3.5 years (IQR 2.7). Fifteen (53.6%) individuals experienced ischemic stroke, 6 (21.4%) individuals experienced hemorrhagic stroke, and 7 (25%) individuals experienced strokes of unknown origin. Right and left limbs were affected equally (n=14 (50%) each). Strokes were of mild to moderate severity as evidenced by mean National Institutes of Health Stroke Scale score of 2 (SD 1.2) (Brott et al., 1989). A comparison of outcome measures between individuals with and without history of stroke are provided in Appendix 5.

*Objective #1A: Examine the associations between global cognitive function, arterial stiffness and sex*

In multivariable regression analysis, there were no associations between MoCA scores and iterative models with cfPWV (Table 5, Model 1), male sex (Model 2), or the interaction of Sex*cfPWV (Model 3) (see Appendix 4 for scatterplots and correlation matrix of variables included in analyses).

*Objective #1B: Determine if the addition of age, systolic blood pressure and history of stroke explains a portion of variance in the relationships between global cognitive function, arterial stiffness, and sex*

We did not proceed with analyses with additional candidate variables of age, SBP, and history of stroke, as the primary analyses with arterial stiffness and sex were not significant.

**Table 5. Stepwise multivariable regression analysis to examine the relationship between global cognitive function (MoCA, dependent variable), arterial stiffness (cfPWV) and male sex**

| Variables | $R^2$ | $R^2$ change | Unstandardized B (SE) | Standardized B | 95% CI | p-value |
|---|---|---|---|---|---|---|
| *Model 1: F (1,54) = 0.06* | 0.001 | | | | | 0.81 |
| cfPWV | | | -0.04 (0.2) | -0.03 | -0.04, 0.33 | 0.81 |
| *Model 2: F (2,53) =2.05* | 0.072 | 0.071 | | | | 0.14 |
| cfPWV | | | 0.02 (0.2) | 0.01 | -0.35, 0.39 | 0.92 |
| Male Sex | | | -1.95 (0.9) | -2.69 | -3.89, -0.003 | 0.05 |
| *Model 3: F (3,52) =1.37* | 0.073 | 0.001 | | | | 0.26 |
| cfPWV | | | 0.15 (0.5) | 0.11 | -0.82, 1.13 | 0.75 |
| Male Sex | | | -0.41 (5.2) | -0.06 | -10.83, 10.01 | 0.94 |
| Male Sex*cfPWV | | | -0.15 (0.5) | -0.25 | -1.21, 0.89 | 0.76 |

***Note.*** cfPWV= carotid-femoral Pulse Wave Velocity

*Objective #2A: Examine the associations between global cognitive function, walking capacity and sex*

Global cognitive function was associated with walking capacity with over 12% of the variance of MoCA scores was explained by 6MWT distance (Table 6, Model 1). The addition of male sex (Model 2), and Sex*6MWT (Model 3, Figure 8) together explained an additional 6.5% of the variance of the MoCA score (see Appendix 4 for scatterplots and correlation matrix of variables included in analyses). Additionally, when data were fully disaggregated by sex, a positive relationship between global cognitive function and walking capacity were observed in females (β= 0.02, SE=0.007, 95%CI: 0.005, 0.03, p=0.01), but not in males (β= 0.009, SE=0.005, 95%CI: -0.0005, 0.02, p=0.06).

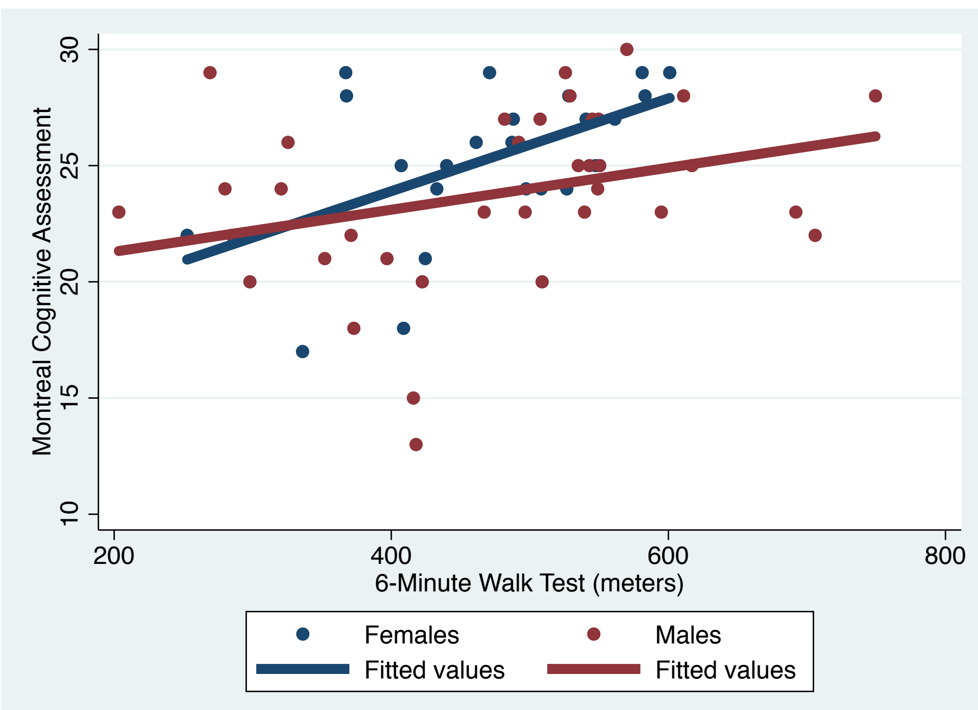



**Figure 8. Association between Montreal Cognitive Assessment scores and 6-Minute Walk Test by sex**

*Objective #2B: Determine if the addition of age, systolic blood pressure and history of stroke explains a portion of variance in the relationships between global cognitive function, walking capacity, and sex*

With the iterative models with additional candidate variables (Table 6, Models 4-6), age, and history of stroke, together with 6MWT, male sex, and Sex*6MWT was the best model fit, explaining 21% of the variance of the MoCA score (Table 6, Model 5). Moreover, the 6MWT remained an independent correlate with global cognitive function (β= 0.02, SE=0.009, 95%CI: 0.001, 0.04, p=0.04). The addition of systolic blood pressure did not enhance the overall model (Table 6, Model 6).

