SEX DIFFERENCES IN THE EFFECT OF EXERCISE ON COGNITION

THE EFFECTS OF EXERCISE ON COGNITION POST-STROKE: ARE THERE SEX DIFFERENCES?

BY SHEREEN KHATTAB, B.SC. KIN

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AUTHOR: Shereen Khattab, B.Sc. Kin

SUPERVISOR: Dr. Ada Tang

SUPERVISORY COMMITTEE: Dr. Julie Richardson and Dr. Joy MacDermid

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LAY ABSTRACT

Exercise can improve thinking and memory in people with stroke, but we do not know if males and females improve to the same degree. This thesis examined if there were differences in thinking and memory between males and females with stroke after exercise. The first study was a review of previous research studies that examined the effect of exercise on memory and thinking. Findings from this study displayed that there were no differences between males and females in memory and thinking. The second study found that females did better on a thinking test after six months of aerobic or balance and flexibility exercise, but males showed no improvement. There were no differences in any other test. Together, these studies show that more studies are needed to examine differences between males and females.

ABSTRACT

Evidence in older adults suggest that the benefits of exercise on cognition may be moderated by sex. To our knowledge, no studies have examined this relationship in individuals with stroke. This thesis investigated whether there were sex differences in the effect of exercise on cognition post-stroke. The first study was a systematic review of the literature on exercise and cognition in individuals with stroke. The second study was a secondary analysis of data from a randomized controlled trial comparing the effect of aerobic vs. balance and flexibility exercise on cognition. Findings from the systematic review revealed no differences between studies of higher and lower female proportions with respect to memory (Verbal Digit Span Forward, Memory Domain of Stroke Impact Scale and Wechsler Memory Scale III - Verbal Pairing Domain: Chi^2 =1.52, p=0.22), executive function (Stroop Test: Chi^2 = 0.56, p=0.45; Trail Making Test B: Chi^2 = 0.00, p=0.98), language (Communication Domain of Stroke Impact Scale: Chi^2 = 3.17, p=0.08) or global cognition (Montreal Cognitive Assessment, Cognitive Domain of Functional Independence Measure and Addenbrooke's Cognitive Examination-Revised: Chi^2 = 0.88, p=0.35). Findings from the secondary analysis indicated that there was a group x time interaction in females (effect size 0.28, p=0.03) that was not observed in males (effect size 0.01, p=0.62). Females demonstrated a Stroop Colour-Word Interference test change of -2.3 seconds, whereas males demonstrated a change of +5.5 seconds following AE. There were no differences between exercise groups in either sex for any of the other outcomes (working memory and set-shifting/cognitive flexibility). Together, these studies suggest that there is a clear need for future clinical trials that incorporate sex-based analysis to adequately investigate sex-dependent effects of interventions.

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LIST OF ABBREVIATIONS

ACE-R	Addenbrooke's Cognitive Examination-Revised
AE	Aerobic Exercise
BDNF	Brain-Derived Neurotrophic Factor
BF	Balance and Flexibility Program
C	Control
CESD	Center for Epidemiologic Studies – Depression Scale:
CMSA	Chedoke-McMaster Stroke Assessment Motor Recovery
CPT	Continuous Performance Test
DSB	Verbal Digit Span Backward
DSF	Verbal Digit Span Forward
FIM-Cognitive	Functional Independence Measure (Cognitive Domain)
HR	Hazard Ratio
I	Intervention
IGF-1	Insulin-Like Growth Facotr-1
IQR	Interquartile Range
K-MoCA	Montreal Cognitive Assessment (Korean Version)
LDL	Low-density Lipoprotein
MMSE	Mini Mental State Exam
MoCA	Montreal Cognitive Assessment
mRNA	Messenger Ribonucleic Acid
NA	Not Applicable
NIHSS	National Institutes of Health Stroke Scale

NR	Not Reported
NS	Not Significant
OR	Odds Ratio
RAVLT	Rey Auditory Verbal Learning Test
RCT	Randomized Controlled Trial
RPMT	Raven's Progressive Matrices Test
SAGER	Sex and Gender Equity in Research
SD	Standard Deviation
Sec	Seconds
SIS-Communication	Stroke Impact Scale (Communication domain)
SIS-Memory	Stroke Impact Scale (Memory domain)
SMD	Standardized Mean Difference
SRTT	Serial Reaction Timed Task
Stroop CW	Stroop Colour-Word Interference Test
TMT A	Trail Making Test A
TMT B	Trail Making Test B
WAIS-IV	Wechsler Adult Intelligence Scale-Fourth Edition
WCST	Wisconsin Card Sort Test
WMS-III	Wechsler Memory Scale-Third Edition

DECLARATION OF ACADEMIC ACHIEVEMENT

This thesis was completed by the candidate and recognizes the contribution of Dr. Ada Tang, Dr. Julie Richardson and Dr. Joy MacDermid in providing helpful insight into its preparation and in the research process. Elise Wiley and Hanna Fang contributed to screening for study selection. Elise Wiley contributed to data extraction and quality assessment. Stephanie Sanger provided insight into the creation of search terms and Dr. Anita Gross provided insight into the analysis for the systematic review.

CHAPTER 1

INTRODUCTION

BRIEF INTRODUCTION AND RATIONALE OF RESEARCH

Cognitive impairment occurs in approximately 70% of individuals post-stroke and is defined as a decline in cognitive abilities (1,2). Post-stroke cognitive impairment can involve deficits in any domain of cognition (2), which can impact activities of daily living and independence, as well as rehabilitation efforts (3).

Non-invasive, low-cost and widely accessible interventions, such as exercise, may be a viable option to mitigate cognitive deficits following a stroke (4). In comparison to the body of research supporting physical rehabilitation, there exists approximately one-fifth of the evidence and fewer randomized controlled trials focused on cognitive rehabilitation, resulting in the effectiveness of these interventions being less clear (4). Recently however, a systematic review of 14 randomized controlled trials reported improvements in attention and processing speed in individuals with stroke following physical activity or exercise training (5).

Sex may play a role in influencing the relationship between exercise and cognition. In older adults, a recent meta-analysis demonstrated that variations in the effect of exercise on cognition may be partially due to sex differences between males and females (6). Whether this association is observed after stroke has not been previously investigated. Thus, the overall objective of this thesis was to examine whether there were sex differences in the effect of exercise on cognition post-stroke.

This thesis will first provide an overview of stroke, post-stroke cognitive impairment, exercise and sex and gender, and explore the relationship between these topics. Two studies will then be presented: a systematic review and meta-analysis of randomized controlled trials, and a secondary analysis of data from a randomized controlled trial investigating the effect of exercise on cognition post-stroke. Finally, this thesis will conclude with a discussion of the main findings

from both studies, possible mechanisms, clinical significance, limitations, future directions, and conclusions.

DESCRIPTION OF KEY COGNITIVE TERMS

The following section describes key terms regarding cognition that will be discussed throughout this thesis.

Table 1: Key Cognitive Terms

Term	Description
Cognition	An umbrella term used to describe our ability to process and understand, perceive and react, make decisions and respond appropriately, and retrieve and store information. Given the vast and complicated sensory information we receive daily, cognitive functioning is crucial for everyday life as it governs our actions and thoughts and assists in understanding and interacting within our environment (7). Cognitive function spans five main domains: attention and processing speed, memory, executive function, visuospatial ability and language; with each involving their respective cognitive sub-types (Figure 1).
Cognitive Impairment	Deficit in at least one cognitive domain with mild or severe impairments in activities of daily living. Cognitive impairment involves a range of cognitive deficits, from mild cognitive impairment to the most severe form of cognitive impairment, dementia (4).
Attention and Processing Speed	Attention refers to the overall ability of focusing and concentrating on a specific stimuli (8). There are three types of attention: sustained, divided, and selective attention (8). Sustained attention is the ability to maintain focus on a stimuli (e.g. reading the newspaper or watching television), divided attention is the ability to focus on multiple tasks simultaneously (e.g. speaking on the phone while writing an email) and selective attention is the ability to focus on a specific stimuli while ignoring other information (e.g. listening to a friend during a loud event) (8). Processing speed refers to the speed at which an individual can understand and react to a stimulus (8). The frontal lobe is the primary location associated with attention and processing speed (9).
Memory	Memory refers to the ability to store and retrieve information (8). Declarative memory is the conscious recollection of events and facts, and is divided into semantic (general knowledge of words, concepts and facts, such as the capital of Egypt) and episodic memory (personal experiences occurring at a specific place and time, such as recalling what a physician stated during an appointment) (8). Non-declarative memory is subconscious memory that is outside one's awareness (8), such as procedural memory that involves knowledge of procedures and skills (e.g. riding a bike) (10). The primary

	region of the brain associated with memory is the temporal lobe (10).
Executive Function	Executive function is a multicomponent and complex cognitive function involving planning, organizing, decision making, working memory, inhibition and cognitive flexibility (10). Working memory is the manipulation of information currently being utilized during an activity (e.g. remembering a recipe while cooking) (10). Inhibition refers to the ability to neglect an involuntary response to produce a novel one (e.g. choosing to eat a salad instead of a donut) (8). Cognitive flexibility is the ability to shift thinking as an adaptation to new stimuli (e.g. thinking of alternative solutions to a problem) (8). Another subtype of executive functioning, known as verbal fluency, is the collective ability to search and generate words in a certain amount of time (8).The region of the brain controlling executive functioning is the frontal lobe (9).
Visuospatial Ability	Visuospatial ability is the ability to understand and recognize space and objects in two and three dimensions (8). This domain is divided into three aspects: object perception (recognizing objects or faces), spatial perception (appreciating the physical location of objects) and visual construction skills (combining individual objects to make a whole) (8). The primary regions of the brain responsible for visuospatial ability are the occipital and parietal lobe (11).
Language	Language refers to the ability to generate (expressive) and comprehend (receptive) language which is needed for social communication (8). The frontal (Broca's area) and parietal lobes, along with the temporal lobe (Wernicke's area), are regions responsible for the domain of language (9).
Global Cognition	Global measures of cognition are also commonly used, which are a multi-component battery of tests to capture all domains of cognition into a single measure.

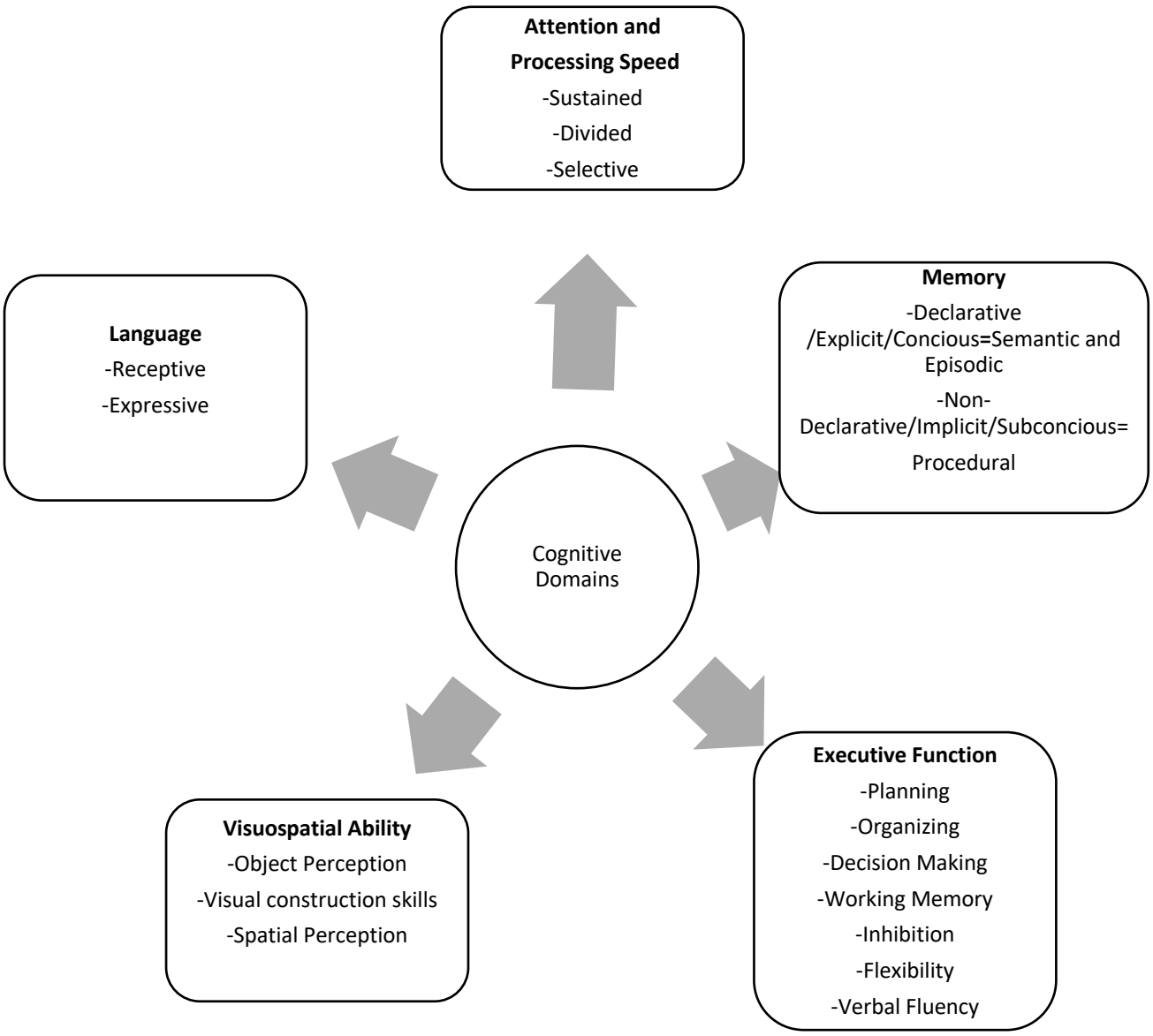

Figure 1: Cognitive Domains and Sub-types

STROKE

CHARACTERISTICS OF STROKE

Stroke, caused by a lack of blood flow to any portion of the brain, is one of the leading causes of morbidity and mortality worldwide (12). Ischemic stroke account for 87% of all cases, and hemorrhagic stroke accounts for 13% (10% intracerebral and 3% subarachnoid) (12). Ischemic stroke is most common and caused by a clot within a blood vessel of the brain, whereas a hemorrhagic stroke is the most fatal and is caused by a rupture of an artery in the brain due to high pressure weakening arteries (12).

Globally, the prevalence of stroke is 80 million, with an incidence rate of 16.9 million and 5.5 million deaths occurring from stroke (13). In Canada, approximately 405,000 Canadians are currently living with the effects of stroke, and this number is expected to reach 726,000 by 2038 (14). The prevalence of stroke also increases with advancing age, predominantly occurring in individuals above the age of 50, with the highest prevalence being among individuals $\geq$80 years of age (12). The incidence of stroke in Canada is 50,000 and stroke is also the third leading cause of mortality, with approximately 13,500 deaths per year (15).

The risk factors of stroke include both non-modifiable and modifiable factors, with 90% of strokes attributable to modifiable risk factors (16). Nonmodifiable risk factors are older age (two-fold increase risk with each decade after the age of 45) (17) and family history of stroke (OR 1.3-1.8) (18). Modifiable risk factors include both metabolic risk factors and lifestyle risk factors. Metabolic risk factors include diabetes (RR 1.27) (19), overweight (RR 1.36) and obesity (RR 1.81) (20), hyperlipidemia (OR 1.84) (21), hypertension (OR 2.98) (21) and atrial fibrillation (five-fold increase risk) (12), while lifestyle risk factors are smoking (HR 1.28) (22), sedentary lifestyle (HR 1.60) (23) and depression (HR 1.45) (24),

Symptoms of a stroke may include the sudden onset of lateralized weakness, vision impairments, headache, confusion or difficulty speaking, or loss of coordination and balance (25). The subsequent consequences of stroke, such as physical, psychosocial and cognitive sequelae, can persist and impact daily function and the quality of life of individuals (25).

POST-STROKE COGNITIVE IMPAIRMENT

Cognitive impairment is a common consequence of stroke and is present in approximately 70% of individuals (1,2). Cognitive impairments occur immediately after stroke, yet there may be a delay before cognitive deficits become apparent, possibly due to the size, type, and location of stroke (26). Risk factors of post-stroke cognitive impairment are similar to that of stroke (older age, family history of stroke, diabetes, overweight and obesity, hypertension, hyperlipidemia, atrial fibrillation, smoking, sedentary lifestyle, depression) with additional risk factors being lower education levels (27,28), stroke severity, pre-stroke cognitive impairment and female sex (29). The mechanisms surrounding post-stroke cognitive impairment are not well-understood, however, a range of pathologies may contribute to its progression, such as multiple infarcts, white matter lesions, or brain hemorrhages (30). Depending on whether these brain damages are focal or diffuse, will result in selective or diffuse cognitive impairment (30).

Cognitive impairments can occur in any of the five main domains of cognition: attention and processing speed, memory, executive function, visuospatial ability and language; with each involving their respective cognitive sub-types (Figure 1). Impairments in executive function, attention and memory (1,31) have been found in 43-78% of individuals with stroke, depending on type, size and location of injury (31,32). These impairments are associated with functional decline (33,34), reduced quality of life (33), increased dependence in activities of daily living (35) and may limit the extent of ability to return to independent living and community re-

integration (29,36). Currently, there is no gold standard for the assessment of post-stroke cognitive impairment, however, common examples of clinical assessments utilized to assess cognition in individuals with stroke are described in Table 2.

Table 2: Description of Common Cognitive Assessments Utilized in Individuals Post-Stroke by Cognitive Domain

Domain/Sub-type	Cognitive Test	Test Description	Psychometric Properties
Attention and Processing Speed			
Attention and Processing Speed	Trail Making Test A (37,38)	Participants trace a line connecting encircled numbers 1-25 in ascending order. Primary outcome of this test is time (seconds).	**Reliability** Test-Retest: Correlation (r=0.78) in individuals with cerebrovascular disease (39) **Validity** Concurrent Validity: Correlation (r=0.21) with Executive Function Performance Test in individuals with stroke (40).
Attention and Processing Speed	Continuous Performance Test (41)	Participant presses space bar when a letter other than X appears. Letters appear on the screen with different time intervals between each one. Primary outcome of this test is reaction time (seconds).	**Reliability** Test-Retest: Intraclass Correlation Coefficient=0.76 in a mixed population of healthy young to older adults (41).
Attention and Processing Speed	Stroop Baseline Test (42)	Participants read names of colours printed in black ink. Primary outcome of this test is time (seconds).	**Reliability** Test-Retest: Intraclass Correlation Coefficient=0.80 in healthy middle aged to older adults (43).
Attention and Processing Speed	Serial Reaction Timed Task (44)	Participants press one of four coloured buttons to correspond with coloured targets appearing on a computer screen. Targets are presented either in a repeating order (sequence blocks) or in random order (random blocks).	No data on reliability and validity

		Participants are instructed to react to the stimulus as fast as possible, but are not informed about whether it is a repeating or random sequence. Primary outcome of this test is reaction time (seconds).	
Attention and Processing Speed	Wechsler Adult Intelligence Scale Fourth Edition – Processing Speed Index (Symbol Search and Coding) (45)	Symbol Search: view rows of symbols and target symbols and mark whether or not the target symbols appear in each row. Coding: Transcribe a digit symbol code using a key. Primary outcome of Symbol Search test is a sum score, primary outcome for Coding test is time (seconds).	**Reliability** Test-Retest: Intraclass Correlation Coefficient=0.82 in older adults (45). Internal Consistency: Cronbach's alpha=0.93 for older adults (45).
Memory			
Memory	Stroke Impact Scale (Memory domain) (46)	The Stroke Impact Scale is a stroke-specific, self-report health status measure. Questions regarding memory and thinking include: In the past week how difficult was it for you to… 1) Remember things that people just told you? 2) Remember things that happened the day before? 3) Remember to do things (e.g. keep scheduled appointments or take medication)? 4) Remember the day of the week? 5) Concentrate? 6) Think quickly?	**Reliability** Test-Retest: Intraclass Correlation Coefficient ranging from 0.57 to 0.92 for all 8 domains in individuals with stroke, separate alpha values unavailable (47). Internal Consistency: Cronbach's alpha of 0.80 (48) and 0.96 (49) in individuals with stroke. **Validity** Concurrent: Correlation (r=0.58) with MMSE in individuals with stroke (47).

