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Relationship Between Exercise Training Adherence and Improvement in Functional Capacity Among Transient Ischemic Attack and Mild Non-disabling Stroke Survivors in Cardiac Rehabilitation

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Abstract

Introduction: Transient ischemic attack (TIA) is characterized by temporary neurological dysfunction and carries a short-term risk of stroke, hospitalization, and death. Cardiac rehabilitation and secondary prevention (CRSP) involving behavior change and exercise reduces morbidity and mortality among heart patients but is typically not offered after TIA, despite similarities in risk factors between coronary artery disease and stroke. Current stroke secondary prevention strategies are suboptimal.

Objectives: To quantify the relationship between exercise adherence and functional capacity at CRSP exit among exercise-trained TIA and mild non-disabling stroke (MNDS) patients and to determine if CRSP improves physical and psychological outcomes.

Methods: From 2004 to 2014, 115 exercise-trained TIA/MNDS across three studies were used for this study. Linear regression was used to analyze the primary objective and paired t-tests were used to compare intake and exit measures of the secondary objectives.

Results: There was a positive relationship between exercise attendance and improvement in functional capacity and the participants had clinically significant improvements in key cardiovascular risk factors and psychometrics.

Conclusion: This study illustrated a “dose-response like” relationship between exercise attendance and functional capacity that reached a clinically significant improvement of 0.5 METS (Canadian Cardiovascular Society quality indicator). Future work should investigate the long-term impact of CRSP for TIA/MNDS patients as well as cost-effectiveness analyses.

Keywords

Transient ischemic attack; mild non-disabling stroke; cardiac rehabilitation; functional capacity; exercise training

Summary for Lay Audience

A transient ischemic attack (TIA) often called a mini-stroke serve as an important warning sign for future vascular events. TIAs have a short-term risk of stroke, hospitalization and death. Current stroke prevention strategies are spread across multiple organizations and the clinical practice is variable. Cardiac rehabilitation and secondary prevention (CRSP) is a program offered to heart patients that is designed to improve their cardiovascular health. The problem is that cardiac rehabilitation is not typically offered to TIA patients despite the fact that they share similar risk factors. This study aimed to investigate the relationship between exercise attendance and exercise capacity among exercise-trained TIA and mild-nondisabling stroke (MNDS) patients enrolled in CRSP. It also aimed to determine if CRSP for TIA/MNDS patients improves their physical and psychological outcomes. We selected 115 exercise-trained TIA/MNDS patients that were a part of three studies that occurred between 2004 and 2014 to conduct the statistical analyses. We found that there was a positive relationship between exercise attendance and improvement in exercise capacity. Additionally, exercise trained TIA/MNDS patients had clinically significant improvements in cardiovascular risk factors and psychological outcomes. In conclusion, we observed a “dose-response like” relationship between exercise attendance and exercise capacity and we observed favourable outcomes that reached clinically significant improvements. Our findings suggest that CRSP may be a more effective means for secondary prevention for this patient population.

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List of Abbreviations

BMI	Body Mass Index
CCS	Canadian Cardiovascular Society
CDT	Clock Drawing Test
CRSP	Cardiac Rehabilitation and Secondary Prevention
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
HADS	Hospital Anxiety and Depression Scale
HDL-C	High Density Lipoprotein Cholesterol
HRQOL	Health-related quality of life
LDL-C	Low Density Lipoprotein Cholesterol
MMSE	Mini Mental State Examination
MNDS	Mild Non-disabling Stroke
NYHA	New York Heart Association Functional Classification
PMS	Post-menopausal Syndrome
RAVLT	Rey Auditory Verbal Learning Test
SBP	Systolic Blood Pressure
SF-12	The Short Form-12 Health Survey
SR-MA	Systematic Review and Meta-Analyses
TC	Total Cholesterol
TG	Triglycerides
TCI	Transient Cognitive Impairment
TIA	Transient Ischemic Attack
TMT	Trail Making Test
WAIS-R	Wechsler Adult Intelligence Scale Revised (WAIS-R)

Chapter 1

1 Introduction

This chapter explores the prevalence of cardiovascular diseases and stroke globally and specifically the prevalence of stroke in Canada. It also defines transient ischemic attack and summarizes Cardiac Rehabilitation and Secondary Prevention (CRSP) components and benefits. Lastly, this chapter discusses the purpose of this thesis, objectives and the thesis outline.

1.1 Overview

Cardiovascular diseases are one of the leading causes of death worldwide (1), and stroke is the second leading cause of mortality globally (2). Stroke has an estimated global lifetime risk of 24.9% starting at age 25 (3). In Canada, the third leading cause of death is stroke (4). Stroke costs the Canadian economy more than $3.6 billion a year in physician services, hospital expenditures, loss of individual income, and diminished productivity. A similar impact can be observed among individuals who have experienced a minor stroke or transient ischemic attack (TIA)(5). TIAs also known as mini-strokes carry a short-term risk of stroke, hospitalization, and death (6), but the risk of subsequent events can be reduced by behavioral risk modification (7). Therefore, the chance to prevent recurrent stroke through risk factor modification efforts signifies a meaningful opportunity to reduce the stroke burden.

Cardiac Rehabilitation and Secondary Prevention uses a multidimensional approach that includes: reducing cardiovascular disease risk factors, using behavior modification strategies to maintain healthy lifestyles, promote pharmacological adherence, and provide therapeutic exercise training (8). Clinically, secondary prevention is designed to stop or slow progression of a disease of disorder when patients have a disease and are at risk for developing something related to their current disease (9). CRSP is typically delivered through a case-managed comprehensive model of secondary disease prevention to individuals with cardiovascular disease including those who have experienced a myocardial infarction, angina or heart surgery (8). CRSP has been proven to reduce morbidity and mortality among patients with known heart disease (10) but is typically not offered to TIA or mild stroke patients despite the many parallels in risk factors between heart disease and stroke. Current research suggests

that in these patients, programs like CRSP may be a more effective means of reducing cardiovascular risk and improving quality of life than standard care. It has been demonstrated that it is feasible and safe for TIA patients to partake in CRSP and it is clear that current secondary prevention strategies for stroke care are suboptimal (11).

1.2 Purpose and Objectives

This thesis provides further evidence of the degree to which individuals with TIA can benefit from a CRSP program. Our primary research question was: how does exercise attendance in CRSP influence TIA/MNDS patient's functional capacity? The primary objective for this project was to quantify the relationship between exercise adherence (attendance) and functional capacity (measured in METS) at CRSP program exit among exercise trained TIA and mild non-disabling stroke (MNDS) patients. The secondary objectives were to: 1) determine whether CRSP programming among exercise trained TIA/MNDS patients resulted in intake-to-exit improvements in functional capacity, blood pressure, lipid profile, blood glucose, body measurements and composition and 2) determine whether CRSP programming among exercise trained TIA/MNDS patients results in significant intake to exit changes in the following psychometric domains: quality of life and health status, anxiety, depression, general cognitive functioning, attention and working memory, verbal learning and memory, pre-morbid intellectual functioning and speed/executive/abstraction.

1.3 Thesis Outline

The following chapter - Chapter 2 includes a review of the literature. A detailed description of study objectives and hypotheses for this project are then provided in Chapter 3. Study methodology is covered in Chapter 4. The results are reported in Chapter 5, with a discussion section reported in Chapter 6.

Chapter 2

2 Review of the Literature

The literature review provided in Chapter 2 includes ten sections. Section 2.1 explores the changing definitions of transient ischemic attack from the 1960s to present day, then Section 2.2 outlines the modifiable, and non-modifiable risk factors for TIA/MNDS. Section 2.3 explores the current treatment strategies for TIA/MNDS. Sections 2.4, 2.5, and 2.6 summarizes literature investigating cognitive impairment among the TIA and minor stroke population, current evidence on depression and anxiety among this patient population, and research investigating quality-of-life among TIA and minor stroke patients respectively. Section 2.7 defines and describes the components and benefits of CRSP while Section 2.8 summarizes studies that have investigated TIA/MNDS in a CRSP or CRSP-like setting and it is organized by type of study. Lastly, Section 2.9 outlines the benefits of exercise training and Section 2.10 outlines the gaps in the literature.

2.1 Transient Ischemic Attack

A transient ischemic attack (TIA), also known as a mild non-disabling stroke (MNDS) or mini-stroke is characterized by temporary neurological dysfunction caused by loss of blood flow in the brain, spinal cord or retina without tissue death (12). There is a long-standing time-based definition for TIA – which is cerebral ischemia in which symptoms last less than 24 hours. This definition originated from the 1960s and was used for about 40 years (12). The time-based definition was developed at a time where there were very few options available for stroke prevention or treatment, and little understanding of stroke risk factors (13). Recently, research advances have illustrated that the time-based definition maybe erroneous, confusing, and could potentially impact patients' outcomes due to the initiation of treatment being delayed. Therefore, the time-based definition has shifted to the tissue-based one so that patients with transient neurological deficits of vascular origin with imaging evidence of acute ischemia are more likely to be diagnosed as "minor stroke" (14), and therefore require treatment (13).

TIAs are an important warning sign for further, more devastating vascular events or death (6). A TIA and ischemic stroke share common pathophysiological mechanisms (15) and

individuals who have suffered from a TIA may also experience cognitive impairment similar to patients with major stroke (7). Recent meta-analyses of individuals with TIA revealed that the short-term risk of stroke after TIA was 10% within the first 48 hours and between 9% to 17% at 90 days (16). Among individuals who present with stroke, the prevalence of a prior TIA has been reported to range from 7% to 40% (12). The risk of subsequent stroke following a TIA can be reduced by risk factor modifications (17).

2.2 Risk Factors

There are modifiable and non-modifiable risk factors for TIAs. Modifiable risk factors include: hypertension, diabetes, hyperlipidemia, cigarette smoking, excessive alcohol consumption, obesity, physical inactivity, metabolic syndrome (18), depression (19), and socioeconomic status (SES) (20). Non-modifiable risk factors include age, family history, sex, and ethnic origin (21).

2.2.1 Modifiable Risk Factors

Being physically inactive can increase the risk of stroke and heart disease (22). The protective effect of habitual exercise has been shown to have a number of benefits on key risk factors such as hypertension, dyslipidemia, diabetes, physical inactivity, obesity, excessive alcohol intake, and tobacco use (23). The relationship between increased physical fitness and reduced risk for TIA/stroke is described in more detail in section 2.9.

Hypertension is defined as systolic blood pressure $\geq$ 140 mm Hg or diastolic blood pressure $\geq$ 90 mm Hg (24). Hypertension is a major risk factor for cerebral infarction and intracerebral hemorrhage, and the risk of stroke increases with high blood pressure (21). Diabetes mellitus is an independent risk factor for stroke and it has been found to more than double the risk of stroke. Individuals with diabetes mellitus are more susceptible to atherosclerosis and have an increased prevalence of other atherogenic risk factors such as hypertension and dyslipidemia (21). Abnormally elevated levels of total cholesterol or low density lipo-protein cholesterol (LDL-C) have been found to be associated with an increased risk of ischemic stroke, and higher levels of high-density lipoprotein cholesterol (HDL-C) have been reported to be associated with decreased risk of stroke (22). Recent epidemiological data suggests that the relationship between HDL-C and all-cause mortality is

U shaped, suggesting that very high and low concentrations are associated with high all-cause mortality (25). Furthermore, there is strong and consistent evidence that cigarette smoking is a risk factor for ischemic stroke (26). Additionally, exposure to environmental smoke (27) or passive smoking (28) is also an established risk factor for heart disease and stroke. The American Heart Association reports that cigarette smoking approximately doubles the risk of stroke (21).

There is strong evidence between heavy alcohol consumption and all stroke subtypes, although there is limited evidence investigating the effect of alcohol consumption and recurrent stroke. It is possible that any elevated risk of recurrent stroke would be resulting from the interrelationship alcohol consumption has with other stroke risk factors (e.g. alcohol-induced hypertension) (18,29). Obesity has been established as an independent risk factor for cardiovascular disease and stroke. However, the association between body weight and stroke has been mostly investigated in primary prevention studies (18). A large body of evidence suggests a graded positive association between obesity and stroke independent of other cardiac risk factors, but it remains unknown whether weight loss reduces the risk of stroke or recurrent stroke due to the other effects weight loss can have on other risk factors such as diabetes and hypertension (21).