**Table 6. Stepwise multivariable regression analysis to examine the relationship between global cognitive function (MoCA, dependent variable) and walking capacity (6MWT) and male sex**

| Variables | $R^2$ | $R^2$ Change | Unstandardized B (SE) | Standardized B | 95%CI | p-value |
|---|---|---|---|---|---|---|
| *Model 1: F (1,57) =8.25* | 0.126 | | | | | <0.01* |
| 6MWT | | | 0.01 (0.004) | 0.36 | 0.003, 0.19 | <0.01* |
| *Model 2: F (2,56) =5.78* | 0.171 | 0.045 | | | | <0.01* |
| 6MWT | | | 0.01 (0.004) | 0.36 | 0.004, 0.02 | <0.01* |
| Male Sex | | | -1.58 (0.9) | -0.21 | -3.40, 0.24 | 0.09 |
| *Model 3: F (3,55) =4.34* | 0.191 | 0.020 | | | | <0.01* |
| 6MWT | | | 0.02 (0.008) | 0.63 | 0.004,0.04 | 0.02* |
| Male Sex | | | 3.58 (4.5) | 0.48 | -5.41,12.56 | 0.43 |
| Male Sex*6MWT | | | -0.01(0.009) | -0.76 | -0.30, 0.008 | 0.25 |
| *Model 4: F (4,54) =3.27* | 0.200 | 0.009 | | | | 0.02* |
| 6MWT | | | 0.02 (0.008) | 0.65 | 0.004, 0.04 | 0.02* |
| Male Sex | | | 3.21 (4.5) | 0.43 | -5.86, 12.29 | 0.48 |
| Male Sex*6MWT | | | -0.01 (0.009) | -0.71 | -0.03, 0.009 | 0.28 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Age | | | -0.04 (0.6) | -0.10 | -0.16, 0.08 | 0.46 |
| *Model 5: F (5,53) =2.83* | 0.211 | 0.011 | | | | 0.02* |
| 6MWT | | | 0.02 (0.009) | 0.59 | 0.001, 0.04 | 0.04* |
| Male Sex | | | 3.17 (4.5) | 0.43 | -5.94, 12.27 | 0.49 |
| Male Sex*6MWT | | | -0.009 (0.009) | -0.66 | -0.03, 0.009 | 0.32 |
| Age | | | -0.07 (0.07) | -0.15 | -0.20, 0.06 | 0.31 |
| Stroke | | | -1.03 (1.2) | -0.14 | -3.41, 1.35 | 0.39 |
| *Model 6: F (6, 51) =2.21* | 0.207 | -0.004 | | | | 0.06 |
| 6MWT | | | 0.01 (0.009) | 0.50 | -0.004, 0.03 | 0.12 |
| Male Sex | | | 0.09 (4.8) | 0.01 | -9.46, 9.63 | 0.99 |
| Male Sex*6MWT | | | -0.004 (0.009) | -0.27 | -0.02, 0.02 | 0.71 |
| Stroke | | | -0.82 (1.2) | -0.12 | -3.27, 1.62 | 0.50 |
| Age | | | -0.08 (0.07) | -0.19 | -0.22, 0.06 | 0.26 |
| SBP | | | -0.002 (0.04) | -0.007 | -0.08, 0.77 | 0.96 |

*P<0.05

***Note.*** 6MWT= 6-Minute Walk Test, SBP= Systolic Blood Pressure, SE= Standard Error, Stroke=History of Stroke

### 3.5 Discussion

This study was the first to examine sex differences in the associations between global cognitive function with arterial stiffness and walking capacity among older males and females with and without stroke. While we did not find an association between cognitive function and arterial stiffness and no moderating effect of sex, we did observe that walking capacity was independently associated with global cognitive function, where greater distance walked on the 6MWT was positively associated with MoCA scores. Moreover, we found that females achieving greater walking distances on the 6MWT attained higher MoCA scores compared to males with similar walking capacities.

A positive relationship between global cognition and 6MWT have been reported in older adults, but potential sex differences in this association is a novel finding. It is well-established that older males experience accelerated declines from the sixth to ninth decade of life in measures of cardiovascular health and function, such as aerobic capacity (Buskirk & Hodgson, 1987; Fleg et al., 2005; Hossack & Bruce, 1982; Stathokostas et al., 2004; Toth et al., 1994; Weiss et al., 2006), cardiac output, and arteriovenous difference (Weiss et al., 2006), compared to older females. Given that cardiac dysfunction is strongly associated with cognitive decline (Oh et al., 2012), sex-based differences in reductions in cardiovascular health appear to suggest that males may be at higher risk for onset of cognitive impairment. Males experience declines in aerobic capacity of 5% at age 30 to 24% beyond age 70 (net 19% reduction), compared to females who change from 6% to 18% (net 12% reduction) (Fleg et al., 2005). Indeed, the mean age of our sample approximates the age where accelerated declines in aerobic capacity become apparent in males and thus may contribute to our findings suggesting that declines in walking capacity may be associated with earlier onset of cognitive impairment in males.

Age and history of stroke were also included in the final model explaining the association between global cognition, walking capacity and sex, with previous literature supporting these findings (Lee et al., 2014; Lord & Menz, 2002; Matthé et al., 2015; Sherwood et al., 2019). Cognitive impairment has been reported in up to 70% of individuals with stroke (Rasquin et al., 2004), whereby white matter lesions and associated cerebral atrophy are the primary underlying mechanisms related to post-stroke cognitive impairment (Koga et al., 2009), in addition to cerebral microbleeds (Cordonnier et al., 2007; Werring et al., 2004). Age has also been linked to progressive reductions in cognitive performance (Murman, 2015), with the greatest declines occurring from the sixth decade but can begin as early as in the second decade of life (Salthouse, 2009). Age-associated reductions in grey matter volume resulting from decreased neuronal sizing and synaptic density occur from the second decade of life onward (Terry & Katzman, 2001), while decreased white matter volume have been implicated in decline in cognitive function beyond age 60 (Breteler, van Swieten, et al., 1994; Lindgren et al., 1994).

Interestingly, systolic blood pressure, which has been related to both aerobic fitness (Blair et al., 1984; Chase et al., 2009) and cognitive impairment (Iadecola et al., 2016), was not included in the final model. Hypertension is known to disrupt cerebral structures and contribute to white matter lesions (Harmsen et al., 2017; Iadecola et al., 2016) with clear scaled response where older adults with Stage 2 hypertension perform worse on measures of global cognition compared to individuals with Stage 1 hypertension and normal SBP values (Heizhati et al., 2020; Muela et al., 2017). Moreover, previous studies in older adults with a high proportion of individuals with hypertension have shown a negative relationship between lower 6MWT and impaired cognitive function (Cavalcante et al., 2018; Ferreira et al., 2015). Of note, the population of interest in these previous studies included individuals with peripheral artery disease and low ankle-brachial index and thus the negative relationships observed may have been as a result of other comorbidities associated with these conditions rather than the presence of hypertension. Thus, the independent contributions of SBP on the relationship of global cognitive function and walking capacity warrants further investigation in the general and clinical populations.