		7) Solve everyday problems? Rated on 5-point likert scale (1=inability to complete and 5=no difficulty). Outcome is score out of 35	Discriminant: Correlation (r=0.49) with the World Health Organization Quality of Life Bref-Scale psychological domain and (r=0.38) with Zung's Self-Rating Depression Scale (50). Convergent: Correlation (r=0.77) between total Stroke Impact Scale and National Institute of Health Stroke Scale (48)
Memory and Verbal Learning	Rey Auditory Verbal Learning Test (51)	An assessor reads aloud a list of 15 words. The participant is then asked to repeat all words from the list that they can remember. This procedure is carried out a total of five times. The examiner then presents a second list of 15 words, allowing the participant only one attempt at recall of this new list. Immediately following this, the participant is asked to remember as many words as possible from the first list. After a 20-minute delay, the participant is again asked to recall as many words as possible from the first list. The participant is then read a list of words and asked to indicate whether each word was from the first list. Primary outcome of this test is number of words remembered (n words).	**Reliability** Test-Retest: Intraclass Correlation Coefficient=0.76 in healthy middle aged to older adults (43). Internal Consistency: Cronbach's alpha=0.86 in healthy young and middle adults (52). **Validity** Convergent: Correlation (r=0.53) between Rey Auditory Verbal Learning Test and Brief Cognitive Screening Battery in healthy older adults (53). Discriminant: Correlation (r=0.44) between Rey Auditory Verbal Learning Test and Benton Visual Retention Test in healthy young and middle

			adults (52).
Episodic Memory	Verbal Digit Span Forward (54)	An assessor reads seven pairs of randomly ordered number sequences, beginning with three digits and increasing one at a time up to nine digits. The participant repeats each sequence aloud in a forward order. Primary outcome of this test is number of correct sequences relayed, maximum score of 14.	**Validity** Concurrent: Correlation (r=0.26) with Executive Function Performance Test in individuals with stroke (40).
Verbal Learning and Memory	Wechsler Memory Scale Third Edition - Verbal Pairing Domain (51)	Verbal Pairing Domain: Verbal Paired Associates I and II Verbal Paired Associates I: The examiner reads 10 or 14 word pairs to the examinee. Then, the examiner reads the first word of each pair, and asks the examinee to provide the corresponding word. Verbal Paired Associates II: Assesses ability to recall associations from Verbal Paired Associates I after a 30-minute delay, as well as assessing recognition of word pairs. The examinee is orally presented with the first word of each pair learned in the immediate condition and asked to provide the corresponding word. The examinee is then read a list of word pairs and asked to identify each as either one of the word pairs he or she was asked to remember or a new word pair. Primary outcome of this test is number of words recalled.	**Reliability** Test-Retest: Correlation (r=0.81) in older healthy adults (55). Internal Consistency: Correlation (r=0.92) in individuals with Alzheimer's (56).
Executive Function			

Set-shifting/ Cognitive Flexibility	Trail Making Test B (37,38)	Participants trace a line alternating between encircled numbers and letters (i.e. 1-A-2-B-3-C etc.). Primary outcome of this test is time (seconds).	**Reliability** Test-Retest: Correlation (r=0.67) in individuals with cerebrovascular disease (39) **Validity** Convergent: Correlation (r=0.31) between Trail Making Test B and Wisconsin Card Sort Test in individuals with stroke (57).
Selective Attention and Conflict Resolution	Stroop Interference Test, Colour-Word (42) or Auditory (58)	Colour-Word: Participants identify the ink colour of words presented in incongruent coloured inks (e.g. the word "blue" printed in red ink). Primary outcome of test is time (seconds). Auditory: Two words, "high" and "low", are pronounced with high and low pitches. Participants are instructed to ignore the word that is said but rather respond to the pitch of the sound as quickly as possible. A switch with two buttons representing the high and low pitches is given to the participants. Primary outcome of test is score (%accurate/average reaction time).	**Reliability** Test-Retest: Intraclass Correlation Coefficient=0.60 in healthy middle aged to older adults (43). **Reliability** Test-Retest: Intraclass correlation coefficient=0.98 in individuals with stroke (59).
Verbal Working Memory	Verbal Digit Span Backward (54)	An assessor reads seven pairs of randomly ordered number sequences, beginning with three digits and increasing one at a time up to nine digits. The participant repeats each sequence aloud in a backward order.	**Validity** Concurrent: Correlation (r=0.49) with Executive Function Performance Test in individuals with stroke (40).

		Primary outcome of this test is number of correct sequences relayed, maximum score of 14.	
Verbal Fluency	FAS Test (60)	Participants orally produce as many words as possible that begin with the letters F, A, and S within a prescribed time frame, usually one min. Primary outcome of this test is number of words produced in time frame (n words).	**Reliability** Test-Retest: Correlation (r=0.74) in healthy young to older adults (61). Internal Consistency: Cronbach alpha=0.83 in healthy young to older adults (61).
Set-Shifting	Wisconsin Card Sort Test (62)	Consists of two card packs having four stimulus cards and 64 response cards in each. Each card contains various geometric shapes in different colors and numbers. The participants sort response cards with one of four stimulus cards through the feedback (right or wrong) given to them based on a rule (e.g. according to the color of its symbols, the shape of the symbols, or the number of the shapes on each card) that changes every 10 cards. Primary outcome of this test is number of rules learned.	**Validity** Convergent: Correlation (r=0.45) between Wisconsin Card Sort Test and Mini-Mental State Exam in individuals with stroke (63).
Executive Function	Raven's Progressive Matrices Test (64)	Participants are presented with geometric figures of progressive design complexity and asked to indicate the design that completed a missing piece. Primary outcome of this test is correct responses, score out of 60.	**Reliability** Test-Retest: Correlation (r=0.96) in a mixed population of individuals with chronic diseases (65). **Validity** Concurrent: Correlation (r=0.75) between Raven's Progressive Matrices Test and the Cambridge Cognitive

			Examination in individuals with stroke (66).
Visuospatial Function			
Spatial Imagination	Mental Rotation Test (67)	Four rotated stimuli are presented on the right, along with a target image on the left. The participant must identify which two stimuli of the four were rotated images of the target image by mentally rotating (i.e., imagine what something looks like when it is rotated) the four stimuli. Primary outcome of this test is number of correct responses.	**Reliability** Test-Retest: Correlation (r=0.68) in healthy young adult individuals (68). Internal Consistency: Cronbach's alpha= 0.92 in healthy young adult individuals (69).
Visuospatial working Memory	Wechsler Memory Scale Third Edition - Spatial Span Domain (51)	Spatial Span: The examinee is briefly shown a series of abstract symbols on a page and then asked to select the symbols from an array of symbols, in the same order they were presented on the previous page. Primary outcome of this test is number of correctly identified symbols.	**Reliability** Internal Consistency: Correlation (r=0.94) in individuals with Alzheimer's (56).
Language			

Expressive and Receptive	Stroke Impact Scale (Communication domain) (46)	The Stroke Impact Scale is a stroke-specific, self-report, health status measure. Questions regarding communication include: In the past week how difficult was it for you to… 1) Say the name of someone who was in front of you? 2) Understand what was being said to you in a conversation? 3) Reply to questions? 4) Correctly name objects? 5) Participate in a conversation with a group of people? 6) Have a conversation on the telephone? 7) Call another person on the telephone, including selecting the correct phone number and dialing? Rated on 5-point likert scale (1=inability to complete and 5=no difficulty). Outcome is score out of 35	**Reliability** Test-Retest: Intraclass Correlation Coefficient ranging from 0.57 to 0.92 for all 8 domains, separate alpha values unavailable (47). Internal Consistency: Cronbach's alpha of 0.78 (48) and 0.95 (49) in individuals with stroke. **Validity** Concurrent: Correlation (r=0.53 and 0.44) for FIM Cognitive Domain and National Institute of Health Stroke Scale, respectively (47). Discriminant: Correlation (r=0.11 and 0.28) with the World Health Organization Quality of Life Bref-Scale psychological domain and Zung's Self-Rating Depression Scale, respectively (50). Convergent: Correlation (r=0.77) between total SIS and National Institute of Health Stroke Scale (48).
Global Cognition			
Global Cognition	Montreal Cognitive Assessment	Screening tool for mild cognitive impairment which assesses the following cognitive domains: attention and concentration, executive functions, memory, language,	**Reliability** Test-Retest: Correlation (r=0.92) in individuals with mild

	(70,71)	visuoconstructional skills, conceptual thinking, calculations, and orientation using several tasks like drawing, memory, naming. Primary outcome of this test is a sum of all subscores. Maximum of 30 points.	cognitive impairment or Alzheimer's disease (70). Internal Consistency: Cronbach's alpha of 0.83 (70) in individuals with stroke. **Validity** Concurrent: Correlation (r = 0.87) between the Montreal Cognitive Assessment and Mini-Mental States Exam in individuals with mild cognitive impairment or Alzheimer's disease (70).
Global Cognition	Mini-Mental State Exam (71,72)	Screening tool to detect presence of cognitive impairment which measures: orientation to time and place, immediate recall, short-term verbal memory, calculation, language, and construct ability. Primary outcome of this test is a sum of all subscores. Maximum of 30 points.	**Reliability** Test-Retest: Correlations ranging from r=0.38 to 0.99 in a mixed population of individuals (from cognitively healthy to dementia) (72). Internal Consistency: Cronbach's alpha ranging from 0.54 to 0.96 in a mixed population of individuals (from cognitively healthy to dementia) (72). **Validity** Concurrent: Correlations ranging from r=0.36 to 0.78 (73–75) with Weschler Adult Intelligence Scale-Verbal scores and from r=0.37 to 0.66 (73–75) with Weschler Adult Intelligence Scale-Performance

			scores in a mixed population of individuals (from cognitively healthy to dementia). Convergent: Correlations of r=0.78 and 0.66 with the Weschler Adult Intelligence Scale-Verbal and Performance scores, respectively (76). Discriminant: Correlation of r=0.36 with the Physical Performance and Mobility Examination (77) and a correlation of 0.15 with the Hierarchical Assessment of Balance and Mobility (78) .
Global Cognition	Functional Independence Measure (Cognitive Domain) (79)	The Functional Independence Measure is a uniform measurement of disability that assesses two domains, motor and cognitive. The cognitive domain consists of five items; comprehension and expression, social interaction, problem solving and memory items. Amount of assistance required to perform each item is recorded. Rated on a 7-point likert scale (1 = total assistance in all areas, 7 = total independence in all areas). Primary outcome of this test is score on cognitive items (ranges from 5-35).	**Reliability** Test-Retest: Correlation ranging from r=0.83 to 0.93 (80–82) for the total FIM in a mixed population of individuals attending rehabilitation centers. Correlation of Intraclass Correlation Coefficient=0.80 (83) for cognitive domain of FIM. Internal Consistency: Cronbach's alpha of 0.95 for total Functional Independence Measure and 0.89 for cognitive domain of Functional Independence Measure in inpatients with neurological disorders (84). **Validity** Concurrent:

			Correlation (r=0.73) between cognitive domain of Functional Independence Measure and Disability Rating Scale (85). Convergent: Correlation (r=0.67) between cognitive domain of Functional Independence Measure and Mini-Mental State Exam in individuals with stroke (86).
Global Cognition	Addenbrooke's Cognitive Examination-Revised (87)	Brief battery that provides evaluation of six cognitive domains (orientation, attention, memory, verbal fluency, language and visuospatial ability). Primary outcome of this test is a sum of all subscores. Maximum of 100 points.	**Reliability** Internal Consistency: Cronbach's alpha of 0.8 in a mixed population of individuals (from mild cognitive impairment to Alzheimer's) (87) **Validity** Convergent: Correlation (r=0.32) between Addenbrooke's Cognitive Examination-Revised and Clinical Dementia Scale in a mixed population of individuals (from mild cognitive impairment to Alzheimer's) (87)

EXERCISE AND COGNITION

Exercise can play an important role in improving or preserving cognitive function (88,89). Randomized controlled trials and systematic reviews have examined the relationship between exercise and cognitive function but there is large variation in the results. Some studies have found that exercise promotes cognitive functioning in older adult populations (6,90–92) and individuals with mild cognitive impairment and dementia (93), while others have found modest to minimal effects in older adult populations (94–96) and individuals with mild cognitive impairment (97), or no effects in older adults (98) .

Despite these mixed results, the domain of executive function appears to benefit most from exercise training in all populations (90), possibly because this domain is one of the first to decline with aging. Most studies have focused mainly on aerobic training, with resistance training and balance and flexibility exercise interventions being much less studied, despite also having beneficial effects on cognitive function (99). Research in male rats suggests that different types of exercise have benefits on cognition, although the specific mechanisms of action underlying these changes may differ (100). For example, while both aerobic and resistance exercises increased levels of neurotrophic factors, aerobic exercise specifically increased brain-derived neurotrophic factor whereas resistance exercise increased insulin-like growth factor-1(100). The mechanism of action of flexibility and balance exercises on cognition is not yet known, despite evidence displaying their positive benefits on cognitive function. The effect of multimodal interventions on cognition (which combine different interventions, such as aerobic and resistance, or aerobic and cognitive training) has also been gaining traction recently and studies suggest that they may have greater benefits than single interventions (6,94,101,102). This has been hypothesized to be due to the activation of several neurobiological pathways with

multimodal interventions in comparison to single interventions (94,101,102). Further studies are required to investigate the influence of different modes of exercise, as well as their combined influence on cognitive function.

EXERCISE AND POST-STROKE COGNITIVE IMPAIRMENT

Physical activity levels in individuals post-stroke are well below those observed in healthy older adults, which may be due to the physical and cognitive impairments negatively affecting participation in exercise (103). Exercise is well established as an effective intervention in post-stroke individuals to improve walking speed, ambulatory capacity (104,105), and may prevent falls (106). Exercise has also been found to improve cardiovascular fitness (104) and reduce cardiovascular disease risk factors such as total LDL cholesterol, triglyceride levels, and blood pressure (107,108).

Previous review papers suggest that there is potential for exercise to benefit cognition post-stroke (5,109). Cumming et al. (109) were the first to provide a review of randomized controlled trials of physical activity and exercise interventions on any domain of cognition in stroke. They found an improvement in global cognition (9 studies, 716 participants, SMD=0.20, p=0.015) though were not able to separate their analysis further by cognitive domain due to the low number of studies (109). More recently, Oberlin et al. (5) conducted a systematic review of randomized controlled trials (14 studies, 736 participants, ≥18 years of age) and reported improvements in attention and processing speed (effect size=0.37) following physical activity or exercise training, but no changes in executive function or working memory were observed. Results from individual randomized controlled trials have been mixed (59,110–125). Studies have used a wide range of exercise modalities including aerobic (110,113,114,119), resistance (118), stretching/balance (yoga, tai chi) (59,115,122) and multimodal

(111,112,116,117,120,121,123–125) training, and several have reported improvements in executive function (116,118,120–122,124), memory (115,118,121,125), attention and processing speed (114,118,120,123), visuospatial abilities (121) and global cognition (110,117,120,125) whereas others have reported no effect (59,111–113,119).

Together, these studies and systematic reviews suggest that exercise may have the potential to benefit aspects of cognitive function post-stroke. The variability in results may be due to differences in study methodology (e.g. outcomes measured, exercise intervention protocols) or in participant characteristics. One particular area of participant characteristics that has not been extensively studied is sex and gender differences in the effects of exercise on cognition.

SEX AND GENDER

SEX AND GENDER IN RESEARCH

Sex and gender-based analyses is a critical area of health research (126). Sex is defined as a biological characteristic (dichotomous male and female) involving physical and physiological features including reproductive/sexual anatomy, gene expression, chromosomes, and hormone function (126). In contrast, gender is a social characteristic referring to socially constructed behaviours, roles and identities of men, women, and gender-diverse individuals (126). Sex and gender differences exist in many forms within research such as in participant recruitment and attendance, and reporting and generalizability of research findings (127). Although the gaps between men and women are narrowing within these aspects, substantial sex and gender differences still exist within research (127).

It is imperative to determine whether interventions being studied differentially affect men, women, and gender-diverse individuals to contribute to our understanding of how to develop effective interventions and optimize health in all subsets of a population. Overall, there are four

main reasons for the importance of incorporating sex and gender within research: 1) explanatory power, 2) risk of harm, 3) missed opportunity, and 4) inefficiency (128). Sex and gender hold explanatory power in terms of describing the mechanisms surrounding the epidemiology of disease, and response to treatment (128). Additionally, there is a risk of harm by assuming that the results of studies are applicable to all individuals and we may miss opportunities to examine biological and social differences if sex and gender are not accounted for in research (128). Finally, when sex and gender are not explicitly accounted for in research, inefficiencies may occur with recruitment, interpretation of findings and the potential implications of results (128). Thus, understanding the sex-and-gender-specific effects of interventions will benefit the health of men, women, and gender-diverse individuals, ultimately by leading to advancing the understanding of optimal, personalized, rehabilitation interventions and parameters.

Despite the advancements in sex and gender research, there are challenges with examining and understanding these factors. While both sex and gender are important determinants of health, the terms "sex" and "gender" have historically been (and continue to be) used interchangeably despite each representing very distinct constructs (126,129). Sex and gender are also often interconnected which creates difficulty in differentiating whether a factor represents a sex or gender construct (126). Finally, studies have not typically presented disaggregated data by sex or gender despite efforts to increase enrollment and representation of women in clinical trials (130). Taken together, these challenges contribute to the limitations that currently exist in research trials which have not allowed us to fully understand participant factors that may contribute to inter-individual variability, such as sex and gender (126).

Organizations and institutions are now committing resources for advancing the sex and gender research agenda to address the needs of men, women, and gender-diverse individuals and

increase the ethics and rigor of health research. For example, to standardize the reporting of sex and gender within research, the Canadian Institutes of Health Research mandated in 2010 that grant applicants describe how gender and sex considerations were incorporated into proposals, when appropriate (131). More recently, the European Association of Science Editors developed the Sex and Gender Equity in Research (SAGER) Guidelines (129) that outline general principles to sex and gender research. These include: 1) the careful use of the terms sex and gender in papers to avoid confusion; 2) differentiating participants based on sex and gender; and 3) designing and conducting research to reveal sex and/or gender differences or similarities adequately in the results, even if not initially expected (129).

SEX AND GENDER DIFFERENCES IN STROKE

The importance of sex and gender differences in stroke has received increasing attention in recent years. In 2014, the World Stroke Organization "I am Woman" campaign highlighted the sex and gender differences observed in stroke individuals (132). In 2018, Heart & Stroke Report outlined the impact of stroke on women in Canada, describing the challenges women face across the healthcare system and highlighting profiles of female stroke survivors (25). Both the campaign and the Canadian report highlighted how women are disproportionately affected by stroke throughout their lives in four key aspects: 1) epidemiology, 2) risk factors and presentation, 3) rehabilitation, and 4) research.

The epidemiology of stroke is different between men and women. The average age of stroke onset in women is 72.9 years and 68.6 years in men (133). The prevalence of stroke increases in both men and women with age (134) and while it is initially higher in men, this reverses after the age of 85 years (133). Stroke-related mortality rates are similar between men and women below the age of 45, but lower in women between 45-74 years of age in comparison to age-matched

men (135). With advancing age, the advantage that women have over men in stroke mortality declines, possibly due to the loss of estrogen as a protective factor post-menopause (133,135). Women also have a longer life expectancy than men, such that they reach ages where risk of stroke is highest and outcomes are worse (134,136). Thus, women are generally older at stroke onset (134,136), experience more severe strokes (137), present with more co-morbidities, and have poorer pre-stroke functionality and greater post-stroke disability (133,135). Women also have less social support during recovery because they are more likely to be living alone (138) and thus are two times more likely than men to be discharged to long term care (139).

Sex and gender differences also exist in the metabolic and lifestyle risk factors for stroke. Diabetes, obesity, hypertension, hyperlipidemia, atrial fibrillation, and depression are the most common risk factors in women (140), and female-specific risk factors for stroke include menopause, oral contraceptives, pregnancy and conditions surrounding pregnancy (e.g. preeclampsia) (12). Although some of the aforementioned risk factors may be more common in males (such as diabetes, hypertension and atrial fibrillation), they have been shown to increase risk of stroke more in females because they live longer than males and their prevalence increases with age. In contrast, the most common risk factors for stroke for males are smoking, alcohol consumption and history of heart attack and heart disease (140).

Women are often less aware of the risk factors and signs for stroke compared to men and often present with more generalized, non-traditional signs of stroke, such as widespread weakness, disorientation, changes in consciousness, urinary incontinence and visual deficits (141,142). This results in the lower likelihood of risk factors being managed optimally (143,144) and can contribute to less timely access to healthcare services to manage risk factors or in the event of stroke itself. Indeed, women are 10% less likely to be admitted to the hospital within the

first three hours of stroke onset than men, decreasing their chances of timely stroke care and treatment (145). Arguably, this may also be related to the higher likelihood of older women living alone (145). Taken together, sex and gender differences in risk factors and stroke presentation put women at risk for worse outcomes post-stroke.