A positive relationship between depressive symptoms and stroke mortality has been reported. After adjustment of other well-known stroke risk factors, it was found that individuals reporting five or more depression symptoms at baseline experienced greater than 50% excess risk of mortality due to stroke during the following 29 years (19). SES has also been found to be associated with stroke. It has been observed that stroke disproportionately affects low-income and middle-income countries (30) but also low-SES groups in high-income countries and such disparities are found in the risk of stroke and the long-term effects after stroke (20,31). Several studies on general populations in developed countries have shown a higher prevalence of common stroke risk factors in low-SES groups. Specifically, in the NHANES I study conducted in the USA, they reported that smoking, heart disease, physical inactivity, use of blood pressure medications and high SBP was highest among white men in the lowest poverty-index-quartile (32).

2.2.2 Non-modifiable Risk Factors

With greater age, the risk of stroke increases (33). There is an accumulation of risk factors with age due to the aging cardiovascular system and the progressive nature of stroke risk factors (21). The rate of stroke is reported to double every ten years after the age of 55 (34). The risk of stroke may be greater with a family history of TIAs or stroke. It has been reported that having a positive family history of stroke increases the risk of stroke by approximately 30% (21). Generally, stroke is more common in men or women at different time periods (22). Women experience stroke later than men potentially because of loss of protection by estrogen after menopause (35). There are racial and ethnic differences found in TIA prevalence and stroke mortality. Blacks and some Hispanic/Latino American's have a greater incidence of all stroke types and higher mortality compared to whites (21).

2.3 Treatment

The current treatment strategies for TIA primarily include the prescription of antiplatelet or anticoagulation agents and blood pressure and cholesterol-lowering medications (16). Non-pharmacological interventions that could play a role in secondary prevention after TIA include exercise, dietary advise, lifestyle counselling, and patient education (36). Exercising has significant health benefits on blood pressure, plasma lipoprotein status, weight loss and glycemic control. Additionally, education programs tailored towards exercise and diet have been found to reduce plasma fasting glucose among individuals at high risk for type 2 diabetes (36). These non-pharmacological interventions are aimed to reduce vascular risk factors which is a multifaceted problem that requires intervention at various levels. There are stroke prevention clinics tailored to provide individuals with access to stroke specialists and diagnostic tests, risk factor screening and referrals to outpatient services as needed. These secondary prevention programs tend to be spread across multiple organizations and the clinical practice is variable and often suboptimal (11). Stroke prevention clinics were established in Ontario is 2001. The *Ontario Stroke Evaluation Report 2013: Spotlight on Secondary Stroke Prevention and Care* suggested that there is room for improvement in the standardization protocols for achieving best practices across the entire network of clinics (37).

2.4 Cognitive Impairment in TIA and Minor Stroke

Conventionally, healthcare professionals and individuals have considered a TIA to be a relatively non-threatening event compared to the disabling characteristics of stroke (12). Despite the resolution of symptoms from a TIA, advances in neuroimaging have shown evidence of infarction in about one third of patients post-TIA (18). Individuals with TIA or ischemic stroke have an increased risk of developing cognitive impairment (38). However, there is a limited amount of research exploring cognitive impairments after a TIA. Cognitive impairments are known to occur after major stroke with a prevalence that varies from 20% to 90% (7). These cognitive impairments are potential sequelae of TIA and minor stroke (38). A recent study reported that most individuals who had a TIA or minor stroke showed deficits in cognitive control or executive function with 57% of the patient population impaired in one or more of the neuropsychological tests employed (39). Compromised executive function can be characterized by troubles in working memory, reasoning, task flexibility, and problem solving (13).

Cognitive deficits due to diseases of vascular origin are well documented in the literature. “Vascular cognitive impairment” and “vascular dementia” are terms used to describe a variety of mild to severe cognitive deficits that are caused by stroke or subclinical vascular brain damage (13). Vascular cognitive impairment is predictive of hospitalization, mortality, and dementia (40). Ganzer et al (2016), suggested that the effects of vascular risk factors such as type 2 diabetes and high diastolic blood pressure can be associated with changes in executive function and contribute to the occurrence of transient cognitive impairment (TCI) post TIA. Additionally, these vascular risk factors in TIA patients increase the risk of progression of white matter hyperintensities, which are related to cognitive decline (41). Additionally, there are shared risk factors between TIA and cognitive function such as advanced age that are associated with cognitive decline.

The frequency of cognitive impairment following a TIA or minor stroke is influenced by the measurement tool used. A systematic review investigating prevalence of cognitive impairment among other psychological outcomes following TIA and minor stroke reported prevalence of cognitive impairment of 17% (95% CI 7,26), 39% (95% CI 28,50), and 54% (95% CI 43,66) using the Mini Mental State Examination (MMSE), Neuropsychological Test

Battery (NTB), and Montreal Cognitive Assessment (MoCA) respectively (38). A recent systematic review by van Rooiji Frank et al., (2016) investigating the prevalence of cognitive impairment in TIA patients and potential causative factors reported a highly variable rate of mild cognitive impairment after TIA ranging from 29% to 68% and severe cognitive impairment in 8% to 22% of the patients (12 studies, n=1,167). The modes of testing included the NTB, MoCA, Modified Telephone Interview for Cognitive Status (TICSm), and MMSE. The researchers also found that deficits in executive function, attention, and information processing speed were most common and suggested that the rate of cognitive impairment was likely higher in the total population with TIA since their patient population was only limited to individuals without dementia (41).

Furthermore, a study investigating TCI defined as "acute cognitive deficits demonstrated early after major stroke that may recover to some extent in TIA and minor stroke at the time of initial assessment and one month later", found that the rate of TCI was higher in cerebral TIA and stroke patients that were seen acutely (1 to 7 days after their presenting event) than those seen after 7 days. A higher rate of TCI was also found in TIA and stroke patients seen acutely versus non-cerebrovascular patients (42). Follow up for the individuals who survived to five years within the same patient population illustrated a higher rate of cognitive impairment in those with TCI versus those without. The authors concluded that, TCI was common after minor cerebrovascular events, was occult in the majority of patients, and was associated with subsequent cognitive decline (42).

In another study, by van Rooiji Frank et al., (2014) among TIA patients without a prior history of stroke or dementia within 3 months of the event (n=188), they found that individuals with TIA performed worse than controls on cognitive tests and domains that measured executive function, information processing speed, working memory, and attention. The opposite trend was observed for episodic memory that remained preserved (43). Among the patient population, silent brain infarct (SBI) but not age-related white matter changes were associated with poorer executive functioning. When patients with SBI were excluded, TIA was still found to be associated with impaired cognition. The authors concluded that future studies should utilize brain imaging techniques in combination with long-term cognitive assessment to identify whether the cognitive effects are transient, stationary, or progress over time. In a study by Sachdev et al, (2014) investigating the progression of

cognitive impairment in stroke/TIA over 3 years it was found that patients did not typically decline more than controls in most cognitive domains, but they had lower baseline measures. Patients with interval stroke/TIA had a significantly greater decline than controls in attention, processing speed, working memory, visuoconstruction, mental flexibility, and verbal fluency. Patients without interval stroke/TIA declined more only on verbal memory (44). The authors concluded that stroke/TIA patients who do not experience interval stroke/TIA have a slow cognitive decline compared to patients who experienced another stroke or TIA during follow up.

An exploratory study investigating patients with TIA or minor stroke's cognitive and communication problems six months after the event compared to patients with angina pectoris, found that TIA and minor stroke patients had deficits in memory (n=24) and/or concentration (n=14). The communication problems were mainly attributed to difficulties in writing and speech and language comprehension and TIA and minor stroke patients reported significantly more difficulties than angina patients (45). Prior et al., (2017) found that frequencies in executive impairments between entry and exit to CRSP remained unchanged and suggested that such impairments were persistent 10 months post TIA/MNDS (46). These findings further support that TIA and minor strokes effects are not as transient as we believed and that this patient population would likely benefit from care after hospitalization.

Overall, cognitive impairment is an important issue in TIA patients, which further justifies research investigating this patient population at high risk of cognitive decline. These unresolved deficits of cognitive functioning after TIA could impact an individuals' ability to learn and understand new information, along with the application of health behaviours intended to reduce vascular risk factors (13). Additionally, these deficits put this patient population at greater future risk of progressive cognitive decline and possibly leading to dementia (47). It has been suggested that multi-domain interventions that include diet, exercise, cognitive training and vascular risk factor monitoring could result in improvement or maintenance of cognitive functioning in the elderly population (48). Thus, further research is in this subject area is needed.

2.5 Depression and Anxiety Among TIA and Minor Stroke Patients

One in three stroke survivors are affected by depression (23,49) and one in four survivors develop post stroke anxiety (49). The pathophysiological mechanisms of post-stroke depression are thought to be multifaceted and influenced by location and magnitude of brain injury, vascular comorbidities and coping with emerging functional disabilities (50). Other studies have suggested that small-vessel brain disease resulting from long-lasting ischemic changes in the brain maybe involved in the pathogenetic pathway of late-life depression (51). Generally, post-stroke psychological outcomes are fairly under researched compared to physical disabilities associated with stroke. Furthermore, there are not many studies that have examined mood disorders in TIA samples. It is possible that psychological effects of TIA maybe similar to that of stroke survivors.

A study by Broomfield and colleagues investigating the prevalence of depression and anxiety using a regional stroke registry in the United Kingdom found that out of 1247 TIA cases reviewed, 179 (14%) and 107 (9%) of cases were classified as definite abnormal anxiety and definite abnormal depression symptoms respectively (49). The authors also investigated cases in a stroke cohort and found that depression and anxiety levels were similar between the TIA and stroke patients. Their data suggested that depression and anxiety symptoms are common following stroke events including TIA, and interventions and psychological assessments should not be limited to stroke patients only. Similar findings were reported in a study by Husseini et al. (2012) investigating depression and antidepressant use after stroke and TIA. The authors found that the proportional frequency of depression was similar with stroke and TIA patients at 3 months (17.9% versus 14.3%) and at 12 months (16.4% versus 12.8%) (50). Additionally, the proportion of antidepressant use, and incident antidepressant use was also similar between stroke and TIA patients. Younger age, poor functional outcome, depression, and inability to work at three months was associated with post-stroke depression at 12 months. Prior et al., (2017) found that at CRSP exit 16.9% of the cohort (n= 70) screened positively for anxiety, which suggested that clinically important levels of anxiety may persist 10 months post event despite treatment, and that further research is merited to determine optimal treatment for this patient population (46).

A recent systematic review found that the prevalence of depression was high within the first month after TIA or minor stroke and decreased between six weeks and three months. Furthermore, there were no significant differences in the prevalence of depression between TIA or minor stroke patients (38). The authors reported a prevalence of anxiety of 52% and 65% for TIA and minor stroke participants respectively, but these findings were observed from only one study. The findings suggested that the prevalence of depression was high in the acute stage after TIA or minor stroke but appeared to decrease over time.

Maaijwee et al., (2016) investigated the long-term depressive symptoms and anxiety after TIA or minor stroke in young adults (<50). The overall prevalence of depression and anxiety for TIA and minor stroke patients was 16.8% and 23% respectively. The prevalence of depression and anxiety was higher than their age and sex matched controls. For individuals with TIA, the prevalence of depression and anxiety symptoms was 12.1%. and 23.1% respectively (52). These findings showed that individuals who experienced stroke at a young age where influenced by psychological outcomes of stroke even 10 years after stroke. These individuals with TIA or ischemic stroke were at risk of depressive symptoms and anxiety of about five times greater than stroke free controls. A similar study investigating TIA and incident depression found that in 325 persons with TIA, about 8% developed depression, and after 12 years of follow-up, twice as many individuals with TIA developed depression (53). Interestingly, TIA was more strongly associated with depression the more strictly depression was defined. These findings further confirm the high risk of post-TIA depression and anxiety and justifies the greater need to pay attention to these psychological outcomes within this patient population.

2.6 Quality of Life in Patients with TIA and Minor Stroke

It is widely known that acute ischemic stroke leads to a decline in an individuals' health-related quality of life (HRQOL), even among individuals who have minimal or no stroke-related deficits (54). It is possible that emotional changes after a stroke event would have an effect on quality of life (QOL), and this may in turn influence how an individual copes, adapts, and overcomes the challenges associated with the event (55). The prevalence of depression is high among stroke patients, and such post-stroke depression decreases QOL among this patient population (53). Additionally, unrecognized cognitive dysfunction may

also affect an individual's QOL (41). Specifically, impaired executive function can manifest as issues in memory, reasoning, task flexibility, and problem solving which are all factors that can affect one's QOL and their capacity to deal with post-stroke medical challenges (13). Despite TIA/MNDS's transient nature, they still exhibit important psychological ramifications, including depression and anxiety (55) and diminished QOL (56).