Contrary to our hypothesis, we did not find any associations between global cognitive function and arterial stiffness. A recent systematic review and meta-analysis revealed a negative association between arterial stiffness and measures of global cognition in both older adults with and without health conditions (Alvarez-Bueno et al., 2020). We note that more than two thirds of our sample presented with cfPWV values within age-referenced values for older adults between 60-70 years of age and thus being at a lower risk for negative cardiovascular health outcomes

(Reference Values for Arterial Stiffness' Collaboration, 2010). Thus, the lack of association may be a result of a relatively small portion of individuals having elevated arterial stiffness. These findings are indeed interesting as individuals with stroke (Tang et al., 2014) and older adults (>50 years old) (Oishi et al., 2011) are known to have elevated arterial stiffness. Thus, future studies may consider examining the association between MoCA scores and arterial stiffness in a broad range of vascular health in a larger cohort.

In addition, there were no sex differences in the association between cognitive function and arterial stiffness in this current study. This is in contrast to previous studies reporting inverse associations between arterial stiffness and memory (Kearney-Schwartz et al., 2009; Singer et al., 2013; Waldstein et al., 2008) and executive function (Sabra et al., 2020) in males only. Arguably, memory and executive function are cognitive domains in which females are known to outperform males, potentially explaining why the associations were more favourable in females in these earlier studies. Future larger-scaled studies should consider examining sex-based differences in arterial stiffness through the administration of a comprehensive cognitive battery, encompassing all five domains of cognition, as little is known if sex differences in this association exists in the attention, language and visuospatial domains.

*Limitations*

We acknowledge that there are limitations to this study. While we aimed to include individuals with and without stroke with a broad range of physical and functional abilities, the sample size of this study may have been underpowered to detect sex-based differences in arterial stiffness and global cognition.

We were also limited by the number of variables that could be accommodated in our regression models. Additional potentially explanatory variables such as antihypertensive medication use, BMI, education level and race may be considered for inclusion into regression analyses in future research.

### 3.6 Conclusion

This study was the first to examine the associations between global cognitive function and arterial stiffness and walking capacity in males and females with and without history of stroke. While we did not find any association between global cognition, carotid-femoral pulse wave velocity, and sex, we did observe that global cognition was positively related to walking capacity, with females achieving greater MoCA scores for a given walking distance. Results from this study are important first steps for examining sex-based differences in the associations between various risk factors for cardiovascular disease. Where possible, research findings should be disaggregated by sex to ensure study rigour and promote health equity, even if sex-based differences are not always observed.

# Chapter 4

# DISCUSSION

**4.1 Discussion**

Sex and gender-based considerations are critical for clinical research in stroke recovery to advance our knowledge, to ensure scientific rigour, and promote health equity in stroke care. Understanding whether gender differences in psychosocial factors for exercise exist in individuals with stroke may incline clinicians to adapt approaches to promote exercise participation for individuals with diverse gender identities, particularly women possessing low exercise self-efficacy. Additionally, examining the relationship between novel and functional markers of cardiovascular health and cognition provides insight into the importance of sex-specific treatment focuses in clinical settings, where strategies aiming to improve cognition in males may be a priority.

*Study 1- Exploring the Associations Between Gender Roles and Identity with Psychosocial Factors for Exercise Post-Stroke*

To our knowledge, this was the first study to date to explore gender-based differences in psychosocial variables for exercise in individuals with stroke. Study findings suggested that individuals with stroke possessing masculine gender identities had the highest exercise self-efficacy, whereas those possessing feminine gender identities had the lowest exercise self-efficacy. Our findings also suggested that there were no associations between gender roles, exercise self-efficacy, outcome expectations and motivation for exercise and no differences between gender identity constructs and outcome expectations and motivation for exercise in individuals with stroke.

Lower exercise self-efficacy observed in the individuals with feminine gender identities is consistent with previous research in young adults (McAuley et al., 1991; Nehl et al., 2012; Pauline, 2013; Rosenkranz et al., 2011; Spence et al., 2010; Wittig et al., 1987), older adults (Chen et al., 2015; Lee, 2005; Scharff et al., 1999), and in individuals with type II diabetes

(Barrett et al., 2007; Chiu & Wray, 2011; Delahanty et al., 2006). Women stroke survivors often report altered perceptions of their physical self and physical function as a result of stroke related impairments (Lever & Pryor, 2017), contributing to lower self-esteem, which is directly linked to lower exercise self-efficacy and lower exercise participation (McAuley et al., 2005). Future studies may benefit from further examining the influence of self-esteem following stroke on exercise self-efficacy and other exercise behaviours.

The low exercise self-efficacy in individuals identifying as women may also have been a result of little opportunity for exercise due to the competing gender roles undertaken prior to stroke and thus providing very little opportunity for past exercise-related mastery experiences in older women. Thus, the low self-efficacy observed in women with stroke could have been established earlier in life, which were then strengthened as a result of stroke.

In contrast, the absence of negative associations between feminine gender roles and exercise self-efficacy, outcome expectations for exercise and motivation for exercise had not been previously reported in previous studies in older adults. Furthermore, we did not observe any gender identity differences in outcome expectations and motivation for exercise, which is also in contrast to previous work. Feelings of vulnerability and anxiety towards exercise (Carin-Levy et al., 2009), in addition to a loss of purpose and willingness to participate in exercise (Reed et al., 2010) and lowered priority of exercise for stroke recovery from perspectives of both stroke survivors (Rimmer et al., 2008) and clinicians (Moncion et al., 2020) may be independent of gender roles or identities. Depressive symptoms and apathy may also contribute to low internal motivation (autonomous) reported by individuals with stroke (van Dalen Jan Willem et al., 2013) and thus lower exercise participation and physical functioning (Mayo et al., 2009; Rochette et al., 2007), independent of gender roles or gender identity. Future studies may also consider collecting data on pre-stroke exercise behaviours and psychosocial status to examine whether our speculations that psychological changes following stroke may supersede the influence of gender-related factors on exercise behaviours are indeed relevant. In addition, future studies may incorporate assessments of apathy and depression to determine if these factors do indeed have an impact on both gender variables and psychosocial factors for exercise. Future studies should also consider examining gender-based differences in psychosocial variables for exercise in larger sample of individuals, particularly when examining the associations between gender roles and psychosocial variables.