Fewer women participate in stroke rehabilitation in comparison to men, which may be due to many factors (12). Women undertake many roles throughout their adult lives at home, work and within the community. When a woman experiences a stroke, these roles can change as a result, potentially causing strain on relationships, threatening their independence and even their identity. Thus, women commonly find it challenging to prioritize their own health and are often conflicted with the amount of time they need to dedicate to rehabilitation versus time needed to focus on their home, work and children, which contributes to increased stress and decreased well-being (25). Lower participation in rehabilitation contributes to the disproportional rates of women within stroke research trials.

There are disparities between men and women in stroke research. Women are underrepresented in stroke randomized controlled trials (146) with an enrollment of 40% (147). Women may perceive that they do not have enough time to participate in research or they are worried about research-associated adverse events. By nature of many study designs, fewer older adults are typically involved in research or those with multiple co-morbidities are often excluded from participation, thereby limiting the opportunities for older women with stroke to participate (148). Strategies to recruit older individuals and women within stroke research and rehabilitation are required to help better understand sex- and age-specific effects of interventions on this population.

SEX AND GENDER DIFFERENCES IN POST-STROKE COGNITIVE FUNCTION

The evidence regarding sex differences in the risk of cognitive impairment post-stroke are inconsistent (149,150) where some studies reported higher risk of cognitive impairment in males (OR 1.6 to 3.07) (151–153) while others showed higher risk in females (OR 1.3 to 8.9) (150,154–161) or no sex differences entirely (28,162–164). However, in a systematic review investigating the prevalence and predictors of post-stroke dementia, it was reported that females were at greater risk for post-stroke (OR 1.3) dementia compared to males (150). The inconsistency in results may be due to the wide range of outcome measures used to assess cognitive impairment, and differences in baseline characteristics with respect to age, time-post-stroke and years of education.

SEX AND GENDER DIFFERENCES IN THE EFFECTS OF EXERCISE ON COGNITION

Colcombe and Kramer (90) conducted a systematic review (18 randomized trials with 197 older adults aged 55 and older) that provided the first evidence that sex may moderate the effect of exercise on cognition. They found that there was a greater benefit on cognition following either aerobic or multi-modal (aerobic and resistance) training in studies with a high percentage of females (>50% females) (effect size=0.604) compared to studies with a high percentage of males ($\geq$50% males) (effect size=0.150) (90). They also noted that, of all domains of cognition, executive function benefited most from exercise, followed by visuospatial abilities and processing speed (90). These results were confirmed in a recent meta-analysis (41 randomized trials with 5156 older adults aged 45 and older) that demonstrated that studies with a higher percentage of females (>71%) was associated with a greater effect size for improved executive functions following aerobic training in comparison to studies with a lower percentage of females ($\leq$71%) (effect size=1.83 vs. 1.46) (6). In particular, studies with a higher percentage of females

were more likely to demonstrate improved executive functions following aerobic, resistance and multimodal training (combined aerobic and resistance training) compared to studies with a lower percentage of females (6).

Sex differences have also been observed in randomized controlled trials of individuals with mild cognitive impairment. In a study of 33 older adults (age 55 to 85, n=17 (51%) females) with mild cognitive impairment, executive function improved to a greater degree in females compared to males following 6 months of aerobic training (165). Additionally, in 152 older adults (age 70 to 80, n=67 (44%) females) with mild cognitive impairment, females demonstrated greater improvements in attention and memory following 12 months of moderate intensity walking, while only memory improved in males (166). Finally, in 71 older adults (age 55 and older) with mild cognitive impairment, 6 months of aerobic training improved executive function in females (36% improvement from baseline), but not males (31% decline from baseline) (167).

Collectively, the body of evidence conducted in both older adults with and without mild cognitive impairment suggest that engaging in exercise results in larger cognitive benefits in females in comparison to males. These differences may be attributed to lower activity levels typically observed in women that can contribute to poorer cognitive performance (168,169) and thus, opportunities to increase physical activity levels in women have a greater effect on cognitive function than in males (99). Additionally, females may display less decline than males in certain aspects of cognition and thus are better able to respond to exercise.

SEX AND GENDER DIFFERENCES IN THE EFFECTS OF EXERCISE ON POST-STROKE COGNITIVE IMPAIRMENT

To date, there have been no studies examining sex and gender differences in cognition following exercise interventions in individuals with stroke. Understanding whether sex and

gender may be potential factors in moderating the effect of exercise interventions post-stroke can help to establish targeted strategies to promote healthy cognitive aging in this population. There is pressing need for research on sex and gender in individuals post-stroke to understand how these factors influence stroke presentation, testing and response to treatment (25). Currently, research is limited by the lack of inclusion of sociocultural factors in order to analyze gender. Few studies have disaggregated data by sex, and none have conducted analyses of gender differences. Both sex and gender are critical determinants of health and well-being, and it is imperative that researchers consider both aspects as potential moderators in stroke rehabilitation. However, the state of the literature is currently in transition with respect to incorporating sex-and-gender based analysis. Thus, there is insufficient evidence in regards to gender differences. Therefore, this thesis focused specifically on exploring sex differences in the effects of exercise on cognition in individuals post-stroke.

OVERALL THESIS OBJECTIVES

This thesis was comprised of two studies that explored sex differences in the effects of exercise on cognition post-stroke. The first study was a systematic review, and the second study was a secondary analysis of data from a previous randomized controlled trial.

Study 1: The Effects of Exercise on Cognition Post-Stroke: Are There Sex Differences? A Systematic Review and Meta-Analysis

Objective: To conduct a systematic review of the literature to examine sex-specific effects of exercise interventions on cognitive functioning in adults with stroke.

Hypothesis: We hypothesized that studies with a higher proportion of females would display greater improvements in cognition, following exercise, compared to studies with a lower proportion of females.

Study 2: The Effects of Exercise on Cognition Post-Stroke: Are There Sex Differences? A Secondary Analysis of a Randomized Controlled Trial

Objective: To determine whether there were differences in changes in cognitive function following a 6-month community aerobic exercise program between males and females living with stroke compared to a 6-month balance and flexibility program.

Hypothesis: Given that preliminary literature has displayed sex-specific improvements in cognition favoring females, we hypothesized that females with stroke would demonstrate greater improvements in executive functioning following aerobic exercise vs. balance and flexibility exercise compared to males.

CHAPTER 2

THE EFFECTS OF EXERCISE ON COGNITION POST-STROKE: ARE THERE SEX DIFFERENCES?

A SYSTEMATIC REVIEW AND META-ANALYSIS

ABSTRACT

Introduction: Sex differences in the effects of exercise on cognitive function have been previously reported in older adults, where larger benefits were observed in studies involving a greater proportion of females compared to a lower proportion of females. Whether this association is present in individuals with stroke has not yet been examined. The aim of this systematic review was to investigate if sex moderated the effect of exercise on cognition in adults post-stroke.

Methods: A systematic review was conducted of randomized controlled trials that involved adults ≥18 years with stroke, any exercise intervention, and reported any outcome related to cognitive function. We compared effect sizes of cognitive outcomes between studies of lower and higher proportion of females (CRD42018092757).

Results: Fifteen studies were included in the meta-analysis. We divided studies into tertiles with respect to the proportion of females within the study samples, and the lowest (n=5 studies) and highest (n=5 studies) tertiles were compared. The effects of exercise did not differ between studies of higher and lower female proportions with respect to memory (Verbal Digit Span Forward, Memory Domain of Stroke Impact Scale and Wechsler Memory Scale III - Verbal Pairing Domain: Chi^2 =1.52, p=0.22), executive function (Stroop Test: Chi^2 = 0.56 , p=0.45; Trail Making Test B: Chi^2 = 0.00, p=0.98), language (Communication Domain of Stroke Impact Scale: Chi^2 = 3.17, p=0.08) or global cognition (Montreal Cognitive Assessment, Cognitive Domain of Functional Independence Measure and Addenbrooke's Cognitive Examination-Revised: Chi^2 = 0.88, p=0.35).

Conclusion: There were no sex differences in the effects of exercise on memory, executive functioning, language or global cognition in individuals with stroke. Further research is

warranted to address sex differences in individuals with stroke to enable better targeting, prevention, and interventions in stroke rehabilitation.

INTRODUCTION

Cognitive impairment is observed in approximately 70% of individuals with stroke (1,2), which can affect independence in activities of daily living (35), contribute to mobility decline (33,34) and reduce quality of life (33). Interventions to promote recovery of cognitive function are a critical component of stroke rehabilitation.

Cognitive rehabilitation is a moderately effective treatment modality in improving cognitive function, but physical interventions such as exercise may also mitigate the effects of stroke on cognitive function. Evidence in randomized controlled trials and systematic reviews suggest that exercise may improve cognitive function in stroke survivors, although findings are equivocal. Liu-Ambrose and Eng (116) demonstrated that a 6-month exercise and recreation program improved selective attention and conflict resolution, and working memory in 28 individuals $\geq$12 months post- stroke, whereas Tang et al (119) found no changes in the same outcomes, following 6 months of exercise in 47 individuals >12 months post-stroke. Recently, a systematic review of 14 randomized controlled trials and 736 participants with stroke reported improvements in attention and processing speed following exercise training, although no changes in executive function or working memory were found (5).

Sex (biological features such as gene expression and hormone function) and gender (sociocultural factors such as marital status, education, and access to healthcare) (129) have been identified as potential moderators of the effect of exercise interventions on cognitive function in various populations (6,90). Despite the many mechanisms by which the effects of exercise on stroke survivors might be affected by both sex and gender, and guidelines emphasizing the

importance of sex and gender-based analysis in clinical research (129), sex and gender are poorly addressed in most clinical trials. Studies where sex disaggregation was performed are small and inconclusive. For example, there have only been three studies that have examined sex-specific effects of exercise on cognition. In a study of 33 older adults with mild cognitive impairment who participated in 6 months of aerobic training, executive function improved to a greater degree in females compared to males (165), and in a 12-month study of a moderate intensity walking intervention in 152 older adults with mild cognitive impairment, females demonstrated greater improvements in attention and memory compared to males (166). Finally, in 71 older adults (age 55 and older) with mild cognitive impairment, 6 months of aerobic training improved executive function in females (36% improvement from baseline), but not males (31% decline from baseline) (167).

Due to the lack of data disaggregated by sex, an alternative approach has been to look at systematic reviews comparing outcomes in samples that predominantly include one sex or the other. For example, a sub-analysis of an early systematic review by Colcombe and Kramer (90) (18 randomized trials with 197 older adults aged 55 and older) found that there was a greater benefit on cognition following exercise training in studies with a high proportion of females (>50%) compared to studies with a high percentage of males (≥50%) (90). Further, a recent systematic review exploring the sex-specific effects of exercise on cognition in older adults reported larger effect sizes in changes in executive function among studies with a higher percentage of females (>71%) compared to those with a lower percentage (≤71%) (6).

The effects of exercise on cognition in individuals with stroke are not clearly established, and it is not known whether there are sex- or gender-based differences in this relationship. One challenge in examining this is that the scientific literature is in transition with respect to clearly

differentiating between constructs of sex and gender, or separating data by sex and gender. Therefore, the purpose of this systematic review was to examine sex-specific effects of exercise interventions on cognitive functioning in adults with stroke by comparing studies that included higher vs. lower proportion of females. We hypothesized that studies with a higher proportion of females would display greater improvements in cognition, following exercise, compared to studies with a lower proportion of females.

METHODS

The protocol for this systematic review was registered in the International Prospective Register of Systematic Reviews (CRD42018092757). We used the Sex and Gender Equity in Research guidelines as a framework to define "gender" and "sex" and guide our systematic review (129) (Appendix A), where "gender" was defined as socially constructed roles, norms, behaviours, identities of women, men, and gender diverse people, and "sex" as biological characteristics in humans, and categorized as females or males (129).

LITERATURE SEARCH AND SEARCH STRATEGY

This systematic review was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 (170). A systematic search of the literature was conducted on October 24th, 2018, and repeated on February 5th, 2019 and July 30th 2019. The following electronic databases were used: EMBASE (1974–present), MEDLINE (1946–present), CINAHL (1982–present), COCHRANE, and PsycINFO (1987–present). To ensure that a comprehensive search was conducted, the search strategy included terms related to three main domains, 1) Stroke, 2) Exercise, and 3) Cognition. The specific search strategies used

for each database are presented in Appendix B. Reference lists of relevant articles were also hand searched.

STUDY SELECTION

Pairs of independent reviewers (SK, HF, EW) screened titles and abstracts for eligibility, then conducted full-text assessments to identify relevant studies using the pre-specified eligibility criteria outlined below. Disagreements were resolved through discussion.

STUDY ELIGIBILITY CRITERIA

Studies: Studies were eligible to be included if they were randomized controlled trials published in English. Ongoing trials, study protocols, dissertations, and conference proceedings (posters or abstracts) were excluded from this review.

Participants: Participants were adults aged 18 years or older with stroke of any type, duration, location and number.

Intervention: Studies were included that involved any exercise intervention, with no limitation to the type (aerobic and/or resistance training, upper and/or lower limb training), frequency, intensity or duration. Interventions conducted in any setting were included, including inpatient rehabilitation, outpatient rehabilitation, and home- and community-based training programs.

Comparators: Since none of the studies included in this review directly compared females and males nor describe effects stratified by sex, we compared effect sizes between studies of lower and higher proportion of females. We divided studies into tertiles with respect to the proportion of females within the study sample, and coded them as lower, middle and higher proportion of females. The lowest and highest tertiles were compared.

Outcomes: Studies that reported any outcome related to cognitive function, including but not limited to: attention and processing speed, memory, executive functioning, visuospatial ability, language, and global cognition were included in this review.

DATA EXTRACTION

For all studies included in this review, two independent reviewers (SK and EW) extracted the following information: author(s) name(s), study title, publication year, eligibility criteria, sample size, intervention and control group participant characteristics, intervention and control group characteristics (frequency, intensity, type, time, duration, and setting), cognitive domains assessed, task name and methodology, main findings for cognitive tasks and mean and standard deviations for each outcome. The qualitative and quantitative data extraction tables can be found in Appendix C and D.

QUALITY ASSESSMENT

The methodological quality assessment was performed by two independent reviewers (SK and EW). Risk of bias and quality were assessed using Cochrane Collaboration's Tool for Assessing Risk of Bias for randomized controlled trials (171) and Grading of Recommendations Assessment Development and Evaluation Table (172), respectively. Discrepancies of the ratings were resolved through discussion.

DATA ANALYSIS AND SYNTHESIS

Qualitative synthesis was performed reporting details of eligibility criteria, participant characteristics, intervention and control group characteristics, and cognitive outcomes. Quantitative analyses were conducted using Review Manager (RevMan version 5.3). We categorized the studies into specific domains: attention and processing speed, memory, executive

functioning, visuospatial ability, language, and global cognition (Appendix E). Outcomes of interest were expressed as the mean and standard deviation of post-intervention scores, as follow-up assessments after the conclusion of interventions were not included in all studies. For studies with more than two intervention groups, groups were combined to create pair-wise comparisons (171). Meta-analyses were performed when comparisons were possible between studies with a lower proportion and higher proportion of females. If more than one test was used for a given domain within a single study, meta-analyses were performed separately for each test. Standardized mean differences (SMD) were reported, and data were analyzed using a random-effect models.

RESULTS

QUALITATIVE SYNTHESIS

Study Characteristics

Results of the search and study selection process are presented in Figure 2. We identified 4100 publications that were assessed for eligibility, of which 17 studies with 840 participants (59,110–113,115–125,173) were included in this systematic review. Of these, two studies (112,123) were not included in the meta-analysis as mean and SD data were not available. Detailed study characteristics are provided in Table 3.

Figure 2: Study flow Diagram

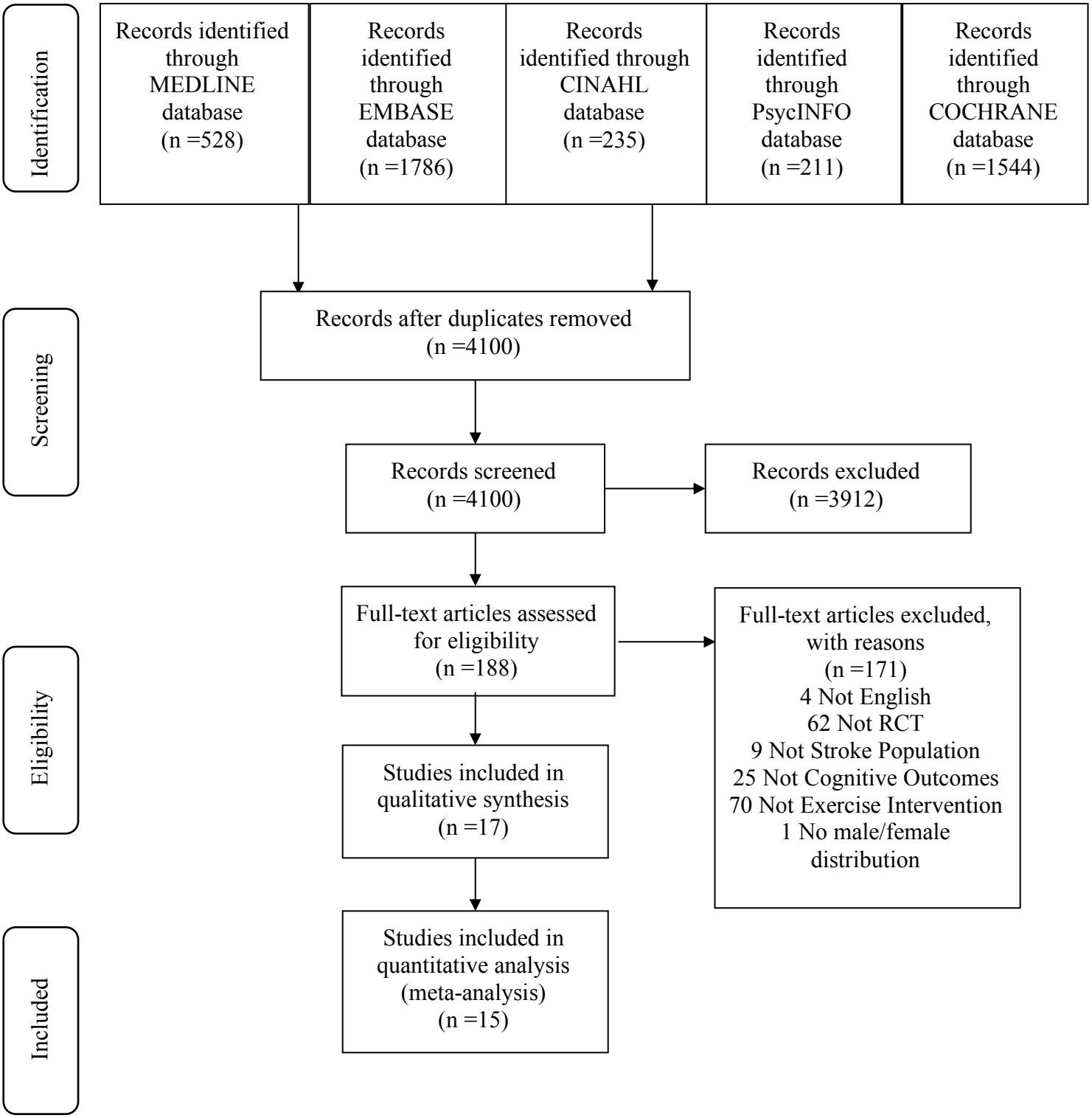

Table 3: Characteristics of Included Studies

Study	Participants: Total n, n (%) female, group n, n (%) female, mean (SD) or median (IQR) age (years), mean(SD) or median (IQR) baseline global cognition (score)	Time from Stroke to Intervention, mean(SD) or median (IQR)	Intervention (Type, Frequency, Intensity, Time)	Control (Type, Frequency, Intensity, Time)	Cognitive Outcomes and Assessment Time Points	Outcomes (units), Relevant Findings (Analyses were two-way repeated measures ANOVA unless otherwise indicated)
Nilsson et al 2001	Total n= 73, 33 females (45%) I: n=36, 16 females (44%), median=54 (24-67) years, NR C: n=37, 17 females (46%), median=56 (24-66) years, NR	I: median 22 (10–56) days C: median 17 (8–53) days	Type: Aerobic Treadmill Walking with Body Weight Support Frequency: 5 times/week for 9.5 weeks Intensity: NR Time: 30 minutes/session	Type: Track Walking (with physiotherapist) Frequency: 5 times/week for 9.5 weeks Intensity: NR Time: 30 minutes/session	Functional Independence Measure (Cognitive Domain) Baseline, 1 month, Post-intervention (9.5 weeks), 10 month follow-up	FIM-Cognitive (score), Fisher's permutation test for within-group change over time: I[a]: P<0.001* C[a]: P<0.001* Fisher's permutation test for between group difference post-intervention, P=NS
Studenski et al 2005	Total n=93, 43 females (46%) I: n=44, 21 females (48%), 68.5(9) years, NR C: n=49, 22 females (45%), 70.4(11.3)	I: 77.5 (28.7) days C: 74.1 (27.2) days	Type: Home-based progressive exercise program (Resistance/Aerobic and Balance) Frequency: 3 times/week for 12 weeks	Type: Usual Care (consisting of education on preventing recurrent stroke, vital signs check, and receiving PT/OT as part of usual care)	Functional Independence Measure (Cognitive Domain), Stroke Impact Scale (Memory domain), and Stroke Impact	FIM-Cognitive (score), ANCOVA for between-group difference post-intervention, P=NS SIS-Memory and Thinking (score), ANCOVA for between-group difference post-intervention, P=NS

	years, NR		Intensity: NR Time: 90 minutes/session	Frequency: Bi-monthly for 12 weeks Intensity: NR Time: 30 minutes/session	Scale (Communication domain) Baseline, Post-intervention (12 weeks), 6 month follow-up	SIS-Communication (score), ANCOVA for between-group difference post-intervention, P=NS
Mead et al 2007	Total n= 64, 30 females (45%) I: n=32, 14 females (44%),72 (10.4) years, NR C: n=34, 16 females (47%), 71.7 (9.6) years, NR	I: median 178 (86-307) days C: median 161.5 (91.8-242.8) days	Type: Combined Progressive Aerobic and Resistance Exercise Program Frequency: 3 times/week for 12 weeks Intensity: 13-16 Rate of Perceived Exertion Time: 75 minutes/session	Type: Seated Relaxation Frequency: 3 times/week for 12 weeks Intensity: NA Time: 75 minutes/session	Functional Independence Measure (Cognitive Domain) Baseline, Post-intervention (12 weeks), 4 month follow-up	Total FIM score reported though Cognitive domain of FIM NR
Rabadi et al 2008	Total n=30, 11 females (37%) I: n=10, 1 female (10%), 69.2 (10.2) years, MMSE: 17.0 (9.3)	I: 22.2 (15.1) days C_1: 19.0 (4.7) days C_2: 22.5 (18.2) days	Type: Arm Ergometer Frequency: 5 times/week for 12 sessions Intensity: #	Type (C_1): Robot Aided Therapy (arm movements) Frequency (C_1): 5 times/week for 12 sessions	Functional Independence Measure (Cognitive Domain) Baseline, Post-intervention	FIM-Cognitive (score), ANCOVA for between-group difference post-intervention, P=0.90