In a study by Sangha et al, (2015) investigating the quality of life of patients with TIA and minor ischemic stroke at three months, the patients completed a series of domain-specific HRQOL assessments using five Neuro-QOL measures: upper extremity function, lower extremity function, satisfaction with social roles and activities, applied cognition-executive function, and applied cognition-general concerns. Out of 332 patients, any HRQOL impairment was found in 119 patients (35.8%), and stratified analysis showed a statistically significant difference between index stroke with more impairments in individuals with mild ischemic stroke compared to TIA (39.7% vs. 22.7%, $p<0.001$) (54). The authors concluded that impairment in HRQOL is common three months following mild ischemic stroke and TIA, and this is observed in patients without disability. Additionally, age, index stroke severity, and recurrent strokes were predictors of compromised HRQOL. They also suggested that Neuro-QOL measures should be employed after TIA and mild ischemic stroke as they may aid in the identification of mild deficits in this patient population (54).

2.7 Cardiac Rehabilitation and Secondary Prevention

Cardiac rehabilitation and secondary prevention (CRSP) is a program that is a component of cardiovascular disease care and chronic disease management (57). CRSP delivers a case-managed comprehensive model of secondary disease prevention to individuals with known heart disease – for example, those who have had a heart attack, angina, or heart surgery (8). CRSP uses a multidimensional approach that includes: reducing cardiovascular disease risk factors, using behaviour modification strategies to sustain healthy lifestyles, promote pharmacological adherence, and provide therapeutic exercise training (8). The current body of knowledge suggests that there is an association between CRSP program participation, and each of improved exercise capacity, obesity indices, lipid profiles, quality of life, reduced inflammation, psychological distress and most notably reductions in mortality and morbidity (58).

There are approximately 220 CRSP programs in Canada, providing services to more than 50 000 new patients annually (59). In Ontario, this program is not typically offered to TIA patients although there has been compelling evidence that this multidimensional approach as secondary prevention strategy after TIA was effective and feasible for TIA and MNDS patients (60,61). A survey found that 24 (60%) of the 40 facilities from the Cardiac Rehabilitation Network of Ontario Directory indicated that the CR program enrolled individuals with stroke (62). However, of the 18 facilities that provided more detailed responses, stroke participants represented only 4.8% of their total annual enrolment.

2.8 Cardiac Rehabilitation for TIA and Mild-Non-Disabling Stroke Patients

There are many shared risk factors between heart disease and stroke yet despite the demonstration of the benefits of risk factor modification interventions such as CRSP, these strategies are not a priority in current stroke practice (62). There is emerging evidence that such a strategy results in improvement of key stroke risk factors.

2.8.1 Observational Studies

Many observational studies have demonstrated feasibility and effectiveness of CRSP for TIA patients. Tanne et al. (2008) found that a supervised exercise program that also involved other components such as patient education and exercise prescription similar to CRSP resulted in improvements in exercise capacity demonstrated by the improvement in the 6 minute walk test among patients that underwent exercise training after a minor ischemic stroke ($n=43$, $p = 0.002$) (63). Additionally, Tang et al., (2010) reported that among participants enrolled in an adapted CRSP program, VO_2 peak improved significantly at the end of the program compared to the baseline period ($n=41$, $p = 0.046$) (64). Prior et al., (2011) demonstrated that a 6-month duration CRSP program of moderately intense exercise training was feasible, safe and effective. They found significant, favourable intake to exit changes in mean aerobic capacity ($p < 0.001$), total cholesterol ($p=0.008$), waist circumference ($p <0.001$), body mass index (BMI)($p=0.003$), and body weight($p=0.001$)($n=80$) (60). A similar study investigating the feasibility and effects of 6-month CRSP for individuals after TIA found significant improvements in VO_2 ($p=0.001$), resting heart rate ($p=0.03$), BMI ($p=0.03$), a reduction in the proportion of people with

obesity ($p < 0.001$), and abdominal obesity ($p = 0.001$) among a retrospective cohort (n=39). In a prospective cohort (n=14), there were significant improvements in pre to post CRSP in VO_2peak ($p=0.01$), oxygen uptake at the ventilatory anaerobic threshold (VAT) ($p=0.04$),but surprisingly, a significant increase in SBP ($p=0.01$) (65). Additionally, there was a significant improvement in the Center for Epidemiologic Studies Depression Scale (CES-D) during the intervention period ($p = 0.007$).

In an observational study investigating psychological profile and outcomes after comprehensive cardiac rehabilitation for TIA patients, the mean depression ($p<0.001$), anxiety($p<0.001$), mental ($p<0.001$) and physical health status ($p=0.031$), word-list learning($p<0.001$), memory, digit symbol coding ($p=0.002$), and oral-verbal fluency scores ($p=0.006$) improved significantly between entry and exit (46). While these changes were not independently associated with CRSP, they suggested that given greater statistical power, increased treatment intensity and/or duration could produce psychological, health status or neurocognitive improvements after TIA/MNDS (46).

2.8.2 Randomized Controlled Trials

A pilot randomized trial evaluating the benefit of the cardiac rehabilitation program for a non-acute ischemic stroke population by Lennon et al (2008) also found that overall cardiovascular fitness ($V0_2$) improved and rated perceived exertion decreased in the intervention group compared to controls ($p<0.001$). Additionally, Hospital Anxiety and Depression Scale (HADS) score improved significantly in the intervention group ($p<0.001$) (66). In a more educationally and behaviorally focused randomized trial exploring enhanced secondary prevention following minor stroke and transient attack, Gillham and colleagues (2010) found that a greater number of individuals in the intervention group (n=25) moved from the contemplation stage of behavior change to the action stage compared to controls (n=25). Exercise frequency($p=0.007$) and fruit and vegetable consumption ($p=0.033$) also increased in the intervention group (67).

Faulkner et al (2013) explored the effects of early exercise engagement (within 2 weeks of symptom onset) on vascular risk among patients with TIA and MNDS enrolled in an 8-week health enhancing physical activity program. They found a significant baseline to post-intervention decrease in SBP and total cholesterol (TC) for the intervention group (n=30) but

not control (n=30) (16). A subsequent study by Faulkner and colleagues (2014) exploring the long-term effect of exercise on vascular risk factors found that participants who took part in the intervention had a significantly greater change in SBP between baseline and post-intervention compared to control ($p < 0.05$)along with improvements in aerobic fitness maintained at the 12-month assessment (68). In a recent study by Faulkner et al (2015) investigating the psychosocial effects of early exercise engagement post-TIA and MNDS, they reported a significant difference between the experimental group and control for the Short Form-36 Health Survey (SF-36) physical health component score ($p<0.01$) (n=55) but there were no differences in participants anxiety or depression between treatment groups (69).

Similarly, Boss et al, (2014) explored post-stroke care and exercise after TIA and minor ischemic stroke at 6 and 12 months post-intervention and demonstrated that in the acute phase, post stroke care similar to CRSP is safe and feasible (n=20) (17). Furthermore, in a study by Kirk et al (2014), they found a statistically significant reduction in cardiovascular disease risk score in the intervention group compared to the control group ($p=0.042$). Additionally, subjective health status measured by the SF-36 domains of physical functioning ($p=0.012$)and mental health ($p=0.039$) found a significant between group improvement in the intervention group compared to the control (70). In a more recent study by Boss et al (2017) exploring cardiorespiratory fitness (CRF) after TIA and minor stroke reporting baseline data concluded that majority of individuals with a TIA or minor stroke had demonstrated poor CRF. Greater age, female sex, a history of cardiac disease, other vascular disease, chronic obstructive pulmonary disease (COPD), use of beta-blockers, hypertension, BMI and smoking were associated with lower VO_2 peak (71).

In a study by Ihle-Hansen et al. (2014), investigating the effect on anxiety and depression from a multifactorial risk factor intervention program similar to CRSP after stroke and TIA, one-year post-stroke 4.7% and 14.5% patients in intervention and the control group suffered from depression respectively (n=174). The difference between the intervention control group for changes in HADS was statistically significant ($p=0.044$). Additionally, 8.2% and 14.6% of the patients in intervention and control group suffered from anxiety, and this difference was not statistically significant post-intervention (55). The author's conclusions suggested that a multifactorial risk factor management program that involves education and vascular

risk factor modification may result in a decreased prevalence of depression and in turn lower the HADS score one-year post stroke which has also been observed in other studies.

The PREVENT (6) and CRAFTS (72) trials are currently investigating the short and long-term effects of a comprehensive program of secondary stroke prevention services which would include exercise, education and counselling programs in modifying vascular risk factors in TIA and MNDS patients within 90 days.

2.8.3 Systematic Reviews and Meta-Analyses

An early systematic review and meta-analyses (SR-MA) by MacKay Lyons et al, (2013) investigating non-pharmacological interventions for preventing secondary vascular events after stroke or TIA suggested that interventions that reduce risk factors after stroke should be given priority in health care (36). At that time, not many randomized controlled trials had evidence to support this. Several new studies of lifestyle interventions with or without an exercise program have been published. In a recent systematic review and meta-analysis (SR-MA) by D'Isabella and colleagues (2017) investigating the effect of exercise on cardiovascular risk factors following stroke or transient ischemic attack (four studies) suggested that there are significant beneficial effects of all interventions (involving exercise alone or exercise with other interventions) with respect to SBP, fasting glucose, fasting insulin, and HDL-C. For meta-analyses for studies only involving exercise interventions, significant effects of SBP, fasting glucose and HDL-C remained (73). The authors suggested that ongoing work should depict the differential effects of exercise of TIA versus stroke. Importantly, they also recommended exploring "dose-response" relationships.

A similar SR-MA by Deijle and colleagues (2017) investigating lifestyle interventions to prevent cardiovascular events with or without an exercise program after stroke and TIA had a total of five trials (n=1800) that used a cardiovascular fitness intervention and five trials (n=222) that use a combined intervention including another behavior change intervention. The main findings from this SR-MA showed a significant 3.6 mmHg reduction in SBP in the lifestyle interventions compared to usual care. Trials with a cardiorespiratory fitness program or combined intervention also showed a significant reduction in SBP and interventions that lasted longer than 4 months and used more than 3 behavior change techniques were more successful in decreasing SBP (74). Another SR-MA by Heron et al, (2017) investigated

lifestyle interventions initiated 90 days after TIA or minor stroke found no improvement in resting or peak SBP. There was also no treatment effect for heart rate and the 6-minute walk test (75).

2.9 Benefits of Exercise Training

Generally, physical activity has been well studied due to its well-known effects on cardiovascular disease (CVD) risks and all-cause mortality and research supports exercise training for primary and secondary prevention of CVD. Several studies have shown that exercise training improves cardiovascular function. Formal cardiac rehabilitation and exercise training programs result in: 1) improvement in exercise capacity; 2) improvement in lipid profiles; 3) reduction in inflammation; 4) reduction in indicators of obesity; 5) improvements in behavioral characteristics; 5) improvement in quality of life and components; 6) Improvement in autonomic tone; and 7) improvement in blood rheology (76). Furthermore, exercise also alters vascular remodeling and results in the upregulation of antioxidant defense mechanisms in various tissues (24).

Inflammation plays a prominent role in the pathology of many cardiovascular diseases. Atherosclerosis results from plaque build-up within arterial walls and is an inflammatory disease that is caused by monocyte derived macrophages that collect in arterial plaques and are activated to release cytokines that damage vascular tissue (24). Exercise training has been found to prevent and treat many established atherosclerotic risk factors such as high blood pressure, insulin resistance, glucose intolerance, elevated triglycerides, low HDL-C, and obesity (77). One study investigating healthy young adults in a 12-week exercise program found that high intensity aerobic training down-regulated cytokine release from monocytes (78). Other studies have reported that exercise stimulates cardio-protective anti-inflammatory effects that may have a dose-response relationship (24). Additionally, physical activity has been found to reduce inflammatory markers such as C-reactive protein (CRP) in a dose-response manner as well.

Vascular endothelium contains a monolayer of cells that lines the entire circulatory system and is involved in vascular homeostasis (79,80). The endothelium regulates arterial dilation and constriction by producing vasodilator and vasoconstrictor agents (80). An important

component of functional vascular endothelium is the production of nitric oxide (NO) by endothelia nitrous oxide synthase (eNOS). NO has anti-inflammatory, vasodilatory and platelet inhibitory effects that have key roles in the upkeep of vascular homeostasis. Exercise training has been found to be associated with the increase in vascular expression of eNOS in animals and humans. It is believed that exercise training improves endothelial function through the increased shear stress on artery walls mediated by increased blood flow during exercise (80).