It is also important to note that all studies examining exercise self-efficacy, outcome expectations for exercise, and motivation for exercise in older adults have been performed in sex-typed individuals identifying as either men or women without any consideration of individuals with androgynous or undifferentiated gender identities. It is critical that future studies examining these associations encompass individuals of all gender identities. Validated tools, such as the BSRI-12 may be used to evaluate gender identity between individuals.

Nonetheless, our findings provide a framework for examining gender-related factors in future studies in stroke. Currently, a validated tool for the measurement of gender roles in stroke has not yet been developed, thus a gender role index was constructed based on gender roles that have been well-established in the general older adult population. However, given that we did not observe any relationships, it is possible that stroke-specific impairments and functional limitations may have affected their capacity to perform roles undertaken prior to stroke (for example, a women with stroke may be unable to take primary responsibility for caregiving and household tasks), thus contributing to reversal from stereotypical gendered roles. These findings suggest that a gender role index constructed on typical roles in older adults may have not been applicable in our given cohort or that individuals with stroke undertake converge towards neutral roles, rather than distinct masculine or feminine gender roles. Future studies aimed at understanding what gender roles are undertaken in individuals with stroke may be the first step in better understanding gender-based differences in stroke.

*Study 2- Is Cognitive Function Associated with Arterial Stiffness and Walking Capacity and Sex in Older Males and Females with and without Stroke?*

We did not observe any association between cognitive function and arterial stiffness, and sex. The MoCA, a global measure of global cognition (Nasreddine et al., 2005), was used to assess cognitive function, whereas previous studies have examined specific domains, namely executive function (Sabra et al., 2020) and memory (Kearney-Schwartz et al., 2009; Singer et al., 2014; Waldstein et al., 2008). More than two thirds of our sample presented with cfPWV values within age-referenced values for older adults between 60-70 years of age and thus being at a lower risk for negative cardiovascular health outcomes (Reference Values for Arterial Stiffness' Collaboration, 2010). Thus, the lack of association may be a result of a relatively small portion of individuals having elevated arterial stiffness. Future studies should examine the association between global cognitive function, arterial stiffness, and sex in broader range of cfPWV values.

We observed an association between global cognitive function and 6MWT, with potential sex differences favouring female sex. It is well-established that older males experience accelerated declines from the sixth to ninth decade of life in measures of cardiovascular health and function (Buskirk & Hodgson, 1987; Fleg et al., 2005; Hossack & Bruce, 1982; Stathokostas et al., 2004; Toth et al., 1994; Weiss et al., 2006) compared to older females. Indeed, mean age of our sample approximates the age where accelerated declines in aerobic capacity become apparent in males and thus may contribute to our findings suggesting that declines in walking capacity may be associated with earlier onset of cognitive impairment in males.

Moreover, history of stroke and age explained an additional small proportion of the variance in cognitive function. We expected that these variables would be jointly predictive of cognitive function, as previous research has reported cognitive impairment in up to 70% of individuals with stroke (Rasquin et al., 2004; Yu et al., 2013), whereby white matter lesions and associated cerebral atrophy are the primary underlying mechanisms related to post-stroke cognitive impairment (Koga et al., 2009). Age-associated reductions in grey and white matter volumes have been implicated in decline in cognitive function for those aged 60 years and older (Breteler, van Swieten, et al., 1994; Lindgren et al., 1994; Terry & Katzman, 2001). Poorer performance on clinical measures of global cognition have indeed been associated with lower walking capacity in community dwelling older adults (Lord & Menz, 2002; Matthé et al., 2015; Sherwood et al., 2019) and individuals with stroke (Lee et al., 2014) and thus aligned with the findings in the current study. Future directions include examining if sex moderates the association between global cognition and walking capacity in individuals with stroke, as no study to date has examined sex-based differences in this population.

Interestingly, systolic blood pressure, which has been related to both aerobic fitness (Blair et al., 1984; Chase et al., 2009) and cognitive impairment (Iadecola et al., 2016), was not included in the final model. Previous studies in older adults with a high proportion of individuals with hypertension have shown a negative relationship between lower 6MWT and impaired cognitive function (Cavalcante et al., 2018; Ferreira et al., 2015). Of note, the population of interest in these previous studies included individuals with chronic conditions and thus the negative relationship observed may have been as a result of other comorbidities associated with these conditions rather than the presence of hypertension. Thus, the independent contributions of resting blood pressure on the relationship of global cognitive function and walking capacity warrants further investigation in the general and clinical populations.

### 4.2 Clinical Significance

Given that sex and gender considerations in clinical research is significantly underreported and misunderstood (Tannenbaum et al., 2016), studies incorporating sex-and gender-based considerations at all levels of the research process, which include the planning of the research question, the research design, data collection and analysis, reporting and dissemination contribute the narrowing the gaps in this critical field (Government of Canada, 2019).

Findings from the first study contributed to our knowledge regarding the assessment of gender roles (e.g. construction of a gender role index) and gender identities (e.g. BSRI-12) in individuals with stroke. The use of the BSRI-12 allowed us to determine that individuals with stroke with feminine identities had the lowest exercise self-efficacy. Women with stroke are known to have poorer outcomes in their ability to perform activities of daily living, are less likely to regain independence (Sue-Min et al., 2005), and less likely to participate in stroke rehabilitation than men (Persky et al., 2010). Participation in rehabilitation programs is influenced by many factors which includes psychosocial functioning (Di Carlo et al., 2003; Holroyd-Leduc et al., 2000; Kapral et al., 2005; Paolucci et al., 2006). Thus, women with stroke who are more likely to have lower exercise self-efficacy may contribute to less favourable outcomes in stroke recovery and lower participation in rehabilitation.

While we did not find any associations between gender roles and psychosocial factors for exercise, our study provides a framework for future work into this area of research. Women with stroke often feel that they cannot prioritize their own health and recovery because they perceive an obligation to attempt to resume various household roles and responsibilities and in turn influencing participation in rehabilitation programs (Heart and Stroke Foundation of Canada, 2018). Future adequately powered studies are needed to determine whether women with stroke are able to resume their previous roles and to further determine if gender roles are associated with psychosocial factors for exercise, including exercise self-efficacy, outcome expectations for exercise, and motivation for exercise.