	C_1: n=10, 5 females (50%), 79.5 (6.2) years, MMSE:16.6 (8.4) C_2: n=10, 5 females (50%), 67.8 (12.7) years, MMSE: 16.0 (11.5)		rotations/minute (2200 rotations/session) Time: 40 minutes/session	Intensity (C_1): # movements/minute (1024 movements/session) Time (C_1): 40 minutes/session Type (C_2): Occupational Therapy Frequency (C_2): 5 times/week for 12 sessions Intensity (C_2): # movements/session (640 movements/session). Time (C_2): 40 minutes/session	(12 sessions)	
Quaney et al 2009	Total n= 38, 21 females (55%) I: n=19, 9 females (47%), 64.1 (12.3) years, MMSE: 28.2 (2.1) C: n=19, 12 females (63%), 59.0 (14.7)	I: 4.6 (3.2) years C: 5.1 (3.5) years	Type: Progressive Resistive Cycle Ergometer Training Frequency: 3 times/week for 8 weeks Intensity: 40-70% maximal heart rate	Type: Home-based Stretching Exercises Frequency: 3 times/week for 8 weeks Intensity: NR Time: 45	Wisconsin Card Sort Test, Stroop Colour-Word Interference Test, Trail Making Test B, Serial Reaction Timed Task	WCST (# of rules learned), T-test on change scores for between-group difference over time, P=0.14 Stroop CW (sec), T-test on change scores for between-group difference over time, P=0.13

	years, MMSE: 29.0 (1.4)		Time: 45 minutes/session	minutes/session	Baseline, Post-intervention (8 weeks), 8 week follow-up	TMT B (sec), T-test on change scores for between-group difference over time, P=0.28 SRTT Repeated (sec), T-test on change scores for between-group difference over time, P=0.02* SRTT Random (sec), T-test on change scores for between-group difference over time, P=0.20
Immink et al 2014	Total n= 22, 13 females (59%) I: n=11, 5 females (45%), 56.1(13.6) years, NR C: n=11, 8 females (73%), 63.2 (17.4) years, NR	I: 81.6 (77.5) months C: 23.3 (12.5) months	Type: Yoga Frequency: 1 time/week for group classes and 6 days/week for home practice for 10 weeks Intensity: NR Time: 90-minute group classes and 40-minute individual home practice sessions	Type: Waitlist Control Frequency: NA,10 weeks Intensity: NA Time: NA	Stroke Impact Scale (Memory domain), and Stroke Impact Scale (Communication domain) Baseline, Post-intervention (10 weeks)	SIS-Memory (score), Group Effect: P=0.06 Time Effect: P=0.02* Interaction: P=0.05* Post-hoc Analysis, intervention group improved over time: I: P=0.02* C: P=0.66 SIS-Communication (score) Group Effect: NS Time Effect: NS Interaction: NS
Liu-Ambrose and Eng	Total n= 25, 10 females (40%)	I: 2.4 (1.0) years	Type: Combined Resistance, Aerobic, Balance Exercise	Type: Waitlist Control Frequency: NA, 6	Stroop Colour-Word Interference	Stroop CW (sec), ANOVA on change scores for between-group difference

2015	I: n=11, 7 females (64%), 62.9 (12.1) years, MoCA= 24.8 (2.6) C: n=14, 3 females (21%), 66.9 (9.0) years, MoCA: 21.8 (6.9)	C: 2.9 (1.1) years	Training Program + Recreation and Leisure session Frequency: 2 times/week for 6 months for exercise program + 1 time/week for 6 months for recreation and leisure Intensity: Started at 40–50% HRR, with increment of 10% HRR every 4 weeks, up to 70–80% HRR, as tolerated Time: 60 minutes/session	months Intensity: NA Time: NA	Test, Trail Making Test B, Verbal Digit Span Backwards Baseline, 3 months, Post-intervention (6 months)	over time, P=0.02* TMT B (sec), ANOVA on change scores for between-group difference over time, P=NS DSB (n sequence), ANOVA on change scores for between-group difference over time, P=0.04*
Moore et al 2015	Total n= 40, 6 females (15%) I: n=20, 2 females (10%), 68 (8) years, MMSE: 28 (2) C: n=20, 4 females (20%) years, 70 (11), MMSE: 29 (1)	I: 21 (34) months C: 16 (12) months	Type: Combined Resistance, Aerobic, Balance and Stretching Exercise Program Frequency: 3 times/week for 19 weeks Intensity: 40-50%	Type: Home Stretching Program Frequency: 3 times/week for 19 weeks Intensity: Strength/balance exercises were progressed by	Addenbrooke's Cognitive Examination-Revised, Stroke Impact Scale (Memory domain), and Stroke Impact Scale (Communicatio n domain)	ACE-R (score), T-test for within-group difference over time: I: P<0.01* C: P=0.19 T-test on change scores for between-group difference over time, P=0.04* SIS-Memory (score), T-test

			maximum heart rate, increased by 10% every 4 weeks up to 70-80%, as tolerated Time: 45-60 minutes/session	increasing repetitions and loading Time: 45-60 minutes/session	Baseline, Post-intervention (19 weeks)	for within-group difference over time: I: P=0.81 C: P=0.52 T-test on change scores for between-group difference over time, P=0.64 SIS-Communication (score), T-test for within-group difference over time: I: P=0.70 C: P=0.76 T-test on change scores for between-group difference over time, P=0.62
Fernandez-Gonzalo et al 2016	Total n=29, 7 females (24.1%) I: n=14, 3 females (21%), 61.2 (9.8) years, MMSE: 28.1(1.8) C: n=15, 4 females (27%), 65.7 (12.7) years, MMSE: 27.7 (2.3)	I: 3.5 (3.6) years C: 4.3 (4.9) years	Type: Resistance Exercise Frequency: 2 times/week for 12 weeks Intensity: Maximal Intensity Time: 4 sets of 7 maximal repetitions	Type: Usual Care Frequency: NA, 12 weeks Intensity: NA Time: NA	Verbal Digit Span Forward and Backward, Rey Auditory Verbal Learning Test, Continuous Performance Test, Wechsler Memory Scale III - Spatial Span Domain (Forward and Backward), Stroop	DSF (n sequence) Group Effect: P=NS Time Effect: P=NS Interaction: P = 0.02* Post-hoc Analysis, intervention group did not improve over time: I: P=NS C: P=NS DSB (n sequence) Group Effect: P=NS Time Effect: P=NS Interaction: P = 0.03*

					Baseline, Stroop Colour-Word Interference Test, Trail Making Test A and B, FAS Test Baseline, Post-intervention (12 weeks)	Post-hoc Analysis, intervention group did not improve over time: I: P=NS C: P=NS RAVLT Learning (n words) Group Effect: P=NS Time Effect: P=NS Interaction: NS RAVLT Recall (n words) Group Effect: P=NS Time Effect: P=NS Interaction: NS CPT (reaction time, sec) Group Effect: P=NS Time Effect: P=NS Interaction: NS WMS-III Spatial Span Fwd (score) Group Effect: P=NS Time Effect: P=NS Interaction: NS WMS-III Spatial Span Bwd (score) Group Effect: P=NS Time Effect: P=NS Interaction: NS

						Stroop Baseline (sec) Group Effect: P=NS Time Effect: P=NS Interaction: P = 0.01* Post-hoc Analysis, intervention group improved over time: I: P=0.04* C: P=NS Stroop CW (sec) Group Effect: P=NS Time Effect: P=NS Interaction: NS TMT A (sec) Group Effect: P=NS Time Effect: P=NS Interaction: NS TMT B (sec) Group Effect: P=NS Time Effect: P=NS Interaction: NS FAS (n words) Group Effect: P=NS Time Effect: P=NS Interaction: P = 0.02* Post-hoc Analysis,

						intervention group improved over time: I: P=0.01* C: P=NS
Tang et al 2016	Total n= 50, 21 females (42%) I: n=25, 11 females (44%), median=66 (62–71) years, MoCA: median=26 (23–28) C: n-25, 10 females (40%), median=64 (62–75) years, MoCA: median=25 (21–27)	I: median 3.5 (2.2–6.7) years C: median 2.3 (1.8–5.1) years	Type: Aerobic Exercise Frequency: 3 times/week for 6 months Intensity: 40-80% Heart rate Reserve Time: 60 minutes/session	Type: Balance and Flexibility Exercise Frequency: 3 times/week for 6 months Intensity: Below 40% Heart rate Reserve Time: 60 minutes/session	Verbal Digit Span Forward and Backward, Trail Making Test B, Stroop Colour-Word Interference Test Baseline, Post-intervention (6 months)	DSF (n sequence), T-test for within-group change over time: P=0.04* T-test on change score for between-group difference over time: P=0.49 DSB (n sequence), T-test for within-group change over time : P=0.91 T-test on change score for between-group difference over time: P=0.18 TMT B (sec), T-test for within-group change over time: P=0.54 T-test on change score for between-group difference over time: P=0.68 Stroop CW (sec), T-test for within-group change over time: P=0.98

						T-test on change score for between-group difference over time: P=0.38
Chan and Tsang 2017	Total n=23, 11 females (48%), I_1: n=9, 4 females (44%), 63.9 (6.1) years, MMSE: 29.2 (0.4) I_2: n=5, 2 females (40%), 63.2 (9.7) years, MMSE= 27 (1.9) C: n=9, 5 females (56%), 63.2 (6) years, MMSE= 27.3 (2.7)	I:3.3 (3) years I_2:8.8 (7.9) years C: 4.6 (3) years	Type (I_1): Tai Chi Frequency (I_1): 2 times/week for 12 weeks Intensity (I_1): NR Time (I_1): 1 hour/session Type (I_2): Conventional Exercise Frequency (I_2): 2 times/week for 12 weeks Intensity (I_2): NR Time (I_2): 1 hour/session	Type: No Training Frequency: 2 times/week for 12 weeks Intensity: NA Time: NA	Auditory Stroop Test Baseline, Post-intervention (12 weeks), 1 month follow-up	Auditory Stroop (score) Group Effect: P= 0.62 Time Effect: P=0.06 Interaction: P=0.95
Kim and Yim 2017	Total n= 30, 10 females (34%) I: n=14, 5 females (36%), 50.7 (14.8) years, MMSE: 26.4 (5.3)	I: 12.8 (7.3) months C:11.7 (8.0) months	Type: Exercise (Handgrip Exercises and Treadmill Walking) + Conventional Physical Therapy	Type: Conventional Physical Therapy Frequency: 2 times/day and 5 times/week for 6 weeks	Montreal Cognitive Assessment (Korean Version), Trail Making Test A and B, Stroop	K-MoCA(score), T-test for within-group change over time: I: P=0.00* C: P=0.24 T-test on change score for

	C: n=15, 5 females (33%), 51.9 (17.4) years, MMSE: 25.5 (3.3)		Frequency: conventional therapy=2 times/day 5 times/week and exercise protocol=3 times/day for 6 weeks Intensity: NR Time: 90 minutes/session (Conventional therapy=60 minutes, exercise protocol 30 minutes)	Intensity: NR Time: 60 minutes/session	Test Baseline , Stroop Colour-Word Interference Test Baseline, Post-intervention (6 weeks)	between-group difference over time: P=0.05* TMT A(sec), T-test for within-group change over time: I: P=0.28 C: P=0.07 T-test on change score for between-group difference over time: P=0.86 TMT B(sec), T-test for within-group change over time: I: P=0.03* C: P=0.11 T-test on change score for between-group difference over time: P=0.49 Stroop Baseline (sec), T-test for within-group change over time: I: P=0.02* C: P=0.00* T-test on change score for between-group difference over time: P=0.37

						Stroop CW(sec), T-test for within-group change over time: I: P=0.01* C: P=0.11 T-test on change score for between-group difference over time: P=0.14
Bo et al 2018	Total n=179, 79 females (44%) I_1: n=42, 19 females (45 %), 65.1 (2.6) years , MMSE: 16.8 (5.8) I_2: n=44, 19 females (43%), 66.7 (2.4) years, MMSE: 17.5 (5.6) C_1: n=45, 21 females (47%), 67.5 (2.2) years, MMSE: 15.7 (6.2) C_2: n=47, 20 females (43%), 64.4 (2.3) years, MMSE: 16.8 (6.3)	I: NR C: NR	Type (I_1): Physical Exercise (Aerobic/Resistance/ Balance) Frequency (I_1): 3 times/week for 12 weeks Intensity (I_1): 13–15 Rate of Perceived Exertion Time (I_1): 50 minutes/session Type (I_2): Physical Exercise (Aerobic/Resistance/ Balance) and Cognitive Training Frequency (I_2): 3 times/week for 12	Type (C_1): Cognitive Training Frequency (C_1): 3 times/week for 12 weeks Intensity (C_1): N/A Time (C_1): 60 minutes/session Type (C_2): Usual Care and Video Documentaries Frequency (C_2): 3 times/week for 12 weeks Intensity (C_2): NR Time (C_2): 45 minutes/session	Trail Making Test B, Stroop Colour-Word Interference Test, Verbal Digit Span Forward and Mental Rotation Test Baseline, Post-intervention (12 weeks), 6 month follow-up	Trail Making Test B (sec), repeated measures ANOVA for within-group change over time: I_1: p=0.03* I_2: p=0.00* C_1: p=0.03* C_2: p=0.59 ANOVA for between-group difference post-intervention: I_2 vs C_2: P=0.03* Stroop CW (sec), repeated measures ANOVA for within-group change over time: I_1: P=0.68 I_2: P=0.00* C_1: P=0.40 C_2: P=0.53 ANOVA for between-group

			weeks Intensity (I_2): Each of the participants exercised at a self-determined moderate intensity level using Rate of Perceived Exertion, with ratings of 13–15 as the desired range Time (I_2): 60 minutes for cognitive training, followed by a 45 minutes break, then 50 minutes for exercise			difference post-intervention: I_2 vs C_2: P=0.03* DSF (n sequence), repeated measures ANOVA for within-group change over time: I_1: P=0.58 I_2: P=0.00* C_1: P=0.00* C_2: P=0.27 ANOVA for between-group difference post-intervention: I_2 vs C_2: P=0.00* I_2 vs I_1: P=0.00* C_1 vs C_2: P=0.00* Mental Rotation Test (score), repeated measures ANOVA for within-group change over time: I_1: P=0.94 I_2: p=0.01* C_1:P=0.29 C_2: P=0.49 ANOVA for between-group difference post-intervention: I_2 vs C_2: P=0.02*

						I_2 vs I_1: P=0.03* I_2 vs C_1:P=0.05*
Chan and Tsang 2018	Total n= 47, 20 females (43%) I_1: n=15, 6 females (40%), 63 (7) years, MMSE: 28.5 (1.7) I_2: n=17, 7 females (41%), 62.7 (7.3) years, MMSE= 27.9 (1.9) C: n=15, 7 females (47%), 62.3 (7.3) years, MMSE= 26.9 (2.9)	I: 4.6 (4.8) years I_2:7.8 (6.1) years C:5.9 (3.8) years	Type (I_1): Tai Chi Frequency(I_1): 2 times/week for 12 weeks Intensity (I_1): NR Time (I_1): 1 hour/session Type (I_2): Conventional Exercise (Aerobic/Resistance/ Stretching) Frequency (I_2): 2 times/week for 12 weeks Intensity (I_2): NR Time (I_2): 1 hour/session	Type: No Training Frequency: 2 times/week for 12 weeks Intensity: NA Time: NA	Auditory Stroop Test Baseline, Post-intervention (12 weeks), 1 month follow-up	Auditory Stroop (score), Group Effect: P=0.50 Time Effect: P<0.00* Interaction: P=0.60 Post-hoc Analysis, groups improved over time: I: P=NS I_2: P=0.02* C: P=0.04*
Debreceni-Nagy et al 2019	Total n= 35, 11 females (31%) I_1: n=19, 6 females (32%), median=59	I: median=10 (4.5–13.5) months C: median= 13	Type: Low intensity Aerobic Training by Cycle Ergometer + Physiotherapy + Occupational	Type: Physiotherapy + Occupational Therapy Frequency: 5 times/week for 4	Functional Independence Measure (Cognitive Domain),	FIM-Cog (score), T-test for within-group change over time: I: P=0.11 C: P=0.68

	(50-63) years, MMSE: median=28 (27–29) C: n=16, 5 females (31%), median=62 (52.8–68.3) years, MMSE: median=28 (27–28.3)	(3–26.5) months	Therapy Frequency: 5 times/week for 4 weeks Intensity: 40-60% Heart rate reserve Time: Aerobic Training=30 minutes, Physiotherapy=30 minutes and Occupational Therapy=30 minutes, Total=90 minutes	weeks Intensity: NR Time: Physiotherapy=60 minutes and Occupational Therapy=30 minutes, Total=90 minutes	Verbal Digit Span Backward, Wechsler Adult Intelligence Scale IV-Coding and Symbol Domains Baseline and Post-intervention (4 weeks)	T-test for between-group difference post-intervention: P=0.96 DSB (n sequence), T-test for within-group change over time: I: P=0.16 C: P=0.69 T-test for between-group difference post-intervention: P=0.48 WAIS-IV-Coding (score), T-test for within-group change over time: I: P=0.00* C: P=0.03* T-test for between-group difference post-intervention: P=0.47 WAIS-IV-Symbol (score), T-test for within-group change over time: I: P=0.04* C: P=0.01* T-test for between-group difference post-

						intervention: P=0.67
Ploughman et al 2019	Total n= 52, 16 females (31%) I_1: n=12, 5 females (42%), 62.1 (14.2) years, MoCA: 23.3 (7.5) I_2: n=13, 4 females (31%), 58.4 (11.7) years, MoCA= 24.9 (4.8) C_1: n=15, 3 females (20%), 63.9 (8.5) years, MoCA=24.9 (4.7) C_2: n=12, 4 females (33%), 69.7 (8.9) years, MoCA=21.9 (5.4)	I_1: 40.9 (33.8) months I_2: 36.0 (53.4) months C_1: 35.2 (33.9) months C_2: 53.9 (37.4) months	Type (I_1): Aerobic Treadmill Walking + Cognitive Training Frequency (I_1): 3 times/week for 10 weeks Intensity (I_1): 60-80% VO_2 peak Time (I_1): 50 to 70 minutes Type (I_2): Aerobic + Cognitive Games Frequency (I_2): 3 times/week for 10 weeks Intensity (I_2): 60-80% VO_2 peak Time (I_2): 50 to 70 minutes	Type (C_1): Physical Activity + Cognitive Training Frequency (C_1): 3 times/week for 10 weeks Intensity (C_1): NR Time (C_1): 50 to 70 minutes Type (C_2): Physical Activity + Cognitive Games Frequency (C_2): 3 times/week for 10 weeks Intensity (C_2): NR Time (C_2): 50 to 70 minutes	Raven's Progressive Matrices Test Baseline, Post-intervention (10 weeks), 3 month follow-up	RPMT (score) Group Effect: P=NS Time Effect: p=0.44 Interaction: p=0.01* Post-hoc Analysis, groups improved over time: I_1: P<0.05* I_2: NS C_1: P<0.05* C_2: NS
Yeh et al 2019	Total n=30 , 9 females (30%) I: n=15, 7 females	I: 47.8 (SEM=11.5) months	Type: Progressive Resistive Cycle Ergometer Training + Cognitive Training	Type: Flexibility/Balance Exercise + Unstructured Mental	Montreal Cognitive Assessment, Wechsler	MoCA (score), ANCOVA for between-group difference post-intervention, P=0.03*