Furthermore, exercise is also involved in beneficial vascular remodeling (24,76,80), specifically exercise training has a substantial impact on the morphology of numerous blood vessels. Structural changes in blood vessels are followed by functional changes that lead to improved blood flow (80). Exercise promotes angiogenesis, which is the formation of new blood vessels and the process involves the migration, growth and differentiation of endothelial cells. Moreover, exercise training promotes arteriogenesis, which is the increase in the diameter of large arterial vessels. Arteriogenesis compensates for the loss of function of occluded arteries (80). These adaptations can contribute to the significant cardiovascular performance and benefits gained by physically active individuals (81).

It has been reported that cardiac rehabilitation exercise training has important effects on psychological stress including levels of depression, anxiety, hostility, and total psychological stress (76). The prevalence of anxiety has been reported to fall by 61% in younger patients and 32% in older patients after formal cardiac rehabilitation exercise training. The authors also reported a reduction greater than 50% in the prevalence of depression among coronary heart disease (CHD) patients (82). These findings align with other research that suggests that structured exercise can alleviate clinical symptoms of depression, anxiety, and improve general wellbeing (83).

2.10 Gaps in the Literature

TIA and MNDS carry a short-term risk of stroke and other vascular events, and there remains a critical window of opportunity to deliver an appropriate and effective secondary prevention program. Current research suggests that programs like CRSP may be a more effective means of reducing cardiovascular risk and improving quality of life than standard care. It has been demonstrated that it is feasible and safe for TIA/MNDS patients to partake in CRSP.

Exercise training has been proven to be effective in this patient population, but there remains an area of inquiry of how much exercise produces the best outcomes. Additionally, cognitive impairment, quality of life, depression and anxiety remain important issues in TIA/MNDS patients, and research remains inconclusive in this subject area which further justifies work investigating this patient population at high risk of such deficits.

There remain gaps in the literature demonstrating the effect of CRSP on TIA and MNDS patients due to small studies that incompletely assessed all relevant risk factors. Further research is required to support a mandate to include TIA/MNDS patients in a readily available community-based lifestyle modification program such as CRSP. It has been suggested in a recent SR-MA that future work should investigate the differential effects of exercise post-TIA versus post-stroke as well as exploring dose-response relationships (73). Another SR-MA on cognitive impairment in TIA patients suggested that future studies should utilize long term cognitive assessments to identify whether the cognitive effects are transient, stationary, or progress over time in this patient population (41). Hence, a significant gap still remains in the literature. Therefore, further studies are needed to assess cardiac rehabilitation exercise training in a dose response manner and replicate the effects of CRSP strategies after TIA/MNDS, as the CRSP model of care might fill this gap (62).

Chapter 3

3 Thesis Objectives and Hypotheses

The **primary objective** of this thesis was to quantify the relationship between exercise attendance (number of scheduled facility-based exercise sessions attended) and exit functional capacity (METS) among the exercise trained TIA/MNDS patients.

The **primary hypothesis** was that there is a relationship between the number of exercise classes attended among exercise trained individuals enrolled in CRSP and improvement in functional capacity.

The **secondary objectives** for this thesis were:

i) to determine whether CRSP programming among exercise-trained TIA/MNDS patients is associated with significant improvements in intake to exit measures of exercise capacity, lipid profile (HDL-C, LDL-C, TC, TG, non-HDL cholesterol), fasting blood glucose, blood pressure (resting SBP and DBP) body measurements and composition (weight, waist circumference, BMI).

ii) to determine whether CRSP programming among exercise trained TIA/MNDS patients results in significant pre-post changes in the following psychometric domains: quality of life, anxiety, depression, general cognitive impairment, attention and working memory, pre-morbid intellectual functioning, speed/executive/abstraction, oral-verbal fluency, verbal memory and learning.

The **secondary hypotheses** were that exercise trained patients would have significant improvements in their intake to exit measurements of exercise capacity, lipid profile, blood glucose, blood pressure, body measurements and composition. Furthermore, they would have intake to exit improvements in the aforementioned psychometric domains.

Chapter 4

4 Methods

This chapter describes the methodology used to the complete this study. Section 4.1 provides a description of the data source. Section 4.2 outlines the study design and participants. Section 4.3 details the inclusion and exclusion criteria. Section 4.4 describes Cardiac Rehabilitation and Secondary Prevention procedures. Section 4.5 describes the measurements (independent and dependent variables, demographic characteristics, and risk factors). Section 4.6 outlines the statistical analyses for the demographic statistics, objectives, exploratory analyses and other statistical considerations and section 4.7 outlines the ethics approval.

4.1 Data Source

Data from the St. Joseph's Health Care London – CRSP Program research unit was used. The St. Joseph's CRSP program is a six-month outpatient program. During the study period (2004 to 2014) the CRSP program served on average 490 patients each year. The program features include: medical evaluation, comprehensive patient care coordination, exercise program, lifestyle education, psychological services and smoking cessation. The St. Joseph's CRSP program is partnered with the YMCA in London, and exercise prescribed by the CRSP team is carried out at the downtown YMCA supervised by CRSP staff. Along with evidence-based practice and improving outcomes for patients, the program also has a research component and participants have an opportunity to participate in various studies. The research unit collaborates with other CRSP teams such as the Ottawa Heart Institute Cardiac Rehabilitation program to facilitate collaborative research that improves care and outcomes for patients.

4.2 Participants and Study Design

This present study is a retrospective database review of the London CRSP clinical database. This data source allowed us to examine participants utilization of CRSP in routine clinical care and allowed us to investigate longer observation periods within specific subpopulations. Additionally, a pre and post study design was used, which examines whether participants in an intervention improve or regress during the course of the intervention. For this study design, participants are their own control. Without reference to another control group we cannot make causal inferences with this study design.

From January 4th, 2004 to 2014, a total of 271 TIA/MNDS patients were study eligible for three studies conducted by London and Ottawa cardiac rehabilitation programs. Patients who had presented in the Emergency Department with a TIA were referred to a Stroke Prevention Clinic (SPC) and were generally assessed as outpatients within 48 hours to one week of the event. A SPC is an outpatient clinic for people who are at risk of having a TIA or stroke. They also provide care for those who have already experienced a stroke. The SPC provides investigative testing, medical evaluation, medical counselling, and attempts to provide home-based risk factor management by providing patients with information about self-referral to risk reduction programs in the community. Case management within these services is limited and typically TIA clinic patients do not have access to CRSP. Both London and Ottawa have SPCs and CRSP programs and participants for these studies were recruited from a SPC. From these participants, we used the 115 facility-based exercise-trained individuals to conduct the study. Figure 1 illustrates the participant selection flow chart.

The first study was an observational study investigating the feasibility and risk factors of comprehensive CRSP after transient ischemic attack or mild stroke at the St. Joseph's CRSP program (60). The second study was a pilot randomized single blind controlled trial investigating CRSP among survivors of transient ischemic attack, also at the London Cardiac Rehabilitation program (84). Lastly, the third study was a multi-site randomized controlled trial investigating CRSP programming as secondary prevention for survivors of TIAs (unpublished). This study was conducted in both London and Ottawa.

For the first observational study, 100 participants receiving usual care per the SPC were enrolled in comprehensive cardiac rehabilitation for about 7 months at the St Joseph's CRSP program. This was delivered in addition to usual care, which followed the Heart and Stroke Foundation of Ontario/Coordinated Strategy Guidelines plus standard secondary prevention advise to the patient and family doctor to adhere to risk factor targets, including exercise (14). For the second randomized controlled trial, of the 39 individuals eligible, 19 subjects were randomized to SPC usual care (UC) and 20 subjects we randomized to UC and comprehensive 6-month cardiac rehabilitation. In the third multi-center trial, of the 132 subjects, 72 were randomized to UC and cardiac rehabilitation and 60 were randomized to UC.

4.3 Inclusion and Exclusion Criteria

The inclusion and exclusion criteria were similar across all three studies. The first observational study, second pilot randomized controlled trial and third multi-center randomized controlled trial inclusion criteria were as follows:

i) Patients were eligible if they were at least 20 years old; had sustained a documented TIA/MNDS within the previous 12 months; had at least 1 of the following risk factors: hypertension, diabetes mellitus, dyslipidemia, ischemic heart disease (i.e., self-report of angina pectoris, myocardial infarction, or coronary angioplasty within the previous year) acknowledged cigarette smoking within the previous year and spoke and understood English.

ii) 1) Aged 20 years or more; 2) Documented TIA and/or MNDS within the previous three months; 3) Has at least one of the following vascular risk factors: hypertension, diabetes mellitus, dyslipidemia, ischemic heart disease (angina pectoris and/or myocardial infarction within the last one year), cigarette smoking; 4) Has a modified Rankin Scale of < 3; 5) Has a mini-mental status examination score >20; 6) No evidence of intracranial hemorrhage on CT scan or magnetic resonance imaging study; 7) No anticipated or recent (< 30 days) carotid endarterectomy, angioplasty and/or stenting; 8) Speaks and understands English; 9) Able to communicate verbally; 10) Able and willing to provide written, informed consent.

iii) 1) Aged 20 years or more, 2) Documented TIA and/or MNDS within the previous 3 months, 3) Speaks and understands English, 4) Able to communicate verbally and willing to provide written, informed consent, 5) At least one of the following vascular risk factors: a) hypertension b) Diabetes mellitus by self-report or use of oral hypoglycemic agents or insulin, c) Dyslipidemia , d) Ischemic heart disease (self-report of angina pectoris and/or myocardial infarction and/or coronary angioplasty within the previous one year), e) Cigarette smoking within the previous year.

The exclusion criteria for the first observational study, second pilot randomized controlled trial and third multi-site randomized controlled trial inclusion criteria were as follows:

i) Patients were ineligible if they had evidence of intracranial hemorrhage on a CT or MRI study; anticipated or had undergone recent (<30 days) carotid endarterectomy or percutaneous coronary intervention; showed evidence of disabling stroke or dementia as measured by modified Rankin Scale score of ≥3 or a Mini-Mental Status Examination (MMSE) score ≤20; had previously participated in CRSP; were unable to perform CRSP exercise training; or were participating in another clinical study that could interfere with the intervention or outcomes of the current study.

ii) 1) Reside > 1-hour travel time from London, 2) Prior participation in CRSP, 3) Inability to perform expected exercise of CRSP program.

iii) 1) Evidence of intracranial hemorrhage on CT scan or magnetic resonance imaging study, 2) Anticipated or recent (< 30 days) carotid endarterectomy, angioplasty and/or stenting, 3) Evidence of disabling stroke or dementia as measured by modified Rankin Scale of >= 3 (103;104) or a MMSE =< 20 (94), 4) Reside > 1 hour travel time from London or Ottawa 5) Prior participation in CRSP, 6) Inability to perform expected exercise training of CRSP program, 7) Evidence of a cardioembolic source for TIA/stroke such as atrial fibrillation, valvular disease, septal defect or left ventricular wall motion abnormality, 8) Participating in another clinical study which could interfere with the intervention, or outcomes of the current study.

4.4 Cardiac Rehabilitation and Secondary Prevention Intervention

CRSP at both London and Ottawa comprises 1) an initial medical assessment by a nurse case manager and a CRSP physician to determine CRSP strategies 2) an entry exercise stress test 3) nutrition counselling, kinesiology, and psychological (where needed) assessment and intervention to achieve risk factor targets 4) individualized and prescribed twice per week supervised exercise training and twice per week supplementary home-based training 5) exit assessment at six months.

Participants were required to attend a two-hour orientation/ information session to familiarize themselves with the program. Orientation was in a group setting and the subjects received risk factor and service education, screening with the HADS and SF12, a requisition for blood

work, and advice to quit smoking. The participants where then advised to return for an intake appointment where they were approached to consent to the use of their program data for various research purposes. Subjects then attended an intake clinic for medical and risk factor assessment by the nurse case manager and physician, with anthropometric measurements, a 45-to-60-minute neuropsychological battery and additional support to join the CRSP smoking cessation program. Furthermore, subjects underwent standardized, physician supervised, exercise stress testing using a "ramp" protocol which consists of an initial two-minute stage at two mph and 0% grade, followed by one-minute stages at three mph continually, grade increasing by 1.7% each minute. All participants were enrolled in a CRSP exercise program administered by a kinesiologist. The program offers standard on-site, twice weekly, 50-session option with additional home-based exercise training at least twice weekly; or subjects had the choice to do a full home-based training which comprised at least 4 days recommended exercise weekly and monthly telephone or onsite check-in.