Our findings provide clinically important information regarding the need to develop rehabilitation programmes that are specific to the needs of stroke survivors identifying of women, by promoting exercise self-efficacy and thus aiding in optimizing recovery outcomes. Research has shown that older women prefer supervised exercise and exercising with others (van Uffelen et al., 2017). As such, rehabilitation programs incorporating group-based interventions and receiving feedback from trained professionals may improve exercise self-efficacy in individuals with stroke and other clinical conditions (Damush et al., 2007; Rajati et al., 2014; Resnick et al., 2008; Shaughnessy et al., 2006). These strategies are aligned with the construct of vicarious experience to promote self-efficacy (Bandura, 1997). Moreover, as women with stroke often possess negative perceptions of their bodies resulting in psychological changes (Lever & Pryor, 2017), clinicians may find that strategies that address low self-esteem may also improve exercise self-efficacy and exercise participation (McAuley et al., 2005). Regular exercise behaviours have been associated with increased self-esteem in both younger and older adults (Zamani Sani et al., 2016) and thus the prescription of a sustainable exercise program may be the focus of rehabilitation programs in women.

With regards to androgynous and undifferentiated gender, sex-typed (i.e. masculine males and feminine females) younger adults tend to associate more masculine traits to individuals participating in stereotypical masculine physical activities such as weightlifting, and more feminine traits to those participating in stereotypical feminine activities such as aerobic dance, whereas non-sex typed individual (i.e. androgynous and undifferentiated identities) may not be affected by the gender specific perceptions associated with various types of physical activity (Matteo, 1988). Individuals with androgynous gender identities have been deemed to be significantly more adaptable to various forms of physical activities than those possessing either masculine or feminine gender identities (Vafaei et al., 2014). Thus, non-sex types stroke survivors may actually be the most adaptable to various forms of rehabilitation programs due to their neutral perceptions of exercise behaviours. Future studies are indeed warranted to confirm these speculations regarding the adaptability and perceptions of exercise in individuals with androgynous or undifferentiated identities.

Findings from the second study of this thesis provided insight into the potential sex differences in the association between global cognitive function and walking capacity in individuals with and without stroke. These findings challenge the conventional "one size fits all approach" taken in clinical research studies, whereby both males and females are considered equal and interchangeable (Regitz-Zagrosek, 2012). Rather, our results provide further evidence that sex-based considerations are critical in heath research to ensure that findings are not inadvertently generalized to both sexes. Indeed, biological factors of sex may have contributed to less favourable associations in males. Greater brain atrophy have been reported in older males (Cowell et al., 1994; Luders et al., 2004), along with poorer walking capacity as result of slower peripheral and pulmonary oxygen uptake (Beltrame et al., 2017) and greater reductions in aerobic capacity throughout the lifespan (Buskirk & Hodgson, 1987; Fleg et al., 2005; Hossack & Bruce, 1982; Stathokostas et al., 2004; Toth et al., 1994; Weiss et al., 2006).

The individuals with chronic stroke exhibited poorer performances on both the 6MWT and MoCA in comparison to the older adults without history of stroke (See Appendix 5). Thus, interventions such as aerobic exercise that aim to improve both cognitive outcomes (Oberlin et al., 2017), and walking capacity (Saunders et al., 2020) are important for people with stroke. Our results suggesting that improved walking outcomes are related to better global cognitive function contribute to the research priorities identified by individuals with stroke to address walking impairments (Rudberg et al., 2020). Interventions aimed at improving both cognitive function and walking capacity may result in an even stronger relationship between cognitive function and walking capacity.

Although we did not find any association between MoCA scores and cfPWV, this work increases our knowledge regarding the use of screening tools to assess global cognition. Previous studies examining sex differences in the association between cognitive function and arterial stiffness have utilized domain-specific function measures (Kearney-Schwartz et al., 2009; Sabra et al., 2020; Singer et al., 2014; Waldstein et al., 2008), which may suggest that thorough cognitive function screening batteries may be in order to detect sex-based differences. Thus, our findings highlight the potential limitations regarding the sensitivity of measures of global cognition in detecting sex differences in the association between cognitive function and arterial stiffness.

Overall, this thesis advances our knowledge regarding the incorporation of sex and gender considerations into clinical research. Collectively, our findings suggest that exercise self-efficacy varies in individuals with stroke with different gender identities and that various factors including sex, age, and history of stroke are influential in the association between walking capacity and cognitive function in older males and females. These findings may encourage future studies to incorporate sex-and gender-based considerations into their research question, design, collection and reporting, as our studies add to the growing body of evidence highlighting that men and women and males and females often do not exhibit the same outcomes. Thus, researchers aiming to conduct studies of the highest rigour and promoting health equity should without a doubt include sex-and gender-based considerations into all phases of the research process, as we have done.

**4.3 Limitations**

We acknowledge that the studies included in this thesis have limitations. We were unable to enroll more participants into both studies as a result of university directives in response to the COVID-19 pandemic to suspend primary research activities. Our first study did not take into account other psychosocial variables such as apathy and depression, which have been to be associated with exercise self-efficacy, outcome expectations for exercise and motivation for exercise in individuals with stroke.

With regards to our second study, our sample size limited our ability to include additional potential variables that may have mediated these associations, such as antihypertensive medication use, BMI, race and education level.

**4.4. Future Research Directions**

Future research is warranted to determine if gender roles are associated with psychosocial factors for exercise in a larger cohort of individuals with stroke. The construction of a validated stroke-specific gender index used to evaluate gender roles in individuals with stroke is warranted.

Additional focus should also be placed on examining exercise behaviours and psychosocial factors for exercise in non-sex typed individuals, such as androgynous and undifferentiated individuals. The majority of research to date has been focused on individuals identifying as men and women, but little is known in individuals of other gender identities in any area of research.

Future research may also incorporate tools used to assess the remaining two constructs of gender not studied in this current thesis, institutionalized gender and gender relations. To date, there have been no studies that have assessed the four domains that make an individual's gender, nor have examined if each of these constructs are related (Tannenbaum et al., 2016) or independent of one another (e.g. an individual identifying as a woman may not necessarily take on gender roles typically assigned to women).

The evaluation of the association between global cognitive function and arterial stiffness in older males and females with and without history of stroke in a larger cohort is warranted. Future research may also disaggregate findings by males and females with stroke to better understand potential sex-based differences in the associations between cognitive function and markers of cardiovascular health and function. Finally, a comprehensive cognitive battery examining separate domains of cognition may be the focus of future work, as little is known about sex differences in the relationship between each domain of cognition, arterial stiffness, and walking capacity in individuals with stroke.

### 4.5 Conclusion

This thesis contributes to our understanding of gender roles undertaken by men and women with stroke, thereby providing a framework for future work attempting to examine gender differences in stroke, and whether sex moderates the association global cognitive function, arterial stiffness and walking capacity. Findings from these studies underscore the importance of sex-and gender-based considerations in stroke-related research, guide rehabilitation and exercise-based interventions that aim to optimize psychosocial and physiological determinants of health, and may inform future larger-scaled studies aiming to increase the generalizability of their findings to males and females and individuals of all gender identities.