	(40%), 50.6 (SEM=4.0) years, MMSE: 25.8 (SEM=0.9) C: n=15, 2 females (41%), 62.7 (SEM=7.3) years, MMSE: 24.6 (SEM=0.8)	C: 94.4 (SEM=30.8) months	Frequency: 2 or 3 times/week for 12 to 18 weeks Intensity:40-70% max Heart rate Time: Exercise=30 minutes, Cognitive Training=30 minutes, Total=60 minutes	Activities Frequency: 2 or 3 times/week for 12 to 18 weeks Intensity: NR Time: Exercise=30 minutes, Cognitive Training=30 minutes, Total=60 minutes	Memory Scale III - Spatial Span and Verbal Pairing Domains Baseline and Post-intervention (12 to 18 weeks: 36 training sessions)	WMS-III-Spatial Span (score), ANCOVA for between-group difference post-intervention, P=0.01* WMS-III-Verbal Pairing (score), ANCOVA for between-group difference post-intervention, P=0.64

Abbreviations: I=Intervention, C=Control, NR=Not Reported, NA=Not Applicable, NS=not significant, sec=seconds, MMSE=Mini Mental State Exam, MoCA=Montreal Cognitive Assessment, FIM-Cognitive=Functional Independence Measure (Cognitive Domain), SIS-Memory= Stroke Impact Scale (Memory domain), SIS-Communication=Stroke Impact Scale (Communication domain), WCST= Wisconsin Card Sort Test, SRTT=Serial Reaction Timed Task, ACE-R= Addenbrooke's Cognitive Examination-Revised, DSF= Verbal Digit Span Forward, DSB= Verbal Digit Span Backward, RAVLT= Rey Auditory Verbal Learning Test, CPT= Continuous Performance Test, Stroop CW= Stroop Colour-Word Interference Test, TMT A= Trail Making Test A, TMT B= Trail Making Test B, K-MoCA= Montreal Cognitive Assessment (Korean Version), WAIS-IV= Wechsler Adult Intelligence Scale-Fourth Edition, WMS-III= Wechsler Memory Scale-Third Edition, RPMT=Raven's Progressive Matrices Test

*P<0.05

[a] Pre-intervention to 10 month follow-up mean(SD)

Participants

Sample sizes ranged from 22 to 179 individuals, and ages of participants ranged from 51 to 72 years. Twelve studies (70%) reported on occurrences of adverse events (59,110,112,113,115–119,122–124), of which eight (59,113,115–118,122,124) reported no incidence of adverse events during or outside the intervention or control conditions. Two studies reported falls that occurred during the control conditions (seated relaxation and low-intensity balance and flexibility exercise) (112,119) and outside of the intervention and control conditions (112). One study (123) reported an episode of hypertension during training in which training had to be temporarily suspended. Another study (110) reported that two participants (total n=73) died over the course of the study, however, it was unclear whether these incidents were related to the intervention. Attendance rates were reported in eight studies averaging 89% attendance, and ranging from 59% to 100% in intervention conditions and 50% to 100% in control conditions.

Intervention

Four studies (110,113,119,173) involved an aerobic exercise intervention (ex. treadmill training), one study (118) consisted of a resistance exercise intervention, three studies (59,115,122) included a balance and flexibility exercise intervention (ex. yoga and tai chi), and nine studies (111,112,116,117,120,121,123–125) consisted of a multi-modal intervention (ex. aerobic exercise combined with resistance). Most interventions were conducted 2-3 times per week. Interventions varied from 4 to 24 weeks in duration. The intensity of interventions were reported in eleven studies (112,113,116–119,121,123–125,173) typically utilizing a progressive intensity (e.g. beginning at 40-50% heart rate reserve and progressing to 70-80%) (113,116–119,123–125,173) or a scale (Rate of Perceived Exertion) (112,121). The duration of each session varied between 30 to 90 minutes.

Control

Control conditions included track walking (110), usual care (111,118,121), relaxation (112), robot aided therapy (113), occupational therapy (113), stretching (117,173) , waitlist (115,116), balance and flexibility exercise (119), no training (59,122), physical therapy (120), cognitive training (121), physiotherapy combined with occupational therapy (123), physical activity combined with cognitive training (124) and balance and flexibility exercise combined with unstructured mental activities (125).

Cognitive Outcomes

Four studies (118,120,123,173) employed tests of attention and processing speed, which included Trail Making Test A (118,120), Continuous Performance Test (118), Serial Reaction

Timed Task (repeated and random) (173), Stroop Baseline Test (118,120) and Wechsler Adult Intelligence Scale IV - Symbol Search and Coding Domains (123). Eight studies (111,115,117–119,121,123,125) incorporated tests of memory, including Verbal Digit Span Forward (118,119,121,123), Rey Auditory Verbal Learning Test (118), Stroke Impact Scale (Memory domain) (111,115,117) and Wechsler Memory Scale III - Verbal Pairing Domain (125). Ten studies (59,116,118–124,173) assessed executive functioning using the Trail Making Test B (116,118–121,173), Stroop Colour-Word Interference Test (116,118–121,173) or Auditory Stroop Test (59,122), Verbal Digit Span Backward (116,118,119,123), FAS Test (118), Wisconsin Card Sort Test (173), and Raven's Progressive Matrices Test (124). Three studies (118,121,125) utilized tests of visuospatial function such as the Mental Rotation Test (121) and Wechsler Memory Scale III - Spatial Span Domain (118,125) and three studies (111,115,117) included a measure of language using Stroke Impact Scale (Communication domain) (111,115,117). Eight studies (110–113,117,120,123,125) measured global cognitive function using Montreal Cognitive Assessment (120,125), Functional Independence Measure (Cognitive Domain) (110–113,123), and Addenbrooke's Cognitive Examination-Revised (117).

Quality Assessment

Details on the risk of bias of studies are presented in Table 4 and the methodological quality of each study in Table 5. Five studies (116,119,121,124,125) were considered to have high methodological quality because they had low risk of bias on all six criteria, and one study (110) was evaluated to have a high risk of attrition bias (Table 4). Two outcomes were rated as very low overall quality, eleven outcomes had a low overall quality, and three were of moderate quality (Table 5).

Table 4: Risk of Bias Assessment of Included Studies Using the Cochrane Collaboration Risk of Bias Tool

Study	Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants and Personnel (Performance Bias)	Blinding of Outcome Assessors (Detection Bias)	Incomplete Outcome Data (Attrition Bias)	Selective Outcome Reporting (Reporting Bias)
Nilsson et al 2001 (110)	Low	Low	Low	Low	High	Low
Studenski et al 2005 (111)	Low	NR	Low	Low	Low	Low
Mead et al 2007 (112)	Low	Low	NR	Low	Low	Low
Rabadi et al 2008 (113)	Low	Low	NR	Low	Low	Low
Quaney et al 2009 (173)	Low	NR	Low	Low	Low	Low
Immink et al 2014 (115)	Low	Low	NR	Low	Low	Low
Liu-Ambrose and Eng 2015 (116)	Low	Low	Low	Low	Low	Low
Moore et al 2015 (117)	Low	NR	Low	Low	Low	Low
Fernandez-Gonzalo et al 2016 (118)	Low	Low	NR	Low	Low	Low
Tang et al 2016 (119)	Low	Low	Low	Low	Low	Low
Chan and Tsang 2017 (59)	NR	NR	NR	Low	Low	Low
Kim and Yim 2017 (120)	NR	NR	NR	NR	Low	Low
Bo et al 2018 (121)	Low	Low	Low	Low	Low	Low
Chan and Tsang 2018 (122)	Low	NR	Low	Low	Low	Low
Debreceni-Nagy et al 2019 (123)	NR	NR	Low	Low	Low	Low
Ploughman et al 2019 (124)	Low	Low	Low	Low	Low	Low
Yeh et al 2019 (125)	Low	Low	Low	Low	Low	Low

NR=Not Reported

Table 5: Grading of Recommendations Assessment Development and Evaluation Table (GRADE)

Outcome (Citations)	Number of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality
Attention and Processing Speed (118,120,173)								
Trail Making Test A (118,120)	2	RCT	Serious[1]	Not serious	Not serious	Very Serious[2]	None	+ (Very Low)
Continuous Performance Test (118)	1	RCT	Not serious	N/A	N/A	Very Serious[2]	None	++ (Low)
Serial Reaction Timed Task (repeated and random) (173)	1	RCT	Not serious	N/A	N/A	Very Serious[2]	None	++ (Low)
Stroop Baseline Test (118,120)	2	RCT	Serious[1]	Not serious	Not serious	Very Serious[2]	None	+ (Very Low)
Memory (111,115,117–119,121,125)								
Verbal Digit Span Forward (118,119,121,123), Stroke Impact Scale (Memory domain) (111,115,117) and Wechsler Memory Scale III - Verbal Pairing Domain (125)	6	RCT	Not Serious	Not serious	Not serious	Serious[3]	None	+++ (Moderate)
Rey Auditory Verbal Learning Test (118)	1	RCT	Not serious	N/A	N/A	Very Serious[2]	None	++ (Low)
Executive Function (59,116,118–122,124,173)								
Trail Making Test B (116,118–121,173)	6	RCT	Not serious	Not serious	Not serious	Serious[3]	None	+++ (Moderate)
Stroop Colour-Word Interference Test (116,118–121,173), Auditory Stroop Test (59,122)	8	RCT	Not Serious	Not serious	Not serious	Serious[3]	None	+++ (Moderate)

Verbal Digit Span Backward (116,118,119,123)	3	RCT	Not serious	Not serious	Not serious	Very Serious[2]	None	++ (Low)
FAS Test (118)	1	RCT	Not serious	N/A	N/A	Very Serious[2]	None	++ (Low)
Wisconsin Card Sort Test (173)	1	RCT	Not serious	N/A	N/A	Very Serious[2]	None	++ (Low)
Raven's Progressive Matrices Test (124)	1	RCT	Not serious	N/A	N/A	Very Serious[2]	None	++ (Low)
Visuospatial Function (118,121,125)								
Mental Rotation Test (121)	1	RCT	Not Serious	N/A	N/A	Very Serious[2]	None	++ (Low)
Wechsler Memory Scale III - Spatial Span Domain (118,125)	1	RCT	Not serious	N/A	N/A	Very Serious[2]	None	++ (Low)
Language (111,115,117)								
Stroke Impact Scale (Communication domain) (111,115,117)	3	RCT	Not serious	Not serious	Not serious	Very Serious[2]	None	++ (Low)
Global Cognitive function (110,111,113,117,120,125)								
Montreal Cognitive Assessment (120,125), Functional Independence Measure (Cognitive Domain) (110,111,113), Addenbrooke's Cognitive Examination-Revised (117)	6	RCT	Not Serious	Not serious	Not serious	Very Serious[2]	None	++ (Low)

N/A=Not Applicable

1. Most information from studies in which risk of bias was not reported
2. Values were displayed with small sample sizes (n<300)
3. Values were displayed with sample sizes (n>300)

QUANTITATIVE SYNTHESIS

Of the 15 studies included in the meta-analysis, five were categorized as lower female proportion studies (117,118,120,124,125), five were considered higher female proportion studies (59,110,111,115,173) and five were categorized as middle tertile studies (113,116,119,121,122) (Table 6). Five studies (59,113,121,122,124) involved greater than two comparison groups, thus where appropriate, intervention groups were combined (59,121,122,124) and control groups were combined (113,121,124) to create pair-wise comparisons.

Table 6: Studies Coded as Lower, Middle and Higher Proportion of Females

Lower Proportion of Females in Study
Moore et al 2015 **(15%)**
Fernandez-Gonzalo et al 2016 **(24%)**
Yeh et al 2019 **(30%)**
Ploughman et al 2019 **(31%)**
Kim and Yim 2017 **(34%)**
Middle Proportion of Females in Study
Rabadi et al 2008 **(37%)**
Liu-Ambrose and Eng 2015 **(40%)**
Tang et al 2016 **(42%)**
Chan and Tsang 2018 **(43%)**
Bo et al 2018 **(44%)**
Higher Proportion of Females in Study
Nilsson et al 2001 **(45%)**
Studenski et al 2005 **(46%)**

Chan and Tsang 2017 **(48%)**

Quaney et al 2009 **(55%)**

Immink et al 2014 **(59%)**

1

Sex differences in the effect of exercise on memory

The effect of exercise on episodic memory and overall memory was assessed in seven studies using the Verbal Digit Span Forward, Stroke Impact Scale (memory domain), and Wechsler Memory Scale III - Verbal Pairing Domain, with two higher proportion (111,115) and three lower proportion female studies (117,118,125). The effect did not differ between studies with a higher proportion of females and a lower proportion of females (Chi^2 =1.52, p=0.22) (Figure 3).

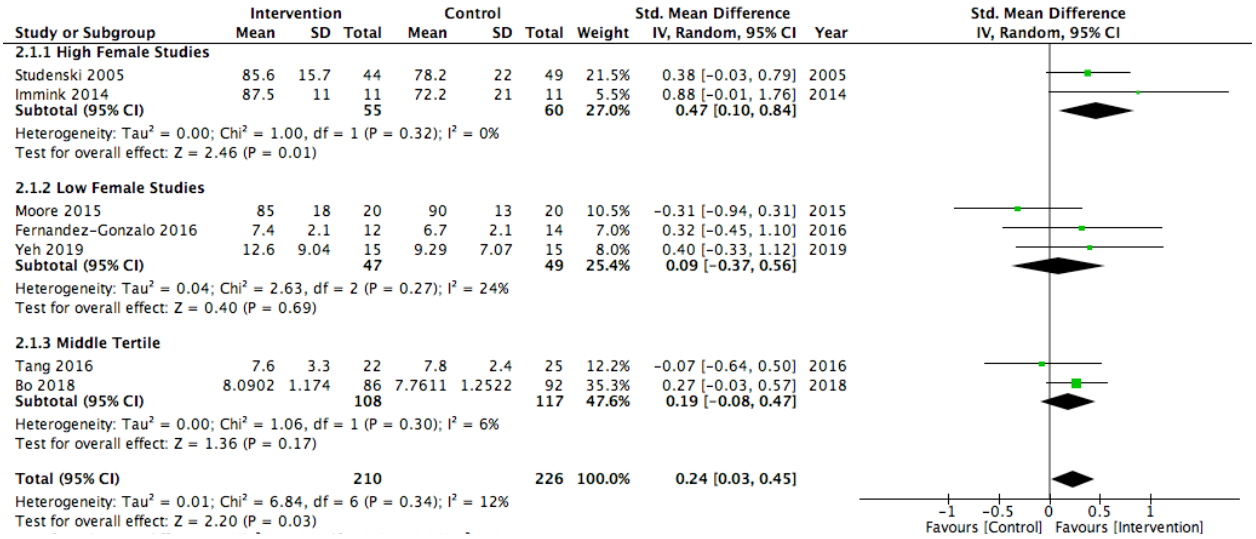

Figure 3: Forest plot of the effects of exercise on Memory (episodic memory and overall memory)

Sex differences in the effect of exercise on executive function

a) Stroop Test

The effect of exercise on selective attention and conflict resolution was assessed in eight studies, with two higher proportion female (59,173) and two lower proportion female studies (118,120). The effect did not differ between studies with a higher or lower proportion of females ($Chi^2 = 0.56$, p=0.45) (Figure 4).

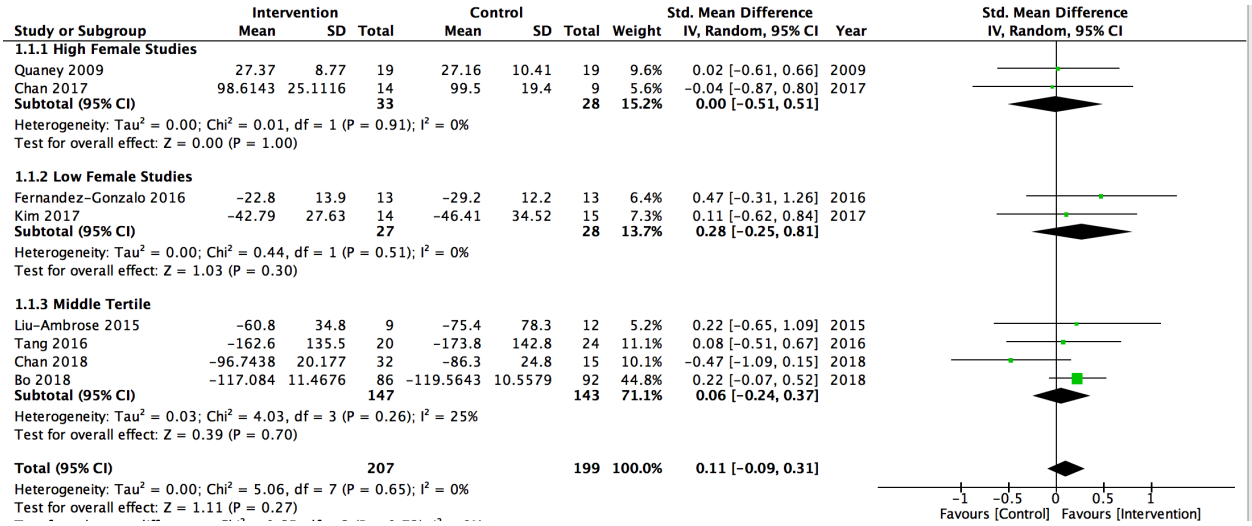

Figure 4: Forest plot of the effects of exercise on Stroop Test (selective attention and conflict resolution)

b) Trail Making Test B

The effect of exercise on set-shifting/cognitive flexibility was assessed in six studies, with one higher (173) and two lower proportion female studies (118,120). The effect did not differ between studies with a higher and lower proportion of females ($Chi^2 = 0.00$, p=0.98) (Figure 5).

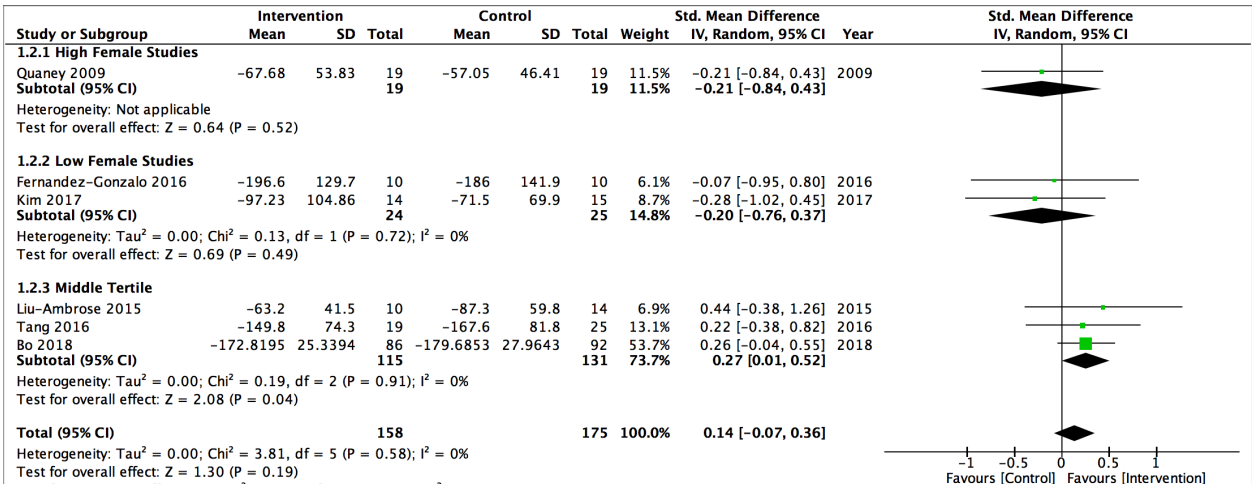

Figure 5: Forest plot of the effects of exercise on Trail Making Test B (set-shifting/ cognitive flexibility)

Sex differences in effect of exercise on language

The effect of exercise on language was assessed in three studies using the Stroke Impact Scale-Communication Domain, two higher female (111,115) and one lower female proportion (117) studies. The effect did not differ between studies with a higher proportion of females and lower proportion of females ($Chi^2 = 3.17$, p=0.08) (Figure 6).