Nutrition counselling by a registered dietician was delivered individually or in a group setting highlighting the Mediterranean diet. If a subject scored a value greater or equal to 8 on the HADS anxiety (HADS-A) or depression (HADS-D) or HADS-A + HADS-D score greater or equal to 14 (85), they were offered referral to a clinical psychologist. Referral to a clinical psychologist was also made based on clinician judgement or patient request. Case management by the nurse continued throughout CRSP programming with a three month-visit or phone call to the subject. Lastly, an exit clinic with the nurse case manager, physician, and psychometrist was made approximately six months after intake and the same intake measurements were taken.

In 2014 the Cardiac Care Network published standards for the provision of cardiovascular rehabilitation in Ontario. These standards aimed to reduce variation in care. Prior to those standards, there were published clinical guidelines by the Canadian Association of Cardiovascular Prevention and Rehabilitation but there were no published standards for delivery of CRSP in Canada. For our study period (2004-2014), it was assumed that the CRSP standard of care was similar across all three studies. Specifically, the first two studies were conducted by the London CRSP program which constituted the majority of the study sample, and the study protocols in terms of service provision were similar across all three studies. Additionally, due to the nature of the study design (retrospective database review),

we can only rely on study protocols. It is possible that following the publication of new standards, CRSP programs may have altered their clinical practice, but that would not affect our study cohort.

4.5 Measurements

Demographic characteristics were collected at intake. These measures included age, sex, education, occupation, occupational status and ethnicity. Number of days in CR was calculated using CR intake assessment date and CR exit assessment date. Risk factor data including dyslipidemia, hypertension, sedentary lifestyle, family history, post-menopausal syndrome (PMS), diabetes, and tobacco use were also collected at intake. Sedentary lifestyle was defined as failure to meet the recommendations of the Canadian Physical Activity Guidelines of 150 minutes of moderate-vigorous-intensity aerobic physical activity per week in bouts of 10 minutes or more (86,87). Family history of CVD, and cerebrovascular diseases was asked as a “yes or no” question with added details.

4.5.1 Independent and Dependent Variables

The primary independent variable was the number of scheduled attended exercise sessions in YMCA-based exercise programming. Additionally, pre and post measurements of exercise capacity, blood pressure, lipid profile, blood glucose, body measurements and composition, Duke Treadmill Score, quality of life, anxiety, depression, general cognitive impairment, attention and working memory, verbal learning and memory, pre-morbid intellectual functioning, and speed/executive/abstraction were also measured.

Exercise training sessions were scheduled by the CRSP program and attendance records where kept for facility-based exercise sessions. Prescribed home-exercise was monitored through check-in phone calls to the participants. Exercise capacity was measured using METS using standardized peak exercise treadmill testing using validated equations that use speed in miles per hour and grade of the treadmill.

METS = [3.5+(2.7× speed) + 48.2 (treadmill speed in mph) × (grade)] ÷ 3.5;

where grade = fractional grade.

Resting systolic and diastolic blood pressure was measured by the clinic nurse. Lipid profile was obtained from blood work. Specifically, TC, HDL-C, and TG, was measured through blood work. Non-HDL-C was calculated (TC÷HDL-C), and LDL-C was calculated using the Friedewald equation (88).

LDL-C = TC – HDL-C – [(TG) ÷2.2]

Fasting blood glucose was also measured through blood work. Height, weight, and waist circumference were measured by the clinic nurse, and BMI was calculated from height and weight measurements. Furthermore, the Duke Treadmill Score, a weighted index combining treadmill exercise time (in "standard Bruce protocol" minutes, maximum net ST segment deviation (depression or elevation), and exercise-induced angina) was calculated. The Duke Treadmill Score (DTS) is a prognostic index value to predict the presence of CAD, has validated mortality risk categories on those with CAD and/or suspected of having CAD (89), and may be calculated using the following equation (90):

DTS = Exercise Time – (5 x Max ST (mm)) – (4 x treadmill angina index)

Ex Time:	Bruce protocol minutes (91)
	= [(METS x 3.5) – 8.545] ÷2.282
Max ST:	Maximum net ST deviation
Angina Index:	0 = No angina during exercise
	1 = Non-limiting angina
	2 = Exercise limited angina

The typical range observed for DTS is from -25 (highest risk) to +16 (lowest risk). A DTS greater or equal to +5 indicates low risk, a score between -10 to +4 indicates moderate risk, and high risk is a value less than -10. Additionally, the low risk category reflects a four-year survival rate of 99%, moderate risk category reflects a four year survival rate of 95%, while the high risk category reflects a four year survival rate of 79% (89). Five-year mortality rates

have also been reported as 3%, 10% and 35% for low-, moderate-, high-risk DTS categories (92).

Quality of life and health status were measured by the SF-12. The SF-12 Health Survey is a standardized questionnaire which includes 12 items selected from the Short Form 36 – item health survey (93). The SF-12 includes the following dimensions: physical functioning, role-limitations – physical, bodily pain, general health vitality, social functioning, role limitations – emotional, and mental health. It is used to assess patients' health-related quality of life and produces two summary scores – physical and mental health summaries denoted PCS and MCS that range from 0 to 100, (US population mean = 50, SD = 10) (94) where a score of zero denotes the lowest level of health measured and a score of 100 indicates the highest level of health (95). HADS was used to assess depression and anxiety (96). HADS is a self-rating patient reported measure with 14 items divided into two equal subscales (HADS-A) and depression (HADS-D) where respondents self-report occurrence of symptoms related to anxiety or depression over the past 7 days. The HADS-A has questions on tension, worry fear, panic and difficulties relating. The HADS-D has questions predominantly measuring anhedonia (97). The responses are rated on a 4-point Likert scale and range from 0 to 3 with the higher score indicating greater severity. The 14 items are summed to a total score of 0 to 42 or for each subscale 0 to 21 (97). The HADS concentrates on non-physical symptoms to avoid confounding of psychological and medical symptoms, so that it can be used to screen individuals who are physically ill (98).

General cognitive impairment was measured using MMSE – a popular measure to screen for cognitive impairment particularly in the elderly, track changes that occur with time, and assess the effect of therapeutic agents on cognitive functioning (99). The MMSE produces a score with the total number of correct answers – the maximum score is 30 points for adults. There are different methods to assess the MMSE score. There is a single cut-off that can be used – a score <24 is considered abnormal. A range method can also be used – a score < 21 means increased odds of dementia, and a score >25 means decreased odds of dementia. Degree of cognitive impairment can be assessed with the following cut-offs: 0-10 (severe), 10-20 (moderate), 20-25 (mild) (100). The North American Adult Reading Test (NAART) was used to measure pre-morbid intellectual functioning (99). The NAART is a reading test that requires participants to read out loud 61 irregularly spelled words. The responses are

individually scored as correct or incorrect based on the pronunciation, and the score can be used to estimate pre-morbid IQ (101).

Attention, working memory and mental flexibility were measured using the Digit Span Forwards and Backwards from the Wechsler Adult Intelligence Scale - Revised (WAIS-R). The WAIS-R is used to provide a measure of general functioning in older adolescents and adults and contains 11 subtests (99,102). Performance of this subset is reported as a single score which is comprised of the additive combination of the Digits Forward and Digits Backward, this score is then converted into a scaled score and age-scaled score (103). The Similarities subtest of the WAIS-R was used to assess judgement and analogical reasoning/abstraction. For the Similarities subset, participants are given two words or concepts and have to describe how they are similar (99) and raw, scaled, and age-scaled scores are derived. Furthermore, the Digit Symbol subset of the WAIS-R was also used to measure psychomotor speed. The Digit Symbol requires the subject, on the basis of a numeric-symbol coding key, to produce a sequence of symbols correctly coded within 90 seconds, and the higher the score the better the subject's performance. Raw, scaled, and age-scaled values are also produced (99). WAIS-R instead of the recent WAIS-III was used to allow for comparability across the three studies.

Attention, speed, and mental flexibility was also measured using the Trail Making Test (TMT). The TMT involves the participant drawing lines sequentially to connect 25 encircled numbers randomly arranged on a page in proper order (Part A) and then connecting 25 encircled numbers and letters in alternating order (Part B) (99). The score is expressed as the amount of time it takes the participant to complete the task for each part (104) therefore, higher scores show greater impairment (99). The Rey Auditory Verbal Learning Test (RAVLT) measures verbal learning and memory. The RALVT evaluates immediate memory span, new learning, vulnerability to interference and recognition memory. The RALVT involves five free-recall trials, recall after interference trial, and a recognition trial (99). The Clock Drawing Test (CDT) was used to assess visual-constructive skills. The CDT also taps into a series of cognitive domains such as verbal understanding, memory, spatial knowledge, abstract thinking, planning, and concentration and as previously mentioned visual-constructional functioning (99,105,106). A score out of 4 on the CDT and time measured in seconds was collected. For the CDT a score less than or equal to 2 indicates 'defined

impairment' (105). Furthermore, oral verbal fluency was measured by the Controlled Oral World Association Test (COWAT) – a widely used test of executive dysfunction (107). The COWAT requires subjects to name as many words beginning with a single letter as they can in one minute, and the most commonly used form of this test uses the letters F, A, and S (99,108).

4.5.2 Demographic Characteristics

The demographic variables collected included: age (date of birth); sex (male, female); ethnic group (Aboriginal, Arab/West Asian, Black, Chinese, Filipino, Japanese, Korean, Latin American, South Asian, South East Asian, White/Caucasian); education (no formal education, elementary: some, elementary: completed, high school: some, high school: completed, trade school: some, trade school: completed, university/college: some, university/college: completed, post graduate: completed); occupational status (full-time, part-time, unemployed, retired, not/never employed outside the home, short-term disability, long-term disability, employed: permanent restrictions, employed: modified duties); occupation (self-employed professionals, semiskilled manual, employed professionals, foreman, skilled clerical-sale-services, farm works, high level managers, skilled blue-collar workers, semiskilled clerical-sales-services, unskilled manual, middle-level managers, supervisors, homemaker); living situation (alone, with spouse/partner, with friends, with family, with others); New York Heart Association Functional Classification (Class I: no limitation in normal physical activity, Class II: mild symptoms only in normal activity, Class III: marked symptoms during daily activities, asymptomatic only at rest, Class IV: severe limitation, symptoms even at rest); and Canadian Cardiovascular Society (CCS) grading of angina pectoris (Class 0: asymptomatic angina, Class I: angina only with strenuous exertion, Class II: angina with moderate exertion, Class III: angina with mild exertion, Class IV: angina at rest).

For the purposes of this study, three of these variables were further categorized. Education was categorized into "Less than High School" (including no formal education, elementary: some, elementary: completed, high school: some), "High School" (including high school: completed), "Some Post-Secondary" (including trade school: some, university/college: some), and "Graduated College/University" (including trade school: completed, university/college: completed, post graduate: completed). Occupational status was

categorized into “Full-time” (including, full-time, employed permanent restriction, employed modified status), “Part-time” (including part-time), “Unemployed/Disability” (including unemployed, not/never employed outside the home, short-term and long-term disability), “Retired”, and “Not obtained/missing”. BMI was further categorized to “BMI > 25” to indicate individuals who are classified as overweight (109). Due to the sample being predominantly White/Caucasian, ethnic group was further categorized into “White/Caucasian” and “Other” (including Aboriginal, Arab/West Asian, Black, Chinese, Filipino, Japanese, Korean, Latin American, South Asian, South East Asian).

4.5.3 Risk Factors

The risk factor data collected included: sedentary lifestyle (yes, no); dyslipidemia (yes, no); hypertension (yes, no); family cardiovascular disease history (yes, no); post-menopausal syndrome (yes, no); diabetes (yes, no); diabetes type (Type 1, Type 2); smoking history (current smoker, former smoker, non-smoker).

4.6 Statistical Analyses

4.6.1 Data Processing

This study included three different study samples and involved some data processing before conducting the statistical analyses. Zhu et al. (2013) guidelines (110) were used as reference during this process. The data processing began with getting to know the studies (research questions, recruitment criteria, and data collection methods). The second step was to check whether common variables were measured in the same manner and checking if the variable coding was similar across studies. The third step was ensuring the data entry across the studies was accurate and identified any missing variables. Once these steps were complete and the datasets were combined, data cleaning was done which involved looking for incorrectly coded variables, correcting coded variables, looking for missing data, checking for any outliers, and correcting the identified data errors.