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# Appendix 1

## TOOLS USED FOR THE ASSESSMENT OF PSYCHOSOCIAL FACTORS FOR EXERCISE

# SELF-EFFICACY FOR PHYSICAL ACTIVITY SCALE

From Research Quarterly for Exercise and Sport. 1992; 63:60-6

Circle the number that indicates how confident you are that you could be physically active in each of the following situations:

| | Not at all confident | Slightly confident | Moderately confident | Very Confident | Extremely Confident |
|---|---|---|---|---|---|
| When I am tired | 1 | 2 | 3 | 4 | 5 |
| When I am in a bad mood | 1 | 2 | 3 | 4 | 5 |
| When I am on vacation | 1 | 2 | 3 | 4 | 5 |
| When it is raining or snowing | 1 | 2 | 3 | 4 | 5 |
| When I feel I don’t have time | 1 | 2 | 3 | 4 | 5 |

# SHORT OUTCOME EXPECTATION FOR EXERCISE SCALE

Please indicate if you agree or disagree with the following statements:

| | Strongly disagree | Disagree | Neutral | Agree | Strongly Agree |
|---|---|---|---|---|---|
| Exercise is enjoyable | 1 | 2 | 3 | 4 | 5 |
| Exercise makes me feel better | 1 | 2 | 3 | 4 | 5 |
| Exercise improves my mood | 1 | 2 | 3 | 4 | 5 |
| Exercise improves my alertness | 1 | 2 | 3 | 4 | 5 |
| Exercise improves my endurance | 1 | 2 | 3 | 4 | 5 |

# Behavioral Regulation in Exercise Questionnaire-3

We are interested in the reasons underlying peoples' decisions to engage, or not engage in physical exercise. Using the scale below, please indicate to what extent each of the following items is true for you. Please note that there are no right or wrong answers and no trick questions. We simply want to know how you personally feel about exercise. **Please circle the number that best describes your reasons for questions 1 through 23**.

| Not true for me | | Sometimes true for me | | Very true for me |
|---|---|---|---|---|
| 0 | 1 | 2 | 3 | 4 |

WHY DO YOU ENGAGE IN EXERCISE?

| | | | | | |
|---|---|---|---|---|---|
| 1. I exercise because other people say I should. | 0 | 1 | 2 | 3 | 4 |
| 2. I feel guilty when I don't exercise. | 0 | 1 | 2 | 3 | 4 |
| 3. I value the benefits of exercise. | 0 | 1 | 2 | 3 | 4 |
| 4. I exercise because it's fun. | 0 | 1 | 2 | 3 | 4 |
| 5. I consider exercise consistent with my values. | 0 | 1 | 2 | 3 | 4 |
| 6. I take part in exercise because my friends/family/partner say I should. | 0 | 1 | 2 | 3 | 4 |
| 7. I feel ashamed when I miss an exercise session. | 0 | 1 | 2 | 3 | 4 |
| 8. It's important to me to exercise. | 0 | 1 | 2 | 3 | 4 |
| 9. I can't see why I should bother exercising. | 0 | 1 | 2 | 3 | 4 |
| 10. I enjoy my exercise sessions. | 0 | 1 | 2 | 3 | 4 |
| 11. I consider exercise a fundamental part of who I am. | 0 | 1 | 2 | 3 | 4 |

| | | | | | |
|---|---|---|---|---|---|
| 12. I don't see the point in exercising. | **0** | **1** | **2** | **3** | **4** |
| 13. I feel like a failure when I haven't exercised in a while. | **0** | **1** | **2** | **3** | **4** |
| 14. I think it is important to make the effort to exercise regularly. | **0** | **1** | **2** | **3** | **4** |
| 15. I exercise because it is consistent with my life goals. | **0** | **1** | **2** | **3** | **4** |
| 16. I feel under pressure from my friends/family to exercise. | **0** | **1** | **2** | **3** | **4** |
| 17. I consider exercise to be part of my identity. | **0** | **1** | **2** | **3** | **4** |
| 18. I get pleasure and satisfaction from participating in exercise. | **0** | **1** | **2** | **3** | **4** |
| 19. I think exercising is a waste of time. | **0** | **1** | **2** | **3** | **4** |
| 20. I find exercise a pleasurable activity. | **0** | **1** | **2** | **3** | **4** |
| 21. I get restless if I don't exercise. | **0** | **1** | **2** | **3** | **4** |
| 22. I exercise because others will not be pleased with me if I don't. | **0** | **1** | **2** | **3** | **4** |
| 23. I don't see why I should have to exercise. | **0** | **1** | **2** | **3** | **4** |
| Notes: | | | | | |

# Appendix 2

# TOOLS USED FOR THE ASSESSMENT OF GENDER

# Bem Sex-Role Inventory-12

Rate yourself on each item, on a scale from 1 (not applicable to you) to 7 (totally applicable to you):

| | Not applicable to you | | | | | | Totally applicable to you |
|---|---|---|---|---|---|---|---|
| 1. Warm | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 2. Gentle | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 3. Affectionate | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 4. Sympathetic | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 5. Sensitive to other's needs | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 6. Tender | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 7. Has leadership qualities | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 8. Strong personality | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 9. Act as leader | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 10. Dominant | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 11. Defends own belief | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 12. Makes decision easily | 1 | 2 | 3 | 4 | 5 | 6 | 7 |

**Average Score (1-6): __________**

**Average Score (7-12): _________**

**The Physical Activity Scale for Individuals With Physical Disabilities (PASIPD)***
Washburn, Zhu, McAuley, Frogley and Figoni (2002)

*The following questions excerpted from the PASIPD were used to construct the gender index

7. During the past 7 days, how often have you done any light housework, such as dusting, sweeping floors or washing dishes?
    1. Never (Go to question #8)
    2. Seldom (1–2d)
    3. Sometimes (3–4d)
    4. Often (5–7d)

8. During the past 7 days, how often have you done any heavy housework or chores such as vacuuming, scrubbing floors, washing windows, or walls, etc?
    1. Never (Go to question #9)
    2. Seldom (1–2d)
    3. Sometimes (3–4d)
    4. Often (5–7d)

9. During the past 7 days, how often you done home repairs like carpentry, painting, furniture refinishing, electrical work, etc?
    1. Never (Go to question #10)
    2. Seldom (1–2d)
    3. Sometimes (3–4d)
    4. Often (5–7d)

10. During the past 7 days how often have you done lawn work or yard care including mowing, leaf or snow removal, tree or bush trimming, or wood chopping, etc?
    1. Never (Go to question #11)
    2. Seldom (1–2d)
    3. Sometimes (3–4d)
    4. Often (5–7d)