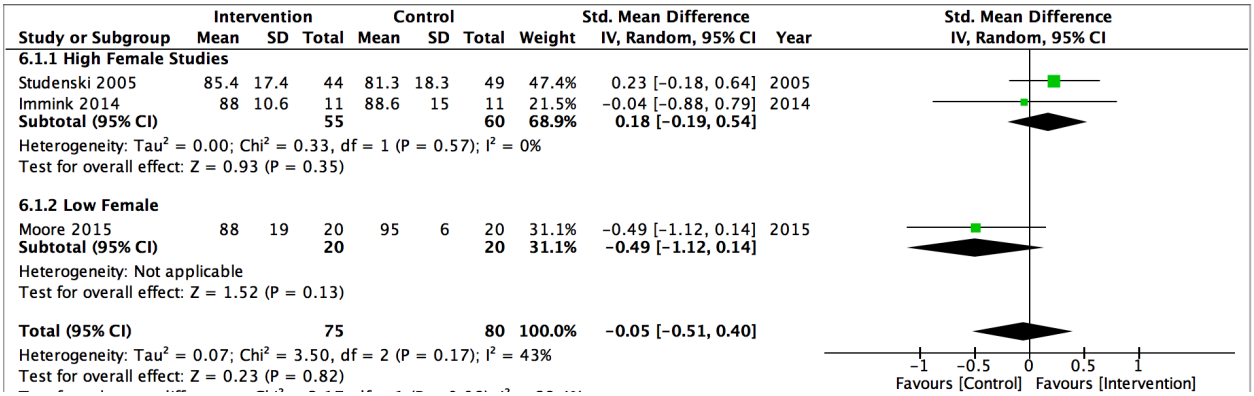

Figure 6: Forest plot of the effects of exercise on Language (Communication)

Sex differences in effect of exercise on global cognition

The effect of exercise on global cognition was assessed in six studies using the Montreal Cognitive Assessment, Functional Independence Measure (cognitive domain) and Addenbrooke's Cognitive Examination-Revised outcomes. Of these, there were two higher female (110,111) and three lower female proportion (117,120,125) studies. The effect did not differ between studies with a higher proportion of females and lower proportion of females (Chi^2 = 0.88, p=0.35) (Figure 7).

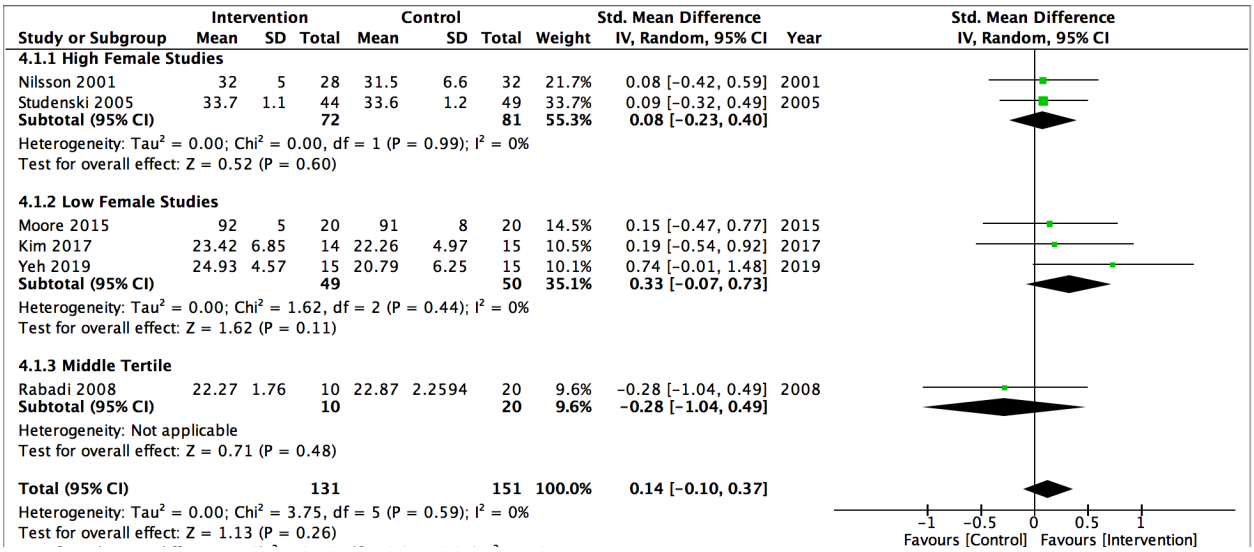

Figure 7: Forest plot of the effects of exercise on global cognitive function

DISCUSSION

The current literature suggests that there is no difference between males and females in the effects of exercise on memory, executive functioning, language or global cognition after stroke. These findings are in contrast to earlier research in older adults and those with mild cognitive impairment that have reported improvements in executive function (6,90,165,167) and attention and memory (166), favoring females, following exercise. Indeed, even within these studies, not all domains of cognition show sex-dependent effects. For example, in a systematic review

involving older healthy adults, sex-dependent effects were only observed in the domain of executive functioning, while no sex differences were displayed in visuospatial function, episodic memory, processing speed or global cognition (6). There are four potential reasons for the lack of sex differences observed in the relationship between exercise and cognition post-stroke: 1) the lack of studies directly investigating sex as a moderator, 2) heterogeneity between studies, 3) lack of control for baseline cognition and 4) similarities between males and females.

The scientific literature is in transition with respect to analyzing sex differences in many areas of research and moreover, the body of evidence related to the effects of exercise on cognition in individuals with stroke is still developing. There have been no studies conducted to date that have directly investigated sex as a moderator in the relationship between exercise and cognition, and even among the studies identified in this systematic review, none reported disaggregated data by sex. As such, it was not possible to directly compare the effects of exercise on cognition between males and females. We were also limited by the small number of studies available for comparison within each cognitive domain.

In previous meta-analyses in which studies have reported on multiple outcome measures, multiple effect sizes were generated per study, thus violating the assumption of independence underlying traditional meta-analytical processes. Strategies such as averaging effect sizes per outcome within studies (5,6) or choosing only one effect size per outcome (98) have been applied. These approaches can misrepresent meta-analytical results by either ignoring or avoiding dependency. As conducted by Gates et al., (97) the current meta-analysis was separated by cognitive test and domain to avoid inflating our total sample size and resulting in a small number of studies being compared within each cognitive domain.

Although there was no statistical heterogeneity between studies, there was considerable variability in time post-stroke among study participants (from 17 days to 8.8 years), and type, frequency, intensity, time and duration of exercise intervention and control groups. Additionally, many studies (n=7, 47%) consisted of various multi-modal interventions, with different combinations of exercise modes and types of concurrent interventions. It may be that the variability within participant characteristics and study interventions explains the lack of sex differences observed in the current study. We were unable to conduct moderation analyses due to the small number of studies within each tertile, but an earlier systematic review (while not focused on sex differences) reported no differences between subgroups with respect to exercise mode, type of cognitive assessment (objective vs subjective), time from stroke to intervention and length of intervention (5).

It is also known that females have lower baseline cognitive function post-stroke than males (150), but the majority of studies included in this review (12 out of 15 studies) did not control for baseline cognitive status in their analysis. It is possible that the relative improvement in females is higher than in males, but such adjusted analyses were not available from all included studies.

It is also possible that males and females post-stroke respond similarly to exercise with respect to its effects on cognition. In a systematic review involving older adults without stroke (6), sex-dependent effects were only observed in the domain of executive functioning, while no sex differences were displayed in visuospatial function, episodic memory, processing speed or global cognition. However, further research is required to confirm this. Indeed, identifying both sex differences and similarities will be important for healthcare professionals working with individuals with stroke in terms of tailoring interventions to individuals or populations.

As this body of literature continues to develop, we can gain insights into exercise parameters that might have optimal effects on cognition. Future studies examining the interplay between participant characteristics, such as sex and gender, and intervention-related characteristics are warranted to examine their influence on the effects of exercise on cognition and may help identify targeted interventions. Additionally, future research should focus on larger scale randomized controlled trials to examine the relationship between exercise and cognition post-stroke and develop strategies to recruit male and female participants in order to directly evaluate the potential moderating effect of sex on the effect of exercise.

Study Limitations

We were limited by the number of studies that were included in the comparison analyses, and the domains of cognition in which we could analyze sex differences (not enough studies to examine differences in attention and processing speed and visuospatial function). The results should be interpreted with caution because there were no studies with a great majority of females enrolled. Indeed, even the study with the highest proportion of females was only 59%. Previous meta-analysis had dichotomized studies based on the median value (71%) (6) or 50% as the division between studies of high and low female proportions (90). We were unable to utilize these methods due to the low proportions of females in the studies included in our meta-analysis. Finally, we were unable to perform gender-based analyses because sociocultural factors were not collected within the studies included in this analysis. Nonetheless, we acknowledge that it is difficult to completely disentangle the direct effects of sex vs. gender, as these concepts may work together in influencing cognition.

CONCLUSION

This study found no differences in executive function, memory, global cognition or language responses to exercise interventions after stroke, when comparing studies of higher and lower proportion of females. Given limitations in the current research and variations in study designs and interventions of the studies included in this review, we cannot be certain whether sex should be taken into account when prescribing post-stroke exercise interventions. There is a clear need for more clinical trials that incorporate sex-and-gender-based analysis for this question to be adequately addressed in a future meta-analysis.

CHAPTER 3

THE EFFECT OF EXERCISE ON COGNITION POST-STROKE: ARE THERE SEX DIFFERENCES?

A SECONDARY ANALYSIS OF A RANDOMIZED CONTROLLED TRIAL

ABSTRACT

Objective: To determine whether there were differences in exercise-associated changes in cognitive function between males and females living with stroke.

Design: Secondary analysis of data from a prospective assessor-blinded randomized controlled trial (NCT01189045).

Participants: Fifty participants (50-80 years, >1 year post-stroke, able to walk ≥ 5 m).

Methods: Participants were allocated into a 6-month aerobic exercise (AE) (14 males, 11 females) or balance and flexibility (BF) program (15 males, 10 females). Working memory (Verbal Digit Span Backwards Test), selective attention and conflict resolution (Stroop Colour-Word Test), and set shifting/cognitive flexibility (Trail Making Test B) were assessed before and after the programs.

Results: There was a group x time interaction in females (effect size 0.28, p=0.03) that was not observed in males (effect size 0.01, p=0.62). Females demonstrated a Stroop Colour-Word Interference test change of -2.3 seconds, whereas males demonstrated a change of +5.5 seconds following AE. There were no differences between exercise groups in either sex for any of the other outcomes (working memory and set-shifting/cognitive flexibility).

Conclusion: Females living with stroke may demonstrate a greater response to exercise on selective attention and conflict resolution compared to males with stroke. These findings suggest that there may be sex-specific effects of exercise on cognitive function in individuals with stroke.

INTRODUCTION

Stroke is one of the leading causes of mortality and morbidity worldwide, and the sequelae from stroke result in physical, psychosocial, and cognitive consequences (174). While individuals may recover from physical disability resulting from stroke, cognitive impairments may limit the extent of independent living and community re-integration (29,36). Approximately 70% of individuals with stroke experience cognitive impairments (1,2), which is associated with functional decline (33,34), reduced quality of life (33) and increased dependence in activities of daily living (35).

Exercise may benefit cognition in individuals living with stroke, such as executive function and memory (109,175). Evidence in both single group studies and randomized controlled trials suggest that exercise may improve cognitive function after stroke. In single group studies, twelve weeks of aerobic and resistance training improved working memory but not attention or executive function in a population of 9 individuals >12 months post-stroke (176). Six months of combined aerobic and resistance training led to improvements in global cognitive function in 41 patients ≥10 weeks post-stroke (177), and a 6-month exercise and recreation intervention improved cognitive flexibility, verbal memory and response inhibition but not working memory or task-switching in 11 participants ≥12 months post-stroke (178). In randomized controlled trials, the findings have been less consistent. Quaney and colleagues (114) found that an 8-week upper body cycling training program was more effective at improving motor learning, processing speed, implicit memory, and motor function, but not executive function, compared to a stretching control intervention in 38 participants ≥ 6 months post-stroke. Liu-Ambrose and Eng (116) demonstrated that a 6-month exercise and recreation program resulted in improved selective attention and conflict resolution, and working memory in 28 individuals ≥12 months post- stroke. In contrast, Tang et al (119) found no changes in working

memory, set-shifting/cognitive flexibility, or selective attention and conflict resolution following 6 months of high or low intensity exercise in 47 individuals >1 year post-stroke. Recently, a systematic review of 14 studies and 736 participants with stroke reported improvements in attention and processing speed but not in executive function or working memory following physical activity training (5). These inconsistencies in the literature may be due to differences in cognitive domains assessed, outcome measures, exercise protocols used, or participant characteristics (5).

Sex refers to biological features related to physical and physiological aspects such as hormone function, gene expression, chromosomes, and reproductive/sexual anatomy (129); whereas, gender is a socially constructed attribute influencing how individuals behave, interact, and perceive themselves and others. Older females are known to be at higher risk of stroke than males (138), have higher rates of stroke-related mortality (138), present with more co-morbidities (133,135), and experience more severe disability (133,135). Sex may also be a potential moderator of the effects of exercise on cognitive function in older adults, given that female sex may positively influence the strength of the relationship between exercise and cognition (90,179). An early systematic review published in 2003 (18 studies, 197 participants) reported that studies involving a high proportion of healthy older females demonstrated greater improvements in cognition following exercise training compared to studies involving a high proportion of healthy older males (90). In 33 older adults with mild cognitive impairment, executive function improved to a greater degree in females compared to males following 6 months of aerobic training (165). Additionally, in 152 older adults with mild cognitive impairment, females demonstrated greater improvements in attention and memory following 12 months of moderate intensity walking (166). Recently, a systematic review of 41 studies

involving 5156 older adults reported that exercise was associated with greater improvements in executive functioning in studies involving a high proportion of females compared to a low proportion of females (180).

To date, there have been no studies examining sex differences in cognition following exercise interventions in individuals with stroke. Therefore, the objective of this study was to determine whether males and females living with stroke demonstrate different responses with respect to changes in working memory, set-shifting/cognitive flexibility and selective attention and conflict resolution following 6 months of aerobic or balance and flexibility exercise. Given that preliminary literature has displayed sex-specific improvements in cognition, favoring females, we hypothesized that females with stroke would demonstrate greater improvements in executive functioning following aerobic exercise vs. balance and flexibility exercise compared to males.

METHODS

This study was a secondary analysis of data from a prospective assessor-blinded randomized controlled trial (181) that examined the effects of aerobic and balance and flexibility exercise on cardiovascular outcomes in 50 participants living in the community with stroke (Clinical Trial Registration; http://www.clinicaltrials.gov. Unique identifier: NCT01189045). Details of the main study are provided elsewhere (181) but in brief, individuals were eligible if they were; between the ages of 50-80 years, >1 year post-stroke, and able to walk ≥ 5 m. Exclusion criteria were stroke from aneurysm, tumor, infection or significant health conditions that would preclude participation in exercise (presence of cardiovascular abnormalities, pacemaker, serious musculoskeletal or other conditions). Eligible participants were randomized into either a 6-month aerobic exercise (AE) program or balance and flexibility (BF) program

using a 1:1 allocation sequence and permuted block sizes of 2 or 4. The flow of participants throughout the study is presented in Figure 8.

The sample size calculated for the original analysis was determined as n=24 per group. This was based on a 10% change in aerobic capacity, the primary outcome of the original study, utilizing an alpha level of 0.05, type II error of 90% and a standard deviation of 3 (181). While the original sample size was not established to examine subgroups of secondary outcomes, this was a preliminary analysis of sex differences in cognitive function following exercise after stroke.

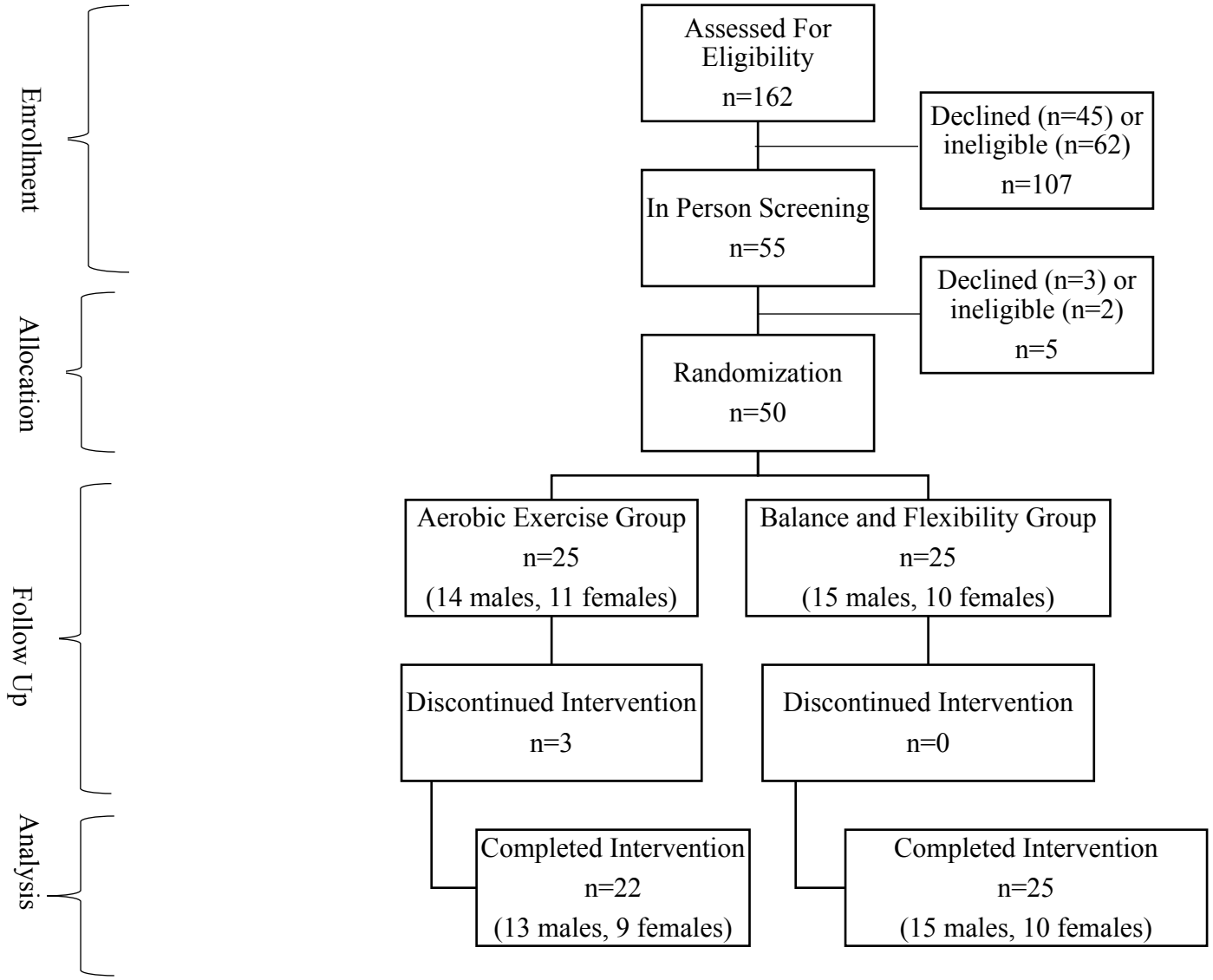

Figure 8: CONSORT Diagram Depicting Participant Flow Through Study

ASSESSMENTS

Upon study entry, participants were assessed for stroke severity and motor recovery using the National Institutes of Health Stroke Scale (182) and the Chedoke-McMaster Stroke Assessment (183), respectively. Aerobic capacity was assessed using a graded maximal exercise cycle ergometry test (181), and walking ability using 5-m self-selected gait speed and the 6-Minute Walk Test (184). The Montreal Cognitive Assessment (70,71) and Center for Epidemiologic Studies– Depression Scale (185) were used to evaluate global cognitive function and presence of depressive symptoms, respectively.