4.6.2 Demographic Statistics

Two approaches were used to describe baseline characteristics of TIA/MNDS patients enrolled in the CRSP program. Continuous variables (i.e. age, BMI) were summarized using means and standard deviations. Categorical variables (sex, ethnic group, education,

employment status, living situation, cardiovascular risk factors, and history of CAD, TIA, and stroke) were summarized using frequencies (n/%).

4.6.3 Confounding Variables

A confounding variable is a variable that influences both the dependent variable and independent variable, causing a spurious association. There are many factors that can confound the association between exercise attendance and functional capacity. Specifically, factors associated with physical inactivity include but are not limited to: older age, female gender, prior physical activity habits, and fitness level (111). Physical activity has been found to be lower in older females, and age related physical deficits can influence adherence as well (112). Additionally, baseline functional capacity, a sedentary lifestyle, can influence adherence and exit functional capacity. For this study sex, age, sedentary lifestyle, and intake functional capacity were controlled for in the regression model.

4.6.3 Analyses for Objectives

Analytic techniques appropriate for pre-post study designs were used where necessary. The statistical analysis corresponding to each study objective is listed as follows:

Objective 1: Quantify the relationship between exercise adherence and functional capacity among exercise trained TIA/MNDS patients.

A multiple linear regression analyses was used to test whether there was an association between exercise adherence (number of scheduled exercise sessions attended) and functional capacity. The regression model included number of scheduled exercise sessions attended as the predictor variable and exit measure of METS as the dependent variable while controlling for intake measure of METS, and confounding variables (age, sex, and lifestyle).

Objective 2a: Determine whether CRSP programming among exercise-trained TIA/MNDS patients is associated with intake to exit improvements in exercise capacity, lipid profile, blood pressure, body measurements and composition.

Objective 2b: Determine whether CRSP programming among exercise trained TIA/MNDS patients results in intake to exit changes in the following psychometric domains (quality of

life, anxiety, depression, general cognitive impairment, attention and working memory, pre-morbid intellectual functioning, speed/executive/abstraction).

To compare the mean intake and exit values for the continuous variables, paired t-tests were used.

All statistical tests were two-tailed with an alpha level of 0.05. To control for type one errors a Bonferroni correction (113) (α=0.05÷ number comparisons) within each domain of dependent variables was employed. For key CRSP outcomes there were 5 domains: functional capacity, lipid profile, blood glucose, blood pressure and body composition. Functional capacity measured in METS and blood sugar has an alpha level of 0.05. Lipid profile (TC, LDL-C, HDL-C, non-HDL-C, TG) had an alpha level of 0.01, blood pressure (SBP, DBP) had an alpha level of 0.03, and body composition (WC, BMI, weight) had an alpha level of 0.02. Additionally, adjustments were made for the seven psychometric domains (depression and anxiety; quality of life; general cognitive impairment; attention and working memory; verbal learning and memory; speed, executive, abstraction; and pre-morbid intellectual functioning). Depression and anxiety (HADS-T, HADS-A, HADS-D) had an alpha level of 0.02, and quality of life (SF12-PCS, SF12-MCS) had an alpha level of 0.03. General cognitive impairment and pre-morbid intellectual functioning had an alpha level of 0.05. Attention and working memory (Digits-Forward, Digits-Backward, Trails A) and verbal learning and memory (RAVLT-sum, A6, A7) had an alpha level of 0.02 while speed, executive and abstraction (Digit Symbol, Trails B, CDT, FAS-OVF, Similarities) had an alpha level of 0.01. Appendix B illustrates these calculations.

4.6.4 Exploratory Data Analysis

For exploratory purposes only, the relationship between exercise attendance (number of scheduled facility-based exercise sessions attended) and exit DTS risk category (low risk, moderate risk, and high risk) was investigated. An ordinal logistic regression (114) was used to predict DTS risk category given exercise attendance. A McNemar's chi-square test was used to explore whether there was an association between intake high-risk DTS category and exit high-risk DTS category.

4.6.5 Missing Data

Missing data is of concern with the key analytical variables collected for the study as it can impact validity and may result in bias. Due to the pre-test, post-test study design, any pairs of values where one of the pairs is missing was excluded. Specifically, cases were excluded analysis by analysis, which maximizes all of the data available. Pairwise deletion assumes that missing data are missing completely at random.

4.6.6 Assessment of Potential Selection Bias

Patients that were excluded in the study sample due to either being in the control group from the RCTs, enrolling in the home-based exercise program, or not completing the program were excluded from the analyses. This information was required to determine their change in functional capacity for the primary objective. To determine the generalizability of the study results, the demographic characteristics were compared between subjects that completed CRSP and subjects that did not complete CRSP. This was conducted to determine whether a systematic difference in the patient characteristics existed between those that completed the program and were selected for the study compared to those that did not complete the program.

4.6.7 Assessment of Potential Non-Response Bias

Non-response bias is defined as a systematic error due to differences in characteristics between respondents and non-respondents (115). Non-response of key variables can result in statistical analyses that are biased and the variability in the data will be incorrectly estimated. The literature suggests that missing data of 10% or more would be of concern (116). All variables with at least 10% missingness were further assessed to determine the extent of response bias present. A comparison of demographic characteristics between subjects that had information on a variable versus subjects that did not have information on a variable was made to determine if the characteristics between the two groups systematically differed. If differences were found, that would suggest that the observed results would be less generalizable compared to if the data was missing at random.

4.6.8 Software

All statistical analyses were completed using IBM SPSS Statistics 21.0.

4.9 Ethics Approval

The studies used in this project were approved by the University of Western Ontario's Research Ethics Board.

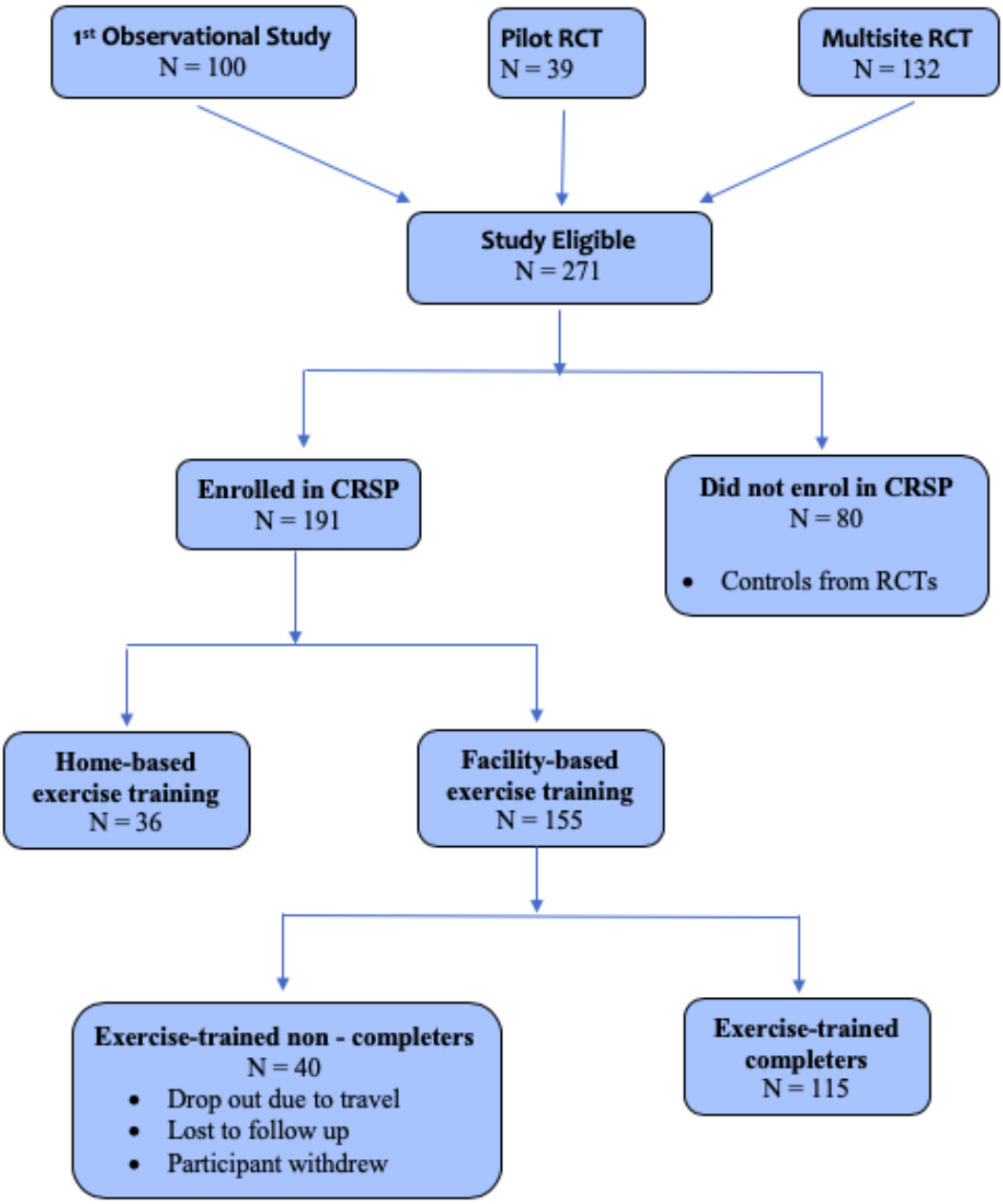

Figure 1. Participant Selection Flowchart

Chapter 5

5 Results

This chapter reports the study results. Section 5.1 reports on the process, while Section 5.2, and 5.3 reports demographic characteristics, and risk factors at baseline. Section 5.4 reports the baseline health status measures while section 5.5, 5.6, and 5.7 reports the results for objective 1, 2a, and 2b respectively. Section 5.8 reports findings from the additional exploratory analyses, and Section 5.9 discusses missingness. Additionally, 5.10, 5.11, and 5.12 reports the assessment of selection bias, assessment of non-response bias, and adverse events respectively.

5.1 Process

Of the 271 TIA/MNDS study eligible participants from the three studies conducted by London and Ottawa CRSP programs, 115 participants met the selection criteria, and the remaining participants where either in the control group for the RCTs or enrolled in the home-based exercise option. Of the 115 participants in this study, 98 (85%) were recruited from the London CRSP program, and 17 (15%) were recruited from the Ottawa CRSP program. Sixty-two participants (54%) were from the first observational study, 13 (11.3 %) from the first randomized controlled trial (RCT) and 40 (35%) participants from the second RCT. Table 1 outlines these characteristics along with other baseline characteristics. The mean interval for CCR intake assessment to exit assessment was 236 days (34 weeks; n =94) and ranging from 140 to 588 days. All subjects selected enrolled in the facility-based exercise option. On average, participants attended 33 (SD = 12.0; 1 – 60, n=109) exercise sessions or 66% of the 50 typically prescribed sessions. Table 4 provides an exercise attendance summary and Appendix A provides the attendance breakdown.

5.2 Baseline Characteristics

A description of the study sample's baseline characteristics is available in Table 1. Of the 115 participants selected, 65 (57%) participants were male, and 50 (43%) were female, with an average age of 66 (10.2) years. The majority of the sample was White/Caucasian (96%) with the remaining individuals being Asian, Black, Aboriginal, and Latin American. Over 50% of participants had high school as their highest level of education (27% less than high

school, 26% graduated high school), while 14% had some post-secondary education, and 29% graduated university/college. Forty-five participants were either employed full-time (34%) or part-time (5%), while 39% were retired and 5% were on disability/unemployed. Twenty-six (23%) participants reported living alone, while 67 (58%) and 3 (3%) participants reported living with a partner/spouse and with others respectively. Furthermore, 81 (70%) participants were classified as Class I (no limitation in normal physical activity) for the NYHA functional classification while 13 (11%) participants were classified as Class II (mild symptoms only in normal activity) and 5 (4%) participants were classified as Class III (marked symptoms during daily activities). For the CCS Grading System of Angina Pectoris, 94 (82%) participants were classified as Class 0 (asymptomatic angina), 4 (4%) participants were classified as Class I (angina only with strenuous exertion), and one participant was classified as Class II (angina with moderate exertion).

5.3 Risk Factors at Baseline

Of the 115 participants, 67 (58%) participants reported having a sedentary lifestyle, while 91(79%) and 89 (77%) had dyslipidemia and hypertension respectively. Additionally, 48 (42%) of participants had a family history of CVD, and 30 (26%) had diabetes (2 participants with type 1 diabetes and 28 with type 2 diabetes). Forty-two (37%) participants were non-smokers while 17 (15%) and 55 (48%) were current smokers and former smokers respectively. The mean BMI for the sample was 29.8 with 93 participants (81%) classified as overweight (BMI >25). Table 2 outlines risk factors at baseline.