12. During the past 7 days, how often did you care for another person, such as children, a dependent spouse, or another adult?
    1. Never (Go to question #13)
    2. Seldom (1–2d)
    3. Sometimes (3–4d)
    4. Often (5–7d)

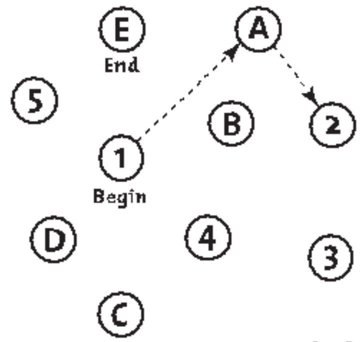
# Appendix 3

## MONTREAL COGNITIVE ASSESSMENT

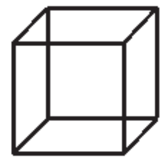
**MONTREAL COGNITIVE ASSESSMENT (MOCA)**

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

**VISUOSPATIAL / EXECUTIVE**




[ ]



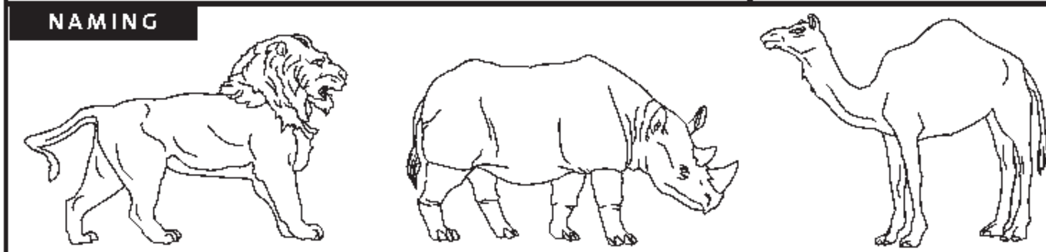
Copy cube [ ]

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

POINTS __/5

**NAMING**



[ ] [ ] [ ] __/3

| MEMORY | Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes. | | FACE | VELVET | CHURCH | DAISY | RED | No points |
|---|---|---|---|---|---|---|---|---|
| | | 1st trial | | | | | | |
| | | 2nd trial | | | | | | |

**ATTENTION** Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 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 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** __/3

**LANGUAGE** Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] __/2

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

**ABSTRACTION** Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler __/2

| DELAYED RECALL | Has to recall words WITH NO CUE | FACE [ ] | VELVET [ ] | CHURCH [ ] | DAISY [ ] | RED [ ] | Points for UNCUED recall only | __/5 |
|---|---|---|---|---|---|---|---|---|
| Optional | Category cue | | | | | | | |
| | Multiple choice cue | | | | | | | |

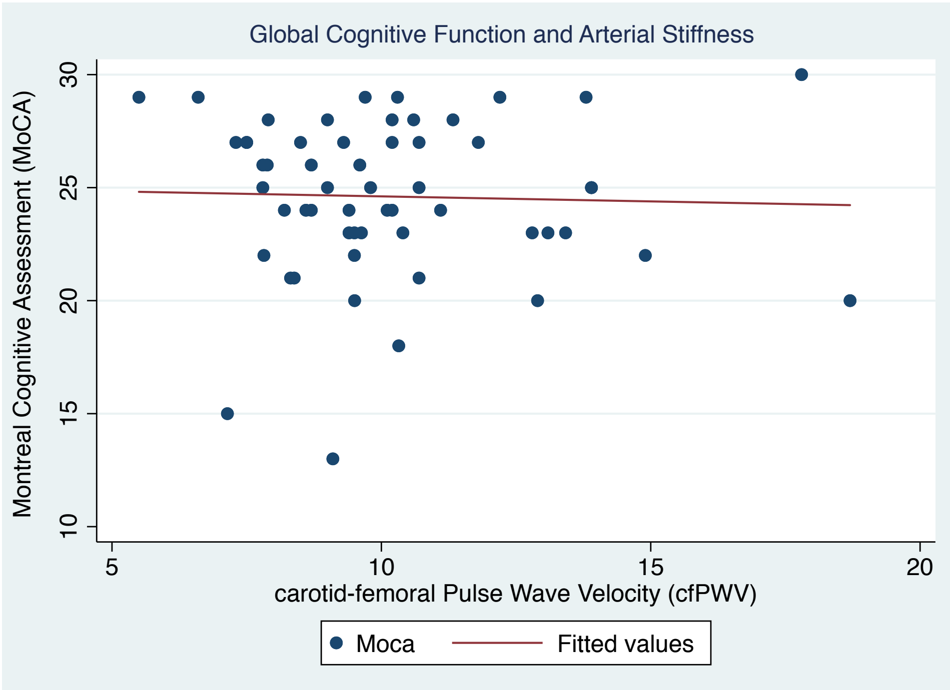
**ORIENTATION** [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City __/6



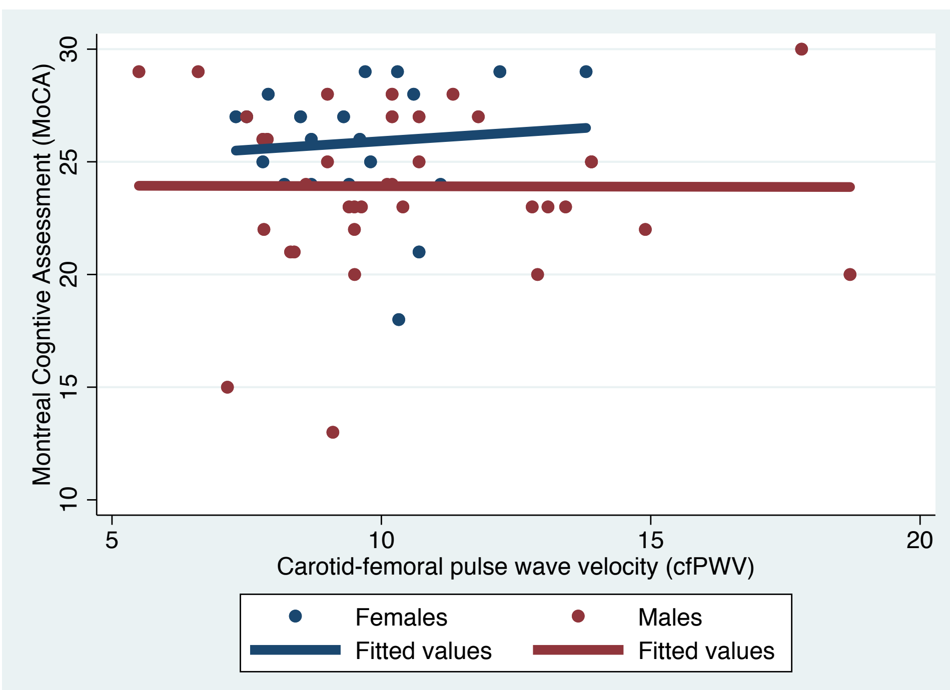
Normal ≥ 26 / 30 TOTAL __/30
Add 1 point if ≤ 12 yr edu