COGNITIVE OUTCOME MEASURES

The Verbal Digit Span Backward Test (54), Trail Making Test B (37,38), and Stroop Test (42) were conducted to evaluate the effects of exercise on executive functioning at baseline and at 6 months (post-exercise). These outcome measures were selected based on the difficulties with executive functions - cognitive processes responsible for controlled, goal-directed behavior - commonly observed after stroke (119).

The Verbal Digit Span Backwards Test (54) assesses working memory by verbally presenting random number sequences of increasing length to the participant, who then relayed the numbers back to the examiner in reverse order. One point was scored for each correct sequence relayed (maximum score 14); higher scores indicate better performance (54). The Verbal Digit Span Backwards Test has moderate concurrent validity with the Executive Function Performance Test in people with stroke (40).

The Trail-Making Test Part B (37,38) was used to assess set shifting/cognitive flexibility, where the participant traced a line alternating between encircled numbers and letters (i.e. 1-A-2-B-3-C etc.). The test was timed (in seconds, maximum 300 s), where shorter times indicate better

cognitive flexibility (38). Selective attention and conflict resolution (problem-solving) were assessed using the Color-Word Stroop Test (42), where the participant identified the ink color of words presented in incongruent colored inks (e.g. the word "blue" printed in red ink). The time (in seconds) required to complete the test was recorded, where shorter times indicate better performance (42). The Trail-Making Test Part B and Color-Word Stroop test have good test-retest reliability in people with stroke and older adults, respectively (39,42,186).

INTERVENTIONS

Both interventions took place 3x/week at 60 minutes/session with three instructors per 12-13 participants. In the aerobic exercise (AE) program, exercise was performed at intensities that progressed from 40 to 80% of heart rate reserve. Each AE session involved a 10-minute warm up and cool down and a 30-40-minute aerobic component (walking, cycle ergometry, marching-on-the-spot, repeated sit-to-stand, and step ups onto platform steppers). In the balance and flexibility (BF) program, exercise was non-aerobic in nature and intensity was maintained below 40% heart rate reserve. Participants in the BF program progressed through activities involving stretching, postural awareness, balance exercises and weight bearing. In order to minimize contamination between groups, the exercise classes were held at different times of the day and different spaces within a multi-purpose research facility.

STATISTICAL ANALYSIS

Descriptive statistics were performed for all variables by sex (mean ± SD or median (IQR) for continuous variables and frequencies for categorical variables). Additionally, chi-squared or fisher's exact tests (if expected counts were less than 5) were performed for all

categorical variables and independent t-tests or Mann-Whitney U Tests were conducted for all continuous variables, by sex.

To evaluate the effects of exercise on cognition, disaggregated analysis (129) using a two-way mixed analyses of covariance were conducted for each cognitive test, for each sex, with age (years) and baseline Montreal Cognitive Assessment scores included as covariates. Older age is an important predictor of cognitive outcome and development of cognitive impairment post-stroke (187), and baseline cognitive status may be a factor influencing the extent of change. There is no nonparametric equivalent of the two-way mixed analyses of covariance, thus this method was used regardless if normality was met, due to the robust nature of the test. Data were analyzed using Statistical Package for the Social Sciences (Version 23.0, Chicago IL). A significance level of $p < 0.05$ was used.

RESULTS

Baseline characteristics for the 50 participants enrolled in the study, separated by sex and group, are presented in Table 7. While National Institute of Health Stroke Scale values indicate that participants had a mild severity of stroke, aerobic capacity and six minute walking test scores were 53.7$\pm$138% (188) and 60$\pm$28.6% (189) of normative values, respectively. Males and females were similar in all characteristics at baseline with the exception of aerobic capacity (males= 19.5$\pm$6.4, females=12.7$\pm$3.8 ml/kg/min, $p<0.001$). There were no other differences between groups, within each sex at baseline. Baseline cognitive outcome scores, separated by sex and group, are presented in Table 8.

Three (2 females and 1 male from the aerobic exercise group) of the 50 participants did not complete the study for reasons unrelated to the intervention and were deemed cases missing completely at random. Thus, analyses were performed from 47 participants who completed the

main study. Pre and post-training data on cognitive outcomes were not obtained for 5 participants due to significant aphasia (1 female with missing data for Stroop Test and Trail Making Test B, 1 male with missing data for Trail Making Test B), difficulty understanding test instructions (2 males, 1 with missing data for Stroop Test and 1 with missing data for Trail Making Test B) and colour blindness (1 male missing Stroop Test data). These individuals were excluded from the analysis. In addition, for individuals who were missing post-training cognitive data; baseline scores were carried forward.

Data for results of cognitive outcomes are presented in Table 9. After controlling for age and baseline Montreal Cognitive Assessment scores, a group x time interaction effect was observed in females for the Stroop test ($F=5.53$, $p= 0.03$, effect size 0.28) that was not seen in males ($F=0.25$, $p=0.62$, effect size 0.01) (Table 9). Specifically, females demonstrated a Stroop Colour-Word Interference test change of -2.3 seconds, whereas males demonstrated a change of +5.5, following AE. There were no differences between exercise groups in either sex for any of the other outcomes (working memory and set-shifting/cognitive flexibility) (Table 9).

Table 7: Baseline characteristics for males and females, by intervention group

	Males(n=29)	Females(n=21)	P-value	Males			Females		
				AE (n=14)	BF (n=15)	P-value	AE (n=11)	BF (n=10)	P-value
Age, years	65.5± 7.5	67.7 ± 6.5	0.28	66.2 ± 7.4	64.8 ± 7.8	0.62	65.6± 5.2	70.1 ± 7.3	0.11
Time Post-Stroke, years	2.6 (3.4)	3.4 (4.6)	0.54	2.9(2.7)	2.6(3.5)	0.98	3.7 (5.3)	2.8 (2.9)	0.25
STROKE TYPE			0.07			1.00			0.45
Lacunar	1	6		0	1		3	3	
Ischemic	12	7		5	7		2	5	
Hemorrhage	10	6		5	5		4	2	
Unknown	6	2		4	2		2	0	
LIMBS AFFECTED			0.64			0.44			1.00
Right	11	7		6	5		4	3	
Left	18	13		8	10		7	6	
Bilateral	0	1		0	0		0	1	
NIHSS *	1(3)	0(3)	0.52	0.5(3)	1(2)	1.00	1(5)	0(1)	0.15
MoCA †	23.5± 5.3	25.9 ± 3.0	0.05	24(8)	25(6)	0.91	27.5(4)	25.5(4)	0.14
CESD ‡	5(6)	4(9)	0.67	5(5)	6(7)	0.31	2.5(6)	7(7)	0.19
CMSA §									
Arm	7(2)	7(1)	0.67	7(4)	7(2)	0.91	6(2)	7(0)	0.08
Hand	6(4)	6(2)	0.84	7(5)	6(2)	0.23	6(4)	7(1)	0.12
Leg	6(2)	6(1)	0.69	7(1)	6(1)	0.15	6(1)	6(1)	0.76
Foot	7(3)	6.5(2)	0.96	7(2)	6(4)	0.35	6(2)	7(2)	0.28
Aerobic Capacity, ml/kg/min	19.5± 6.4	12.7 ± 3.8	<0.001	19.4±7.4	19.7 ±5.6	0.93	12.5± 3.1	12.8± 4.7	0.87
Six Minute Walking Test, m	316.2 ± 148.1	281.4 ± 131.3	0.40	304.1± 140.8	327.5±158 .6	0.68	251.4± 138.0	314.3± 121.9	0.28
Self-paced walking speed, m/s	0.97± 0.38	0.83± 0.37	0.20	0.98± 0.40	0.96± 0.36	0.87	0.74± 0.43	0.93± 0.28	0.25

Values are mean ± SD or median (IQR); * National Institutes of Health Stroke Scale: Ranges from 0 to 42, 0= no stroke, 1-4=minor stroke, 5-15=moderate stroke, 15-20=moderate/severe stroke, 21-42=severe stroke; † Montreal Cognitive Assessment: Ranges from 0 to 30, ≥26 =generally considered normal, <26 = mild cognitive impairment; ‡ Center for Epidemiologic Studies – Depression Scale: Ranges from 0 to 60, 0-16=no to mild depression, 16-24: moderate depression, 24-60=severe depression; § Chedoke-McMaster Stroke Assessment Motor Recovery: Each limb ranges from 1 to 7, 1=paralysis and 7=normal movement

Table 8: Baseline scores for cognitive measures for males and females, by intervention group

	Males	Females	P-value	Males					Females				
				n	Aerobic Exercise	n	Balance and Flexibility	P-Value	n	Aerobic Exercise	n	Balance and Flexibility	P-Value
Digit Span Backward, n sequence	2(4)	3(2)	0.56	14	2.5(5)	15	2(3)	0.68	11	3(2)	10	3(2)	0.92
Stroop Color-Word, s	128.3 (74.5)	108.0 (54.1)	0.08	12	123.2 (124.4)	14	128.3 (52.9)	0.67	10	104.1 (38.6)	10	137.3 (102.1)	0.25
Trail Making Test B, s	154.4 (208.1)	136.9 (94.4)	0.46	12	140.0 (184.1)	15	161.0 (206.6)	0.91	10	119.6 (71.3)	10	170.5 (129.9)	0.14

Values are median (IQR)

Table 9: Changes in cognitive function in males and females, controlling for age and Montreal Cognitive Assessment score

	Males										Females									
	Pre				Post						Pre				Post					
	n	AE	n	BF	n	AE	n	BF	P-Value	ηp^2	n	AE	n	BF	n	AE	n	BF	P-Value	ηp^2
Digit Backward, n sequence	13	3(5)	15	2(3)	13	2(4)	15	3(3)	0.25	0.06	9	3(1)	10	3(2)	9	4(3)	10	3.5(3)	0.10	0.19
Stroop Color-Word, s	12	123.2(124.4)	14	128.3 (52.9)	12	128.7(121.3)	14	134.6(53.3)	0.62	0.01	8	100.6(27.6)	10	137.3(102.1)	8	98.3(23.9)	10	147.5(98.5)	0.03*	0.28
Trail Making Test B, s	11	154.4(212.0)	15	161.0(206.6)	11	134.9(186.0)	15	124.7(159.7)	0.46	0.03	8	119.6(61.0)	10	170.5 (129.9)	8	108.8(73.2)	10	169.9(92.8)	0.50	0.03

Values are median (IQR)

DISCUSSION

Our previous analysis concluded that exercise was not effective in improving cognitive function, whereas this study extends this analysis to indicate that females demonstrated improvements in selective attention and conflict resolution following AE, whereas men did not. Other aspects of cognitive function (working memory and set-shifting/cognitive flexibility) did not demonstrate sex differences in treatment response. The positive benefits of exercise observed in females with stroke is consistent with previous studies that also reported selective improvements in the Stroop test performance among females (190,191). Impairments in executive function are often the first cognitive domains affected by aging (192), and are common after stroke (193,194). Older females without known cognitive impairments perform better on tasks of executive function compared to males (195), suggesting that it may be selectively preserved in females and thus more responsive to improvement with exercise training, although further research to confirm this finding is warranted (180). Previous studies in the stroke population have also demonstrated exercise-associated improvements in the Stroop test (116,121,165,178), but our results are the first to report that the beneficial effects may be influenced by sex.

The mechanisms underlying sex differences in the effects of exercise on executive function are not known. Hormonal and neurotrophic factors have been proposed as potential factors associated with cognitive function. Sex steroid hormones estrogen (females) and testosterone (males) are associated with the preservation of cognitive function (179,196–198), and emerging evidence in older adults suggests that this association may be more pronounced in females (199–201). For example, studies in older adults have demonstrated that, following menopause in females and andropause in males, remaining estrogen levels (and to a smaller

degree testosterone) were associated with improvements in semantic, episodic and working memory, as well as executive function in females only (199–201).

Brain-derived neurotropic factor (BDNF) is a neurotrophic factor that supports neuronal proliferation, growth, survival and synaptic plasticity and is involved in cellular mechanisms required for learning and memory (202). BDNF appears to be a mediator in the relationship between aerobic training and cognitive function, possibly due to its role in enhancing neurogenesis and reducing inflammation in the brain (203). Aerobic exercise results in the upregulation of BDNF in both individuals with (204) and without (205) neurological disorders such as stroke, multiple sclerosis, Parkinson's, and Alzheimer's disease. While BDNF levels are known to decline with age, this decline is associated with cognitive impairment in older females only (206). Recently, it was reported that circulating levels of BDNF increased in older females following 6 months of aerobic training, whereas it decreased in males (167). Estrogen has also been associated with greater BDNF expression in the hippocampus and cortex of females (207,208). In animal models, mice exposed to an enriched environment involving running wheels stimulated greater upregulation of BDNF in several brain regions in female mice compared to male mice (209,210). Similarly, in humans, greater duration, frequency and amount of total daily walking activity was associated with larger hippocampal volume in females, but not males (211). Taken together, these studies suggest that a unique, sex-specific link may exist between exercise and cognition that may be mediated by BDNF (180).

In contrast to the improvements observed in selective attention and conflict resolution in females, we did not find improvements in other domains of executive function of working memory and set-shifting/cognitive flexibility in either males or females. This finding is aligned with previous research. For example, in a systematic review involving older adults, exercise was

effective in improving visuospatial functioning and episodic memory but there were no sex-dependent effects observed (180). This suggests that males and females may perform similarly in certain cognitive domains. While there is still an absence of clear evidence to suggest that clinicians must consider the influence of sex within clinical decision making, it remains important to acknowledge that sex similarities and differences may exist. Further research is warranted.

A possible reason for these domain-specific effects may be that the duration was not sufficient or multi-modal exercise interventions are needed to elicit improvement in more cognitive domains. Specific exercise parameters to optimize improvement in cognitive function after stroke are currently unknown. The duration of exercise may play a role, as research in older adults has suggested that greater benefit is observed with exercise durations greater than 6 months (90). It is also possible that improvements in other cognitive domains may require more complex interventions, as opposed to aerobic training alone. A 12-week combined intervention involving aerobic and resistance exercise and cognitive training resulted in greater improvement in cognitive flexibility, working memory, and selective attention and conflict resolution compared to physical exercise alone in 179 post-stroke individuals (121). Thus, it appears that interventions that use a combined approach, along with those of longer durations, may be required for larger and more diffuse improvements in cognitive function to be observed (212).

Study Limitations

The key limitation of this study is that it was not powered to detect changes in male and female subgroups in cognition post exercise. However, it is likely that this limitation is minimal due to the small effect sizes, thus a fully powered study would potentially find clinically relevant differences. Additionally, examining underlying mechanisms of cognitive improvement post-

exercise was beyond the scope of this study. Furthermore, when measuring sex in the primary analysis, participants were provided with response options that did not differentiate sex and gender, or allow for non-binary responses, leaving potential for misclassification. We acknowledge sex differences were not fully differentiated from gender differences and that these may both influence cognition (129). It is possible that gender, in addition to sex, may be another moderator in the relationship between exercise and cognitive function. Women access life-saving treatments less frequently than men, and fewer women participate in stroke rehabilitation, have higher institutional rates post-stroke, and have less social support during recovery in comparison to men (25). These may influence their participation in and the effect of rehabilitation on cognitive outcomes post-exercise. While we were not able to conduct gender-based analyses in the current study as information related to socio-cultural factors (level of education, hours of work, responsibility for caring for children etc.) were not collected and a gender index could not be created, future research should consider the role of gender in cognitive changes with exercise after stroke.

CONCLUSION

This study provides preliminary evidence to suggest that there may be sex differences with respect to exercise-associated changes in cognition specifically executive functioning after stroke. However, based on our findings, there is no clear rationale to support the consideration of sex in designing interventions post-stroke and it may be that males and females can be treated similarly. Given the prevalence of cognitive impairment post-stroke, further research is warranted to better understand this relationship and ultimately develop optimal sex-specific, evidence-based parameters for exercise training for people living with stroke.

CHAPTER 4

DISCUSSION

SUMMARY OF FINDINGS

The overall objective of this thesis was to investigate whether sex differences exist in the relationship between exercise and cognition in individuals with stroke. Approximately 70% of individuals living with stroke present with cognitive impairment (187), but the body of literature focused on remediating physical impairments from stroke is much greater than the evidence surrounding cognitive impairment (4). Exercise is a strategy that may potentially remediate cognitive function after stroke, and evidence from other populations suggest that females may demonstrate greater improvements in cognition following exercise in comparison to males. Understanding how sex influences cognitive outcomes in response to exercise treatment is needed to help develop targeted interventions for stroke recovery (25) but prior to this thesis, there had been no previous studies examining sex differences in cognition following exercise interventions in individuals with stroke.

STUDY 1: THE EFFECTS OF EXERCISE ON COGNITION POST-STROKE: ARE THERE SEX DIFFERENCES? A SYSTEMATIC REVIEW AND META-ANALYSIS

The first study was a systematic review of literature examining sex differences in the relationship between exercise and cognition in individuals with stroke. Results from this study suggested that the effects of exercise did not differ between studies of higher and lower female proportions in the domains of memory, executive functioning, language or global cognition.

STUDY 2: THE EFFECTS OF EXERCISE ON COGNITION POST-STROKE: ARE THERE SEX DIFFERENCES? A SECONDARY ANALYSIS OF A RANDOMIZED CONTROLLED TRIAL

The second study was a secondary analysis of a randomized controlled trial examining the effects of a six-month community exercise program. At the end of the program, females demonstrated improvements in selective attention and conflict resolution (Stroop Color-Word Test) following aerobic exercise, whereas males did not. There were no sex differences in

treatment response in working memory (Digit Span Backward) and set-shifting/cognitive flexibility (Trail Making Test B).

POSSIBLE MECHANISMS IN THE RELATIONSHIP BETWEEN EXERCISE AND COGNITION

Animal models and emerging evidence in human clinical studies suggest that the mechanisms underlying the relationship between exercise and cognition are mediated by three factors: neurotrophic stimulation, neurotransmitter stimulation and cerebral circulation stimulation (213).

The positive effects of exercise on cognition may be mediated by the upregulation of neurotrophic factors, specifically brain-derived neurotrophic factors (BDNF) and insulin-like growth factor-1 (IGF-1) (214). BDNF is a protein that is found in the central nervous system and blood-stream and is crucial for the maintenance and development of brain activities due to its involvement in every aspect of neuronal activity, including neurogenesis, neuronal survival, neurotransmitter production and release, dendritic branching, and synapse maturation and formation (215). BDNF is also associated with neurodegenerative diseases, as lower concentrations of BDNF is correlated with the prognosis of Alzheimer's disease (216).

Exercise has been observed to increase platelet numbers, which contain BDNF mRNA, thus increasing BDNF (217). The increase in BDNF has a positive influence on cognitive function, potentially by increasing brain volume, specifically in the frontal and temporal regions which are often observed to show substantial age-associated deterioration (218). Thus, it may be possible that cognitive abilities within these enhanced regions (attention, executive function, language and memory) may improve in response to exercise.

The hormone IGF-1 is derived in the liver, but is also found in the blood-stream and central nervous system circulating through cerebrospinal fluid (219). IGF-1 has growth-

promoting and neuroprotective effects, both directly (possibly due to its ability to prevent apoptosis) and indirectly (via BDNF) (219). Exercise increases IGF-1 gene expression in the brain and periphery and increases BDNF expression in the brain, thus preventing or reverting cognitive deficits (220).

The relationship between exercise and cognition may also be mediated by neurotransmitter stimulation (213,221). For example, exercise may elevate brain neurotransmitters such as dopamine, serotonin and norepinephrine, which in turn decreases depressive symptoms (222), regulates stress and increases arousal and wakefulness, thus positively influencing cognitive function (223).

Finally, the relationship between exercise and cognition may be mediated by an increase in cerebral circulation (213). Exercise can enhance cerebral blood flow and volume, and in turn increase oxygen and glucose transportation to the brain (92,224). The increase in oxygenation and glucose availability for neural processes is particularly important in older adults given the known age-associated declines in cerebral blood flow (225,226).

The specific mechanisms by which exercise improves cognition is not yet well-defined, although possible pathways involve neurotrophic factors, neurotransmitters, and cerebral circulation (213). Future research is needed to understand their specific mechanisms of actions and how they might differ (99). It is also not clear whether these mechanisms may vary by sex.

POSSIBLE MECHANISMS OF SEX-BASED DIFFERENCES BETWEEN EXERCISE AND COGNITION

Potential underlying mechanisms of sex-based differences in the relationship between exercise and cognition include hormonal or neurotrophic factors, and brain structure and function. Likely, the influences of these factors are interdependent (227) and no overriding influence supersedes other factors.

Sex hormone levels change over time and play important roles in cognitive functioning in both males and females (197). In females, estrogen declines rapidly with the onset of menopause (to about 10%) (228), occurring at approximately 51 years of age and lasting approximately ten years (229). In males, testosterone decline is not as rapid, with an approximate 1-2% reduction every year beginning in their 30's (230,231).