5.4 Baseline Health Status Measures

Table 3 outlines the baseline health status measures. For the quality of life measures – measured by the SF-12, the mean physical composite score was 43.6 (9.9) ranging from 20.5 – 60.7, and the average mental composite score was 51.4 (8.9), ranging from 24.6 - 64.0. Eighteen (16%) of participants met the cut-off of having HADS depression score greater than or equal to 8, while 29 (25%) participants met the cut-off of having HADS anxiety score greater than or equal to 8. The average HADS total score was 9.3 (6.3), with 23 (20%) participants meeting the cut-off of having a HADS total greater than or equal to 14. Furthermore, the average DTS score was -5.8 (7.3). Specifically, 9 (8%) participants were in

the “low risk” category for the DTS while 65 (57%) and 24 (21%) were in the “moderate risk” and “high risk” categories respectively.

5.5 Objective 1

A multiple linear regression was used to understand the association between the number of exercise sessions attended in CRSP and functional capacity (METS) at exit while controlling for intake METS, sex, age, and sedentary lifestyle. The regression model statistically significantly predicted exit functional capacity, $F(5,97) = 56.7$, $p<0.001$, accounting for 74.5% of the explained variation in exit METS with an adjusted $R^2 = 0.73$, a large effect size according to Cohen (1988) (117). The regression model predicting exit METs predicted an increase of 0.6 METs for every 10 exercise classes attended ($\beta = 0.6$, 95% CI 0.3, 0.9, $p <0.001$). All variables except for sex ($p=0.30$) were statistically significant in the model. Regression coefficients, standard errors, and 95% CI for the crude and adjusted models can be found in Table 5. Other models from the model building process can be found in Appendix C.

5.6 Objective 2a

There were significant intake-to-exit improvements in functional capacity, total cholesterol, non-HDL-C, triglycerides, diastolic blood pressure, waist circumference, BMI and weight. For functional capacity, there was a 28% improvement in functional capacity from intake to exit [intake METS 6.5 (2.7), exit METS 8.5 (3.0), $p < 0.001$]. The proportion of subjects meeting the functional target of ≥ 7 METS from intake to exit improved from 37% to 62%. Figure 2 outlines the intake and exit distribution of METS. For total cholesterol, there was a 6% decrease from intake to exit [intake 4.3(1.2) mmol/L, exit 4.0 (1.1) mmol/L, $p=0.006$] while non-HDL-C decreased by 10% [intake 3.4 (1.1), exit 3.03 (1.0), $p <0.001$]. For triglycerides, there was a 19% decrease from intake to exit [intake 1.6 (1.3) mmol/L, exit 1.3 (0.7) mmol/L, $p=0.004$]. Additionally, DBP decreased by 4% from intake to exit [intake 79.3 (8.8) mmHg, exit 76.5 (8.1) mmHg, $p = 0.004$]. There was a 2% decrease in waist circumference [intake 101.3 (12.6) cm, exit 96.9 (11.8) cm, $p <0.001$], and a 2% decrease in BMI [intake 29.7 (4.9) kg/m^2, exit 29.1 (4.7) kg/m^2, $p <0.001$]. Lastly, there was a 2% decrease in weight from intake to exit as well [intake 83.9 (14.3) kg, exit 82.2 (14.4) kg, $p <0.001$].

There were no statistically significant intake to exit improvements in LDL-C, HDL-C, fasting blood glucose, and SBP. Although LDC-C, and HDL-C did not statistically significantly change from intake to exit, there was an 9% decrease in LDL-C from intake to exit [intake 2.2 (1.0) mmol/L, exit 2.0 (0.9) mmol/L, p=0.014] and there was a 5% increase from intake to exit for HDL-C [intake 1.3 (0.4) mmol/L, exit 1.4 (0.4) mmol/L, p =0.48]. There was not a statistically significant change in fasting blood glucose from intake to exit [intake 5.9 (1.5) mmol/L, exit 5.9 (1.4) mmol/L, p =0.909]. Lastly and although not statistically significant, there was a slight 2% decrease in SBP [intake 133.1 (17.8) mm Hg, exit 130.9 (15.5) mm Hg, p =0.233]. Table 6 outlines these results.

5.7 Objective 2b

There were statistically significant intake to exit improvements in the HADS-D, HADS-A, HADS-T, SF-12 PCS, Digit Symbol, Rey Auditory Verbal Learning Test, and FAS Oral Verbal Fluency. Furthermore, intake to exit changes in SF-12 MCS, MMSE, NAART, Digit Forward and Backwards, Similarities, Trails-A, Trails-B, and CDT were not found to have statistically significant intake to exit changes. Table 7 outlines these findings further.

HADS

For the HADS depression score, the average score had a statistically significant change from intake to exit. There was an average 1.2 unit change from intake and exit points [intake 3.5(3.0), exit 2.3 (2.8), $p < 0.001$]. Additionally, there was a 1.1 unit change in the HADS anxiety points between intake and exit which was also statistically significant [intake 5.3 (3.6), exit 4.2 (3.4), $p < 0.001$]. Consequently, there was a statistically significant intake to exit change in the HADS-T score [intake 8.9 (5.7), exit 6.6 (5.5), $p < 0.001$].

SF12

The SF12 mental composite score did not have a statistically significant intake to exit difference, but there was a 2 unit increase in the average score [intake 51.4 (9.2), exit (11.4), $p < 0.001$], but the SF12 physical composite score had a statistically significant 3.5 unit increase from intake to exit [intake 46.6 (10.0), exit 47.1 (10.3), $p = 0.001$].

General Cognitive Impairment

General cognitive impairment was measured by the MMSE. At intake, three subjects had a score less than 24 which is considered abnormal, and at exit 4 participants had a score less than 24. The mean change in MMSE points from intake to exit was not statistically significant [intake 28.2 (1.6), exit 28.2 (1.9), p=0.669].

Attention and Working Memory

The Digit Span (forwards and backwards) and Trails-A assessed participants attention, working memory, and mental flexibility. There were no statistically significant intake to exit improvements in these psychometric domains. For the Digit Span Forward, there was a 0.2 unit increase in raw points [intake 7.9 (2.4), exit 8.2 (2.4), p=0.246], and there was a 0.2 unit decrease in raw points [intake 6.5 (2.4), exit 6.3 (2.6), p=0.303] for the Digit Span backwards. Lastly, there was an 8% decrease in seconds used to complete the task between intake and exit for the Trails-A [intake 39.3 s (27.0), exit 36.2 s (16.2), p=0.164].

Verbal Learning and Memory

Verbal learning and memory were measured by the RAVLT, and specifically evaluates immediate memory span, new learning, vulnerability to interference, delayed recall and recognition memory. For the RAVLT total which involves the total for the five free recall trials there was a 10% intake to exit improvement in the number of recalled words [intake 42.0 (8.6), exit 46.2 (10.3), p<0.001]. For the recall after interference trial denoted “A6”, there was also a 10% increase in the number of words recalled from intake to exit [intake 8.2 (3.0), exit 9.0 (3.4), p=0.001]. Lastly, for the recognition trial denoted “A7”, there was a 14% increase in the number of words recalled from intake to exit [intake 8.0 (3.0), exit 9.1 (3.5), p<0.001].

Speed, Executive, Abstraction

Speed, executive functioning, and abstraction were assessed by the Digit Symbol, Trails-B, CDT, FAS-OVF, and Similarities. The Digit Symbol is sensitive to psychomotor speed, and there was a 2.1-unit improvement from intake to exit but was not statistically significant [intake 8.2 (3.0), exit 9.0 (3.4), p=0.02]. The Trails-B which also is sensitive to psychomotor

speed and working memory was not found to have statistically significant intake to exit change [intake 99.9 (61.6), exit 96.1 (50.7), p = 0.426], but had an overall 4% decrease in the number of seconds used to complete the task. For the CDT, which assesses visuo-constructive skills and executive functions, there was not a statistically significant intake to exit change [intake 3.2 (0.9), exit 3.1 (0.9), p=0.603]. Furthermore, there was a statistically significant intake to exit change in the FAS-OVF which assesses executive dysfunction [intake 35.0 (12.1), exit 37.5 (12.9), p=0.001] and lastly, for Similarities which assesses abstraction, there was not a statistically significant intake to exit change [intake 17.1 (5.9), exit 17.3 (6.2), p=0.463].

Pre-morbid intellectual Functioning

Pre-morbid intellectual functioning measured by the NAART, the number of correct words were analyzed from the number of errors made during the test with 36.5 (11.5) correct words at intake 36.3 (11.5) and 36.7 (10.8) words at exit, p=0.535. This premorbid intellectual functioning covariate remained the same from intake to exit.

In summary, from intake to exit CRSP there was statistically significant improvements in depression, anxiety, physical health, verbal learning, memory, and executive functioning. There were no changes in mental health-related quality-of-life, attention, and working memory.

5.8 Exploratory Analyses

An ordinal logistic regression was used to assess whether a relationship exists between exit DTS risk category and the number of exercise sessions attended. The assumption of proportional odds was met, as assed by a full likelihood ratio test comparing the fit of the proportional odds model to a model with varying location parameters, X^2 (3) = 0.949, p=0.813. The deviance goodness-of-fit test indicated that the model was a good fit to the observed data, X^2 (72) = 57.67, p=0.873. An increase in the number of exercise classes attended was not associated with the odds of being in a particular DTS risk category at exit, with an odds ratio of 0.99 (95% CI, 0.95, 1.03), Wald X^2 (1) = 0.12, p =0.727. Table 9 outlines the results from the regression. Additionally, Figure 3 outlines the intake to exit changes in DTS risk categories. Generally, the proportion of individuals in the high-risk

category shifted from intake to exit with 24 (21%) participants in the high-risk category at intake and 10 (9%) at exit – a statistically significant shift (p = 0.001). Participants shifted into the moderate risk category with 65 (57%) at intake and 71 (62%) at exit. Lastly, there was a 2% increase from intake to exit in the low risk category, with 9 (8%) participants in this category at intake and 12 (10%) at exit.

5.9 Missingness

For baseline characteristics there was greater than 10 % missing data for the following variables: employment status (17%), living situation (17%), NYHA functional classification (14%), and CCS grading system of angina pectoris (14%). These missing variables were mainly from the Ottawa sample because the data was not collected for those demographic variables. Risk factor variables were relatively complete with no variables having greater than 10% missing data. For baseline heath status measures DTS had greater than 15% missing data. Maximal ST was primarily missing from the Ottawa CRSP program, therefore DTS was unable to be calculated. For exercise attendance, there were 6 participants (5.2%) that had missing attendance. Additionally, key CRSP outcomes that had greater than 10% missing data were FBG (11%) and non-HDL-C (11%). In total 97 participants had complete intake to exit data for all key CRSP variables, but a pairwise deletion was used for all variables. Listwise deletion was also conducted and no major differences were found in the results. These alternative analyses can be found in Appendix F.

Lastly, all of the psychometric variables had missing data greater than 10%. Specifically, HADS-D (16%), HADS-A (11%), HADS-T (16%), SF12 (21%), MMSE (17%), NAART (27%), Digits Forward and Backwards (17%), Trails-A (20%), Trails-B (20%), RAVLT (16%), A6 and A7 (17%), Digit Symbol (17%), CDT (17%), and Similarities (29%). Only 53 participants had complete data for all psychometric variables, but pairwise deletion was used as well. Analyses with listwise deletion were also conducted and minimal differences were observed in the results. These alternative analyses can also be found in Appendix F.

5.10 Assessment of Potential Selection Bias

An assessment of potential selection bias was made between participants that completed CRSP and included our present study versus participants that enrolled in CRSP but did not complete the program. Of the 155 participants enrolled in CRSP, 115 completed the program.

No significant differences were found in age (p=0.731), sex (p=0.584), ethnicity (p=1.0), highest level of education (p=0.679), employment status (p=0.142), living situation (p=0.747), NYHA functional classification (p=0.345), and CCS grading system of angina pectoris (p=0.529). In terms of risk factors at intake, no significant differences were found in sedentary lifestyle (p=0.238), family CVD history (0.189), diabetes (p=0.892), smoking status (p=0.589), PMS (p=0.632), and BMI (p=0.369). A statistically significant difference was found for dyslipidemia (p=0.002), and hypertension (p=0.016). For baseline health status measures, no significant differences were found in HADS-D (p=0.652), HADS-A (p=0.129), SF12-PCS (p=0.703), SF12-MCS (p=0.237), and DTS (p=0.265). Overall, selection bias was not of concern. Detailed tables used to come to this conclusion are available in Appendix D.