# Appendix 4

## SCATTERPLOTS AND CORRELATION MATRICES OF VARIABLES INCLUDED IN ANALYSES




Appendix Figure 1. Scatterplot with regression line of the association between global cognitive function (MoCA scores) and arterial stiffness (cfPWV)



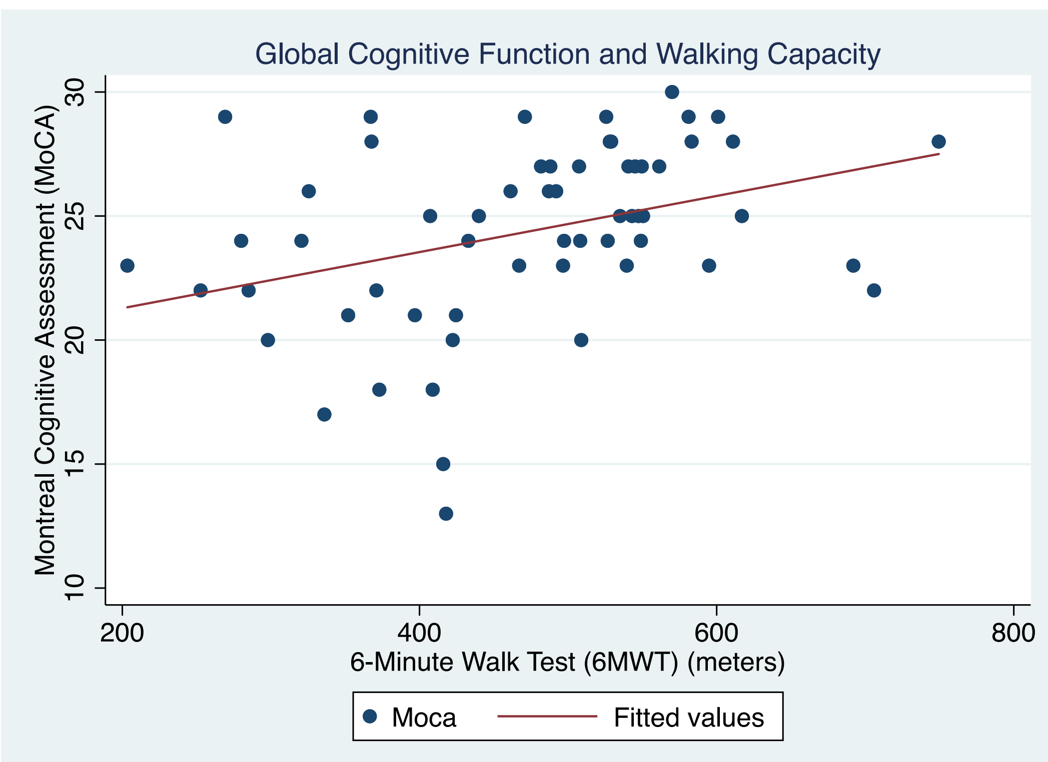

Appendix Figure 2. Scatterplot with regression line of sex differences in the association between global cognitive function (MoCA scores) and arterial stiffness (cfPWV)

Appendix Table 1. Correlation matrix between global cognitive function, male sex, cfPWV, age, history of stroke and systolic blood pressure

| | Moca | PWV | Sex | Age | Stroke | SBP |
|---|---|---|---|---|---|---|
| Moca | 1.0000 | | | | | |
| PWV | -0.0325 | 1.0000 | | | | |
| Sex | -0.2675 | 0.1716 | 1.0000 | | | |
| Age | 0.0140 | 0.5136 | -0.0116 | 1.0000 | | |
| Stroke | -0.1988 | -0.2181 | 0.3192 | -0.4977 | 1.0000 | |
| SBP | -0.0825 | 0.5769 | 0.3877 | 0.3831 | 0.0314 | 1.0000 |

Abbreviations. Moca= Montreal Cognitive Assessment, PWV= Pulse Wave Velocity, SBP= Systolic Blood Pressure

Appendix Table 2. Varian




Appendix Figure 2. Scatterplot with regression line of the association between global cognitive function (MoCA scores) and walking capacity (6MWT)

Appendix Table 2. Correlation matrix between global cognitive function, male sex, walking capacity (6MWT), age, history of stroke and systolic blood pressure

| | Moca | Walking | Sex | Age | Stroke | SBP |
|---|---|---|---|---|---|---|
| Moca | 1.0000 | | | | | |
| Walking | 0.3295 | 1.0000 | | | | |
| Sex | -0.2614 | -0.0075 | 1.0000 | | | |
| Age | 0.0220 | 0.4243 | -0.0473 | 1.0000 | | |
| Stroke | -0.2575 | -0.4782 | 0.2961 | -0.5054 | 1.0000 | |
| SBP | -0.1284 | 0.1127 | 0.3460 | 0.3200 | 0.1285 | 1.0000 |

Abbreviations. MoCA= Montreal Cognitive Assessment, SBP= Systolic Blood Pressure

## Appendix 5

## PARTICIPANT DEMOGRAPHICS FOR VARIABLES OF INTEREST, DISAGGREGATED BY OLDER ADULTS WITH AND WITHOUT STROKE

| | **History of Stroke (n=28)** | **No History of Stroke (n=34)** | **p-value** |
|---|---|---|---|
| Age (years), median (IQR) | 62.5 (15) | 70 (6) | <0.01* |
| Montreal Cognitive Assessment (MoCA), median (IQR) | 23.5 (5) | 25.5 (3) | 0.03* |
| Carotid-femoral pulse wave velocity, m/s, median (IQR), | 9 (3.5) | 10.2 (1.4) | 0.06 |
| 6-Minute Walk Test distance (meters), mean (SD) | 407.7 (113.3) | 521.1 (91.6) | <0.01* |
| Systolic Blood Pressure (SBP), mean (SD) | 131.7 (14.4) | 128.1 (13.2) | 0.51 |
| Diastolic Blood Pressure (DBP), mean (SD) | 76.3 (1.8) | 72.1 (1.6) | 0.09 |

*P<0.05

Abbreviations. IQR=Interquartile Range, SD=Standard Deviation, mmHg= Millimetres of Mercury