There is no definitive sex-specific conclusion related to sex hormones and cognition. Estrogen may effect cognitive function by increasing neuronal growth and the speed of communication between neurons (232). In addition to this, the brain contains an abundance of estrogen receptors in comparison to androgen receptors (233) and there is a reduced amount of estrogen receptors in the male brain. In a systematic review of 26 studies, estrogen was frequently reported to be associated with decreased cognition in males, but better cognition in females (199). The female brain may also be more receptive to the influence of estrogen than the male brain, due to the effects of estrogen in the early stages of development. The relationship between testosterone and cognitive function is less established, with some studies suggesting a neuroprotective effect in males (234) possibly due to the conversion of testosterone into estrogen in the brain (235), while others do not (236). It is evident that estrogen in both males and females has a role in protecting against cognitive decline, however, this effect may be greater in females. Future research is required to understand the relationship between sex hormones and cognition.

The effect of sex hormones on cognition may be mediated by neurotrophic factors, specifically BDNF (237,238) and particularly in females (237,238). While estrogen increases BDNF gene expression (207), testosterone suppresses it (239). Recently, circulating levels of BDNF were reported to have increased in older females following 6 months of aerobic training, whereas it decreased in males (167). In animal models, mice exposed to an enriched

environment involving running wheels stimulated greater upregulation of BDNF in several brain regions in female mice compared to male mice (209,210). Additionally, BDNF levels are known to decline with aging, yet is only associated with deficits in cognition in females (206). This suggests that there may be a greater connection between estrogen and BDNF in females than in males, which may contribute to the greater improvement in cognition observed in females following exercise.

Sex differences also exist in brain structure and function. On average, males have larger absolute brain volumes (240), although the proportional sizes of individual brain regions relative to total brain volume is similar between sexes (241). With aging, whole brain volume as well as frontal and temporal brain volumes decreases to a greater extent in males (242), whereas females experience greater declines in hippocampus and parietal lobe volumes (243). Functionally, changes in the brain occur more slowly in females than they do in males. In a retrospective cohort study of 205 adults aged 20 to 82 years, female brains were found to be metabolically juvenilized (slower physiological development with prolonged periods of myelination and synaptic plasticity) in comparison to male brains (244). Females have also been observed to have greater resting cerebral blood flow compared to males (245,246). These differences may provide some degree of protection to age-related changes in cognition in females (244), and contribute to greater resilience to age-associated brain changes, and subsequent cognitive changes (195). Future research is required to understand the mechanisms underlying the relationship between exercise and cognition as well as how sex differences may play a role in the mechanistic changes.

GENDER DIFFERENCES IN COGNITION

Although not examined in this thesis, gender is also a factor that may influence the relationship between exercise and cognition. Gender is not binary, but rather a continuum between femininity and masculinity (129). Gender differences in cognition can be explained by the influence of gender roles, which are behavioural norms typically applied to women and men in society that influence everyday experiences, actions and expectations and are subconsciously ingrained in society (126).

Boys and girls may be socialized differently by their families and community, thereby influencing an individual's behaviours, interests, aspirations and activities, and ultimately their educational and occupational pursuits (127). In adulthood, gender roles suggest that women will spend most of their time on caregiving and household work, and enter occupations such as nursing or administration (127). Conversely, men would be expected to spend more time on physical work in addition to their role as the breadwinner of the family and pursue occupations such as mathematics, engineering, and law (127).

These gender roles are detrimental to cognitive development because higher education and occupational attainment are protective factors against cognitive impairment, as they are believed to delay the onset of cognitive deficits by increasing cognitive reserve (247–250). Historically, women have had less opportunities to attain higher roles in society, which may put them at greater risk for cognitive impairment in older age. Although gender roles are becoming more flexible with present day cohorts, these assumptions still exist and may influence cognitive skill development (127).

Overall, in addition to biological influences of sex on cognition that were examined in this thesis, gender roles may have an effect on cognition. It is possible that differences in cognitive functioning between men and women is attributable to the combination of these factors (251).

INTERPLAY BETWEEN SEX AND GENDER

It is difficult to distinguish sex differences from gender influences that occur throughout life, and it may be that the interplay between these factors is what accounts for observed sex differences. The majority of literature on sex differences has been conducted in animal models, possibly to factor out the social influences of gender but in human studies, it is challenging to determine whether and to what degree a phenomena under study relates to sex, gender or both. Indeed, in our second study, we acknowledge that while females but not males demonstrated improvements in cognitive abilities following exercise, it is likely that the difference is not solely attributed to sex, but rather that gender may also be a factor moderating this relationship.

Interestingly, the current body of evidence suggests that women are more likely to demonstrate preservation of cognitive abilities more so than men, despite the multitude of factors that might indicate that women would benefit less from interventions that may influence cognition. Cognitive impairment is more prevalent in older women with and without stroke, and due to greater longevity in women, cognitive impairment is often co-existing with other co-morbidities. Women commonly also have less opportunities to attain higher educational and occupational roles in society that can be protective against cognitive decline, and women lead more sedentary lifestyles where physical activity can be protective against cognitive impairment. Finally, women undertake many roles throughout their adult lives at home, work and within the community, leading them to neglect their own self-care, resulting in elevated stress levels and making them vulnerable to cognitive deterioration. Thus, despite the fact that women may have biologically greater resilience to age- and stroke-related cognitive impairment, sex and gender factors may contribute to women starting with lower levels of cognitive function compared to men. This suggests that it is imperative to not only examine sex differences but also consider gender and their interaction together.

CLINICAL SIGNIFICANCE

Successful cognitive aging may be accomplished by engaging in and maintaining an active, intellectually stimulating lifestyle. Given that cognitive impairments seem to be one of the primary reasons for institutionalization post-stroke (252), engaging in interventions that focus on both physical and cognitive impairments are essential for stroke rehabilitation.

Understanding sex differences and potentially similarities in the relationship between exercise and cognition is an important step in enhancing stroke rehabilitation and the development of optimal, sex-specific rehabilitation. Women have historically been underrepresented within stroke research, despite having a greater risk of developing cognitive impairments and experiencing poorer outcomes post-stroke. In a recent study examining recruitment trends of women as well as trends in reporting of sex differences in randomized controlled trials in stroke from 1990 to 2018, women represented 40% enrollment, with only 36% of studies reporting results disaggregated by sex (147). Researchers also found that there has been no change in these values observed even in the past ten years (147). This may be due to researchers believing that results could be generalizable to women (147), and the ease in studying male participants because of the lack of compounding factors (such as hormonal changes and concerns for pregnant women or those considering pregnancy) (147). Thus, minimal progress has been made, highlighting the need for sex and gender exploration within stroke literature and the effective implementation of sex and gender recruitment and reporting.

LIMITATIONS

We acknowledge limitations in both studies of this thesis. The systematic review was limited by the lack of studies that disaggregated their data by sex, thus we were unable to directly investigate the effects of exercise on cognition between males and females. Rather, we compared studies with higher and lower proportion of females. In the secondary analysis of the randomized

controlled trial, the study was not powered to detect changes in male and female subgroups in cognition post exercise. For both studies, it was also possible that gender, in addition to sex, may be a moderator in the relationship between exercise and cognitive function. Finally, we were not able to conduct gender-based analyses in either study, as information related to socio-cultural factors (level of education, hours of work, responsibility for caring for children etc.) was not reported. Future research should consider the role of gender in cognitive changes with exercise after stroke.

FUTURE DIRECTIONS

Incorporating sex and gender in research is essential in every step of the research process, from study design to analysis and reporting. It is important to consider sex and gender within stroke literature and be mindful of these characteristics in order to develop sex-specific, individualized treatment interventions. Future studies should focus on the accurate reporting of sex and gender, disaggregating data by sex and gender, and the utilization of non-binary assessment tools to assess sex and gender. Specifically, research that prospectively and directly examines sex and gender differences in the effect of exercise to improve cognition is required. Conducting sex and gender-based research is only beginning to develop and expand throughout research, thus findings from this thesis form important pilot work that may inform future randomized controlled trials of individuals with stroke.

There are also still many factors we do not know about the relationship between exercise and cognition in many populations, in addition to whether there are sex and gender differences in response to exercise.

CONCLUSION

Exercise is a promising strategy to mitigate the effects of aging and stroke on cognitive functioning. In order to maximize the benefit of exercise, interventions must be tailored and targeted to specific populations and individuals. In this thesis, we provided the first studies to examine the role of sex as a moderating factor in the relationship between exercise and cognition post-stroke. A knowledge gap still exists, as no studies have directly examined the potential sex and gender differences within this relationship, along with mechanisms underlying this. Thus, it is not clear whether or not sex differences exist, given the current research limitations and variations between interventions. Future studies investigating sex and gender differences in the relationship between exercise and cognition are warranted to better understand, adequately examine and contribute to personalized healthcare.

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APPENDIX

Appendix A: SAGER Guidelines

SAGER recommendations according to the sections of the article

Section	Recommendation
Title and abstract	If only one sex is included in the study, or if the results of the study are to be applied to only one sex or gender, the title and the abstract should specify the sex of animals or any cells, tissues and other material derived from these and the sex and gender of human participants.
Introduction	Authors should report, where relevant, whether sex and/or gender differences may be expected.
Methods	Authors should report how sex and gender were taken into account in the design of the study, whether they ensured adequate representation of males and females, and justify the reasons for any exclusion of males or females.
Results	Where appropriate, data should be routinely presented disaggregated by sex and gender. Sex- and gender-based analyses should be reported regardless of positive or negative outcome. In clinical trials, data on withdrawals and dropouts should also be reported disaggregated by sex.
Discussion	The potential implications of sex and gender on the study results/analyses should be discussed. If a gender analysis was not conducted, the rationale should be explained. Authors should further discuss the implications of the lack of such analysis on the interpretation of the results.

Appendix B: Search Strategy

Search Strategy for Medline and PsycINFO

1) Stroke.mp. or exp Stroke/
2) Cerebrovascular Disorders/
3) exp "Intracranial Embolism and Thrombosis"/
4) exp Brain Ischemia/
5) ((brain* or cerebr* or intracran* or intracerebral) adj5 (isch?emi* or infarct* or thrombo* or emboli* or occlus*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
6) isch?emic stroke*.mp.
7) hemorrhagic stroke*.mp.
8) transient isch?emic attack*.mp.
9) cva*.mp.
10) Hemiplegia/
11) hemipleg*.mp.
12) exp Paresis/ or paresis.mp.
13) paretic.mp.
14) (poststroke or post-stroke).mp.
15) 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16) exp Exercise/
17) exercis*.mp.
18) exp Exercise Therapy/
19) physical endurance.mp. or Physical Endurance/
20) physical exertion.mp. or Physical Exertion/
21) physical activ*.mp.
22) Rehabilitation/
23) (run* or physiotherapy or yoga or aerobic or swim* or danc* or walk* or jogging or fitness or resistance or biking or balance or flexibility).mp.
24) 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25) exp Cognition/
26) Cognitive Dysfunction/
27) Neuropsychological Tests/
28) Attention/ or Executive Function/
29) cogniti*.mp.
30) exp Memory/
31) processing speed.mp.
32) executive control.mp.
33) visuospatial abilit*.mp.
34) problem solv*.mp. or Problem Solving/
35) decision making.mp. or Decision Making/
36) (set shift* or conflict resolution or selective attention or working memory or verbal item).mp.
37) (cognit* adj3 (func* or declin* or reduc* or impair* or improve* or deficit* or progress* or perform* or abilit*)).mp.

38) 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
39) exp randomized controlled trial/
40) exp randomized controlled trials as topic/
41) Random Allocation/
42) exp Clinical Trials as Topic/
43) controlled clinical trial.pt.
44) random*.ti,ab.
45) trial.ti,ab.
46) systematic review.ti.
47) meta-analysis/
48) 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47
49) animals/ not (humans/ and animals/)
50) 48 not 49
51) 15 and 24 and 38 and 50

Search Strategy for EMBASE

1) Stroke.mp. or exp Stroke/
2) Cerebrovascular Disorders/
3) exp "Intracranial Embolism and Thrombosis"/
4) exp Brain Ischemia/
5) ((brain* or cerebr* or intracran* or intracerebral) adj5 (isch?emi* or infarct* or thrombo* or emboli* or occlus*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
6) isch?emic stroke*.mp.
7) hemorrhagic stroke*.mp.
8) transient isch?emic attack*.mp.
9) cva*.mp.
10) Hemiplegia/
11) hemipleg*.mp.
12) exp Paresis/ or paresis.mp.
13) paretic.mp.
14) (poststroke or post-stroke).mp.
15) 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16) exp Exercise/
17) exercis*.mp.
18) exp Exercise Therapy/
19) physical endurance.mp. or Physical Endurance/
20) physical exertion.mp. or Physical Exertion/
21) physical activ*.mp.
22) Rehabilitation/
23) (run* or physiotherapy or yoga or aerobic or swim* or danc* or walk* or jogging or fitness or resistance or biking or balance or flexibility).mp.
24) 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25) exp Cognition/

26) Cognitive Dysfunction/
27) Neuropsychological Tests/
28) Attention/ or Executive Function/
29) exp Memory/
30) processing speed.mp.
31) executive control.mp.
32) visuospatial abilit*.mp.
33) problem solv*.mp. or Problem Solving/
34) decision making.mp. or Decision Making/
35) (set shift* or conflict resolution or selective attention or working memory or verbal item).mp.
36) (cognit* adj3 (func* or declin* or reduc* or impair* or improve* or deficit* or progress* or perform* or abilit*)).mp.
37) 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
38) exp randomized controlled trial/
39) exp randomized controlled trials as topic/
40) Random Allocation/
41) exp Clinical Trials as Topic/
42) controlled clinical trial.pt.
43) trial.ti,ab.
44) systematic review.ti.
45) meta-analysis/
46) 39 or 40 or 41 or 42 or 43 or 44 or 45
47) 15 and 24 and 38 and 50

Search Strategy for COCHRANE

1) MeSH descriptor: [Stroke] explode all trees
2) MeSH descriptor: [Cerebrovascular Disorders] explode all trees
3) (brain* or cerebr* or intracran* or intracerebral):ti,ab,kw
4) (isch?emi* or infarct* or thrombo* or emboli* or occlus*):ti,ab,kw
5) (isch?emic stroke* or hemorrhagic stroke* or transient isch?emic attack* or cva* or hemipleg* or paretic or poststroke or post-stroke):ti,ab,kw
6) MeSH descriptor: [Hemiplegia] explode all trees
7) MeSH descriptor: [Paresis] explode all trees
8) #1 or #2 or #3 or #4 or #5 or #6 or #7
9) MeSH descriptor: [Exercise] explode all trees
10) MeSH descriptor: [Physical Endurance] explode all trees
11) MeSH descriptor: [Physical Exertion] explode all trees
12) (run* or physiotherapy or yoga or aerobic or swim* or danc* or walk* or jogging or fitness or resistance or biking or balance or flexibility):ti,ab,kw
13) (physical activ*):ti,ab,kw
14) #9 or #10 or #11 or #12 or #13
15) MeSH descriptor: [Cognition] explode all trees
16) (set shift* or conflict resolution or selective attention or working memory or verbal item or cognit*):ti,ab,kw
17) MeSH descriptor: [Cognitive Dysfunction] explode all trees

18) MeSH descriptor: [Neuropsychological Tests] explode all trees
19) processing speed or executive control or visuospatial abilit* or problem solv* or decision making
20) MeSH descriptor: [Attention] explode all trees
21) MeSH descriptor: [Mental Processes] explode all trees
22) #15 or #16 or #17 or #18 or #19 or #20 or #21
23) (review or randomized controlled trial):ti,ab,kw
24) #8 and #14 and #22 and #23

Search Strategy for CINAHL

1) (MH "Stroke") OR "stroke" OR (MH "Intracranial Embolism and Thrombosis") OR (MH "Intracranial Hemorrhage") OR (MH "Cerebrovascular Disorders") OR (MH "Cerebral Small Vessel Diseases") OR (MH "Cerebral Ischemia")
2) (MH "Ischemia") OR "ischemia" OR (MH "Cerebral Ischemia, Transient") OR (MH "Hypoxia-Ischemia, Brain") OR (MH "Cerebral Ischemia")
3) (MH "Hemiplegia") OR "hemiplegia"
4) S1 OR S2 OR S3
5) (MH "Exercise+") OR (MH "Physical Activity") OR (MH "Physical Fitness")
6) (MH "Rehabilitation+")
7) (MH "Rehabilitation Patients")
8) S5 OR S6 OR S7
9) (MH "Executive Function") OR (MH "Cognition") OR (MH "Cognition Disorders")
10) (MH "Neuropsychological Tests")
11) (MH "Attention")
12) (MH "Memory+") OR (MH "Problem Solving")
13) (MH "Rehabilitation, Cognitive")
14) "cognition"
15) "processing speed"
16) "visuospatial ability" OR (MH "Spatial Perception")
17) S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16
18) (MH "Randomized Controlled Trials") OR "randomized controlled trials" OR (MH "Clinical Trials") OR (MH "Cochrane Library")
19) (MH "Systematic Review") OR (MH "Meta Analysis")
20) S18 OR S19
21) S4 AND S8 AND S17 AND S20

Appendix C: Data extraction Form Used for Qualitative Synthesis

			Sample Population						Intervention Participants							Control1						
Study (Author, Year, Country)	Title of Paper	Eligibility Criteria	N total (randomized and completed study)	n Female and %F	Age in years (mean, SD)	Setting of Participants (Outpatient or Inpatient)	Time Post-Stroke (Years/months/days) (Mean, SD) and Stroke Type/Location/Number of Strokes (n)	Adverse Outcomes	N	n Females and %F	Age in years (mean, SD)	Time Post-Stroke (Years/months/days) (Mean, SD) and Stroke Type/Location/Number of Strokes (n)	Baseline Cognitive (MMSE or MoCA score) (Mean, SD)	Baseline Sociocultural Status(education in years/race/marital status) (Mean, SD)	Attendance Rate (%)	N	n Female and %F	Age in years(mean, SD)	Time Post-Stroke (Years/months/days) (Mean, SD) and Stroke Type/Location/Number of Strokes (n)	Baseline Cognitive (MMSE or MoCA score) (Mean, SD)	Baseline Sociocultural Status(education in years/race/marital status) (Mean, SD)	Attendance Rate (%)

Intervention (FITTS)							Control1 (FITTS)										
Frequency	Intensity	Type	Intervention Protocol	Time/session	Time for Entire Intervention (Months/weeks/days)	Setting	Frequency	Intensity	Type	Control Protocol	Time/session	Time for Entire Intervention (Months/weeks/days)	Setting	Cognitive Outcome Measure (also domain of cognition being measured)	Methodology of Cognitive Measurement	Time Points of outcome measurements	Main Results (in terms of cognitive outcomes)

Appendix D: Data extraction Form Used for Quantitative Synthesis

		INTERVENTION												CONTROL 1											
		PRE			POST			1ST FOLLOW UP			2ND FOLLOW UP			PRE			POST			1ST FOLLOW UP			2ND FOLLOW UP		
Study (Author, Year)	Outcome Measure and Units	N	mean	SD	N	mean	SD	N	mean	SD	N	mean	SD	N	mean	SD	N	mean	SD	N	mean	SD	N	mean	SD

Appendix E: Classification of Neurocognitive Tests by Domain

Cognitive Domain	Cognitive Test (Number of Studies)
Attention and Processing Speed	Trail Making Test A (2 studies)
	Continuous Performance Test (1 study)
	Stroop Baseline Test (2 studies)
	Serial Reaction Timed Task (repeated and random) (1 study)
	Weschler Adult Intelligence Scale-Symbol Search (1 study)
	Weschler Adult Intelligence Scale- Coding (1 study)
Memory	Stroke Impact Scale (Memory domain) (3 studies)
	Rey Auditory Verbal Learning Test (1 study)
	Verbal Digit Span Forward (4 studies)
	Weschler Adult Intelligence Scale-Verbal Pairing Domains (1 study)
Executive Function	Trail Making Test B (6 studies)
	Stroop Colour-Word Interference Test (6 studies)
	Auditory Stroop Test (2 studies)
	Verbal Digit Span Backward (4 studies)
	FAS Test (1 study)
	Wisconsin Card Sort Test (1 study)
	Raven's Progressive Matrices Test (1 study)
Visuospatial Function	Mental Rotation Test (1 study)
	Weschler Adult Intelligence Scale-Spatial Span Domain (2 studies)
Language	Stroke Impact Scale (Communication domain) (3 studies)
Global Cognition	Montreal Cognitive Assessment (2 studies)
	Functional Independence Measure (Cognitive Domain) (5 studies)
	Addenbrooke's Cognitive Examination-Revised (1 study)