5.11 Assessment of Non-response Bias

For demographic characteristic, there appeared to be non-response bias in employment status and living situation, and this was primary observed in the Ottawa sample. This was due to the variable not being measured. For our outcome measures, non-response was primarily of concern in the psychometric variables as non-response was typically observed in those variables. There were no differences in demographic characteristics between participants with “known” vs. “unknown” values for the following variables: SF12, MMSE, RAVLT, Digits, CDT, and Trails. For HADS-T the only observed difference between participants with known HADS-T vs. unknown HADS-T was in the CCS class (p=0.03). For Similarities, there were observed differences between participants that had known Similarities vs. unknown Similarities in the study site (p<0.001), study type(p<0.001), employment status (p<0.001), living situation (p<0.001), NYHA (p<0.001), and CCS (p<0.001). Overall, non-response bias is of concern for psychometric variables. Detailed tables used to come this conclusion can be found in Appendix E.

5.12 Adverse Events

From the first pilot observational study, one subject had two TIAs without hospitalization, two subjects had one TIA without hospitalization, one subject had carotid stent placement in hospital, and one subject had unstable angina, with hospitalization and coronary angiography two days later. Furthermore, one subject had a TIA without hospitalization before intake. There were no recurrent strokes that occurred between CRSP intake and exit among the 80

subjects from the first observational study. From the multicenter RCT, one subject had a second stroke event during the program.

Table 1: Baseline Characteristics

Characteristic at Baseline (n=115)	**Mean (SD) or Frequency N (%)[a]**
Site	
London	98 (85.2)
Ottawa	17 (14.8)
Study	
1 – Observational Study	62 (53.9)
2 – 1st RCT	13 (11.3)
3 – 2nd RCT	40 (34.8)
Age (years)	66 (10.2)
Sex	
Male	65 (56.5)
Female	50 (43.5)
Ethnicity	
White/Caucasian	110 (95.7)
Other	5 (4.3)
Highest Level of Education	
Less than high school	31 (27)
Graduated high school	30 (26.1)
Some post-secondary	16 (13.9)
Graduated university/college	33 (28.7)
Not obtained/missing	5 (4.3)
Employment Status	
Full-time	39 (33.9)
Part-time	6 (5.2)
Unemployed/Disability	6 (5.2)
Retired	45 (39.1)
Not obtained/missing	19 (16.5)
Living Situation	
Alone	26 (22.6)
With spouse/partner	67 (58.3)
With others	3 (2.6)
Not obtained/missing	19 (16.6)
NYHA Functional Classification	
Class I	81 (70.4)
Class II	13 (11.3)
Class III	5 (4.3)
Class IV	-
Not obtained/missing	16 (13.9)
CCS Grading System of Angina Pectoris	
Class 0	94 (81.7)
Class I	4 (3.5)
Class II	1 (0.9)
Class III	-
Class IV	-
Not obtained/missing	16 (13.9)

[a] Percentages for some characteristics may not equal 100% due to rounding error.

Table 2: Risk Factors at Intake

Risk Factor	**Mean (SD) or Frequency N (%)[a]**
Sedentary lifestyle	67 (58.3)
Dyslipidemia Missing	91 (79.1) 2 (1.7)
Hypertension	89 (77.4)
Family cardiovascular disease history	48 (41.7)
Coronary artery disease history Missing	11 (9.6) 39 (33.9)
Diabetes Type 1 Type 2	30 (26.1) 2 (0.1) 28 (93.3)
Smoking history Current smoker Former smoker Never smoked Not obtained/missing	 17 (14.8) 55 (47.8) 42 (36.5) 1 (0.9)
Post-menopausal Syndrome Females (n=49) Missing	27 (23.5) 27 (55.1) 1 (0.9)
Mean BMI (n = 114) BMI > 25 Missing	29.8 (4.9) 93 (80.9) 1 (0.9)

[a] Percentages for some characteristics may not equal 100% due to rounding error.

Table 3: Baseline Health Status Measures

Psychometric	**Mean (SD) or Frequency N (%)**[a]
Depression and Anxiety at intake (n=115)	
HADS-D ≥ 8 (n=111)	18 (15.7)
Missing	4 (3.5)
HADS-A ≥ 8 (n=113)	29 (25.2)
Missing	2 (1.7)
HADS-Total ≥ 14 (n=111)	23 (20.0)
Missing	4 (3.5)
Quality of Life (n = 105)	
SF-12 PCS	43.6 (9.8)
SF-12 MCS	51.4 (8.9)
Duke Treadmill Score (n =98)	-5.8 (7.3)
Duke Treadmill Score Risk Category (n=98)	
Low Risk	9 (7.8)
Moderate Risk	65 (56.5)
High Risk	24 (20.9)
Missing	17 (14.8)

[a] Percentages for some characteristics may not equal 100% due to rounding error.

Table 4: Exercise Attendance Summary (n=115)

Number of Classes Attended	**Frequency N (%)**[a]
1 to 10	7 (6.0)
11 to 20	12 (10.3)
21 to 30	20 (17.3)
31 to 40	42 (36.3)
41 to 50	26 (22.6)
> 50	2 (1.8)
Missing	6 (5.2)

[a] Percentages for some characteristics may not equal 100% due to rounding error.

Table 5: Regression Analyses for the Association between Exercise Attendance and Functional Capacity (METS) at Exit (n=102)

	Crude Model		
Variable	B	SE	95% CI
Attendance	-0.00	0.03	-0.06, 0.05
Intake METS			
R^2	0.00		
	Adjusted Model		
Variable	B	SE	95% CI
Attendance	0.06	0.01	0.03, 0.09
Intake METs	0.90	0.07	0.77, 1.03
Sex (male)	-0.33	0.32	-0.97, 0.30
Age (years)	-0.05	0.02	-0.08, -0.01
Sedentary Lifestyle	0.72	0.32	0.08, 1.36
R^2	0.75		

Table 6: Intake Versus Exit Mean Scores – Key CRSP Outcomes

Outcome	n	Intake Mean (SD)	Exit Mean (SD)	Change Units (%)	P Value	Effect Size
METs	109	6.5 (2.7)	8.3 (3.0)	1.8 (27.6)	<0.001*	0.9
TC, mmol/L	103	4.3 (1.3)	4.0 (2.7)	-0.3 (-6.3)	0.006*	0.3
LDL-C, mmol/L	103	2.2 (1.0)	2.0 (0.9)	-0.2 (-8.6)	0.014	0.3
HDL-C mmol/L	103	1.3 (0.4)	1.4 (0.4)	0.1 (4.5)	0.480	0.3
Non-HDL-C	102	3.4 (1.1)	3.0 (1.0)	-0.3 (9.8)	<0.001*	0.5
TG, mmol/L	103	1.6 (1.4)	1.3 (0.7)	-0.3 (-18.5)	0.004*	0.3
FBG, mmol/L	102	5.9 (1.6)	5.9 (1.4)	-0.0 (0.0)	0.909	0.0
SBP, mm Hg	108	133.1 (17.8)	130.9 (15.5)	-2.2 (-1.6)	0.233	0.1
DBP, mm Hg	108	79.3 (8.8)	76.5 (8.1)	-2.8 (-3.5)	0.004*	0.3
WC, cm	108	101.3 (12.6)	98.9 (11.8)	-2.4 (-2.4)	<0.001*	0.5
BMI, kg/m^2	108	29.7 (4.9)	29.1 (4.7)	-0.6 (-2.0)	<0.001*	0.4
Body weight, kg	110	83.9 (14.8)	82.2 (14.4)	-1.8 (-2.1)	<0.001*	0.4

* Statistically significant p-values; SD = standard deviations;

Table 7: Intake Versus Exit Mean Scores – Psychometric Domains

Outcome	n	Intake Mean (SD)	Exit Mean (SD)	Change, Units (%)	P Value	Effect Size
HADS-D, points	97	3.5 (3.0)	2.3 (2.8)	-1.2 (-33.8)	<0.001*	0.5
HADS-A, points	102	5.3 (3.6)	4.2 (3.4)	-1.1 (-21.1)	<0.001*	0.4
HADS-T, points	97	8.9 (5.7)	6.6 (5.5)	-2.3 (-25.3)	<0.001*	0.6
SF12 - MCS	91	51.4 (9.2)	53.3 (11.4)	2.0 (3.9)	0.121	0.2
SF12 - PCS	91	43.6 (10.0)	47.1 (10.3)	3.5 (8.0)	0.001*	0.3
MMSE, points	96	28.2 (1.6)	28.2 (1.9)	0.1 (0.3)	0.669	0.0
NAART, correct	84	36.3 (11.5)	36.7 (10.8)	0.3 (0.9)	0.535	
Dig-Fwd, raw points	96	7.9 (2.4)	8.2 (2.4)	0.2 (2.9)	0.246	0.2
Dig-Back, raw points	96	6.5 (2.4)	6.3 (2.6)	-0.2 (-3.1)	0.303	0.1
Dig-Sym, raw points	95	44.0 (13.7)	46.1 (13.1)	2.1 (4.6)	0.020	0.2
Similarities	82	17.1 (5.9)	17.3 (6.2)	0.3 (1.9)	0.463	0.0
Trails-A, s	92	39.3 (27.0)	36.2 (16.2)	-3.1 (-7.9)	0.164	0.2
Trails-B, s	92	99.9 (61.6)	96.1 (50.7)	-3.8 (-3.8)	0.426	0.1
RAVLT, words; sum A1-5	97	42.0 (8.6)	46.2 (10.3)	4.1 (9.8)	<0.001*	0.7
A6	96	8.2 (3.0)	9.0 (3.4)	0.8 (9.9)	0.001*	0.3
A7	95	8.0 (3.0)	9.1 (3.5)	1.1 (14.3)	<0.001*	0.6
Clock-drawing, points	96	3.2 (0.9)	3.1 (0.9)	-0.1 (-1.6)	0.603	0.1
FAS-OVF, words	96	35.0 (12.1)	37.5 (12.9)	2.9 (8.3)	<0.001*	0.3

* Statistically significant p-values; SD = standard deviations
Note: A greater exit measure compared to intake measure represents improvement for that outcome. This is observed for all variables except for HADS, MMSE, and Trails.

Table 8: Number of Subjects Meeting Targets at Intake Versus Exit

Outcome	Target	Intake Frequency (%)	Exit Frequency (%)	P value
METs	≥7.0	42/115 (36.5)	71/109 (65.1)	<0.001*
TC, mmol/L	<4.0	59/113 (52.2)	56/104 (53.8)	1.000
LDL-C, mmol/L	<2.0	54/113 (47.8)	64/104 (61.5)	0.005*
HDL-C mmol/L	>1.0	92/113 (81.4)	88/104 (84.6)	0.531
Non-HDL-C	<4.0	86/113 (76.1)	92/104 (88.5)	0.001*
TG, mmol/L	<1.8	83/113 (73.5)	88/104 (84.6)	0.043*
FBG, mmol/L	<6.0	76/112 (67.9)	69/104 (66.3)	0.664
SBP, mm Hg	<140	69/114 (60.5)	68/109 (62.4)	0.742
DBP, mm Hg	<90	92/114 (80.7)	101/109 (92.7)	0.007*
WC, cm	Males <102; Females <88	29/64 (45.3) 10/49 (20.0)	32/64 (50.0) 11/46 (22.0)	0.595 0.681
BMI, kg/m^2	<25	21/114 (18.4)	24/109 (22.0)	0.250
HADS-D	< 8	93/111 (80.9)	92/99 (92.9)	0.039*
HADS-A	< 8	84/113 (73.0)	88/103 (76.5)	0.064
HADS-Total	< 14	88/111 (79.3)	90/99 (90.9)	<0.001*

*Statistically Significant

Table 9: Ordinal Logistic Regression Analyses for the Relationship between Duke Treadmill Risk Category at Exit and Exercise Attendance (n=93)

Parameter	***B***	**SE**	**Odds Ratio**	**95% CI**
Threshold				
Exit DTS Risk Category 1 (Low)	-2.16	0.79	0.12	0.03, 0.54
Exit DTS Risk Category 2 (Low and Moderate)	1.87	0.77	6.48	1.41, 29.68
Attendance	-0.01	0.02	1.00	0.95, 1.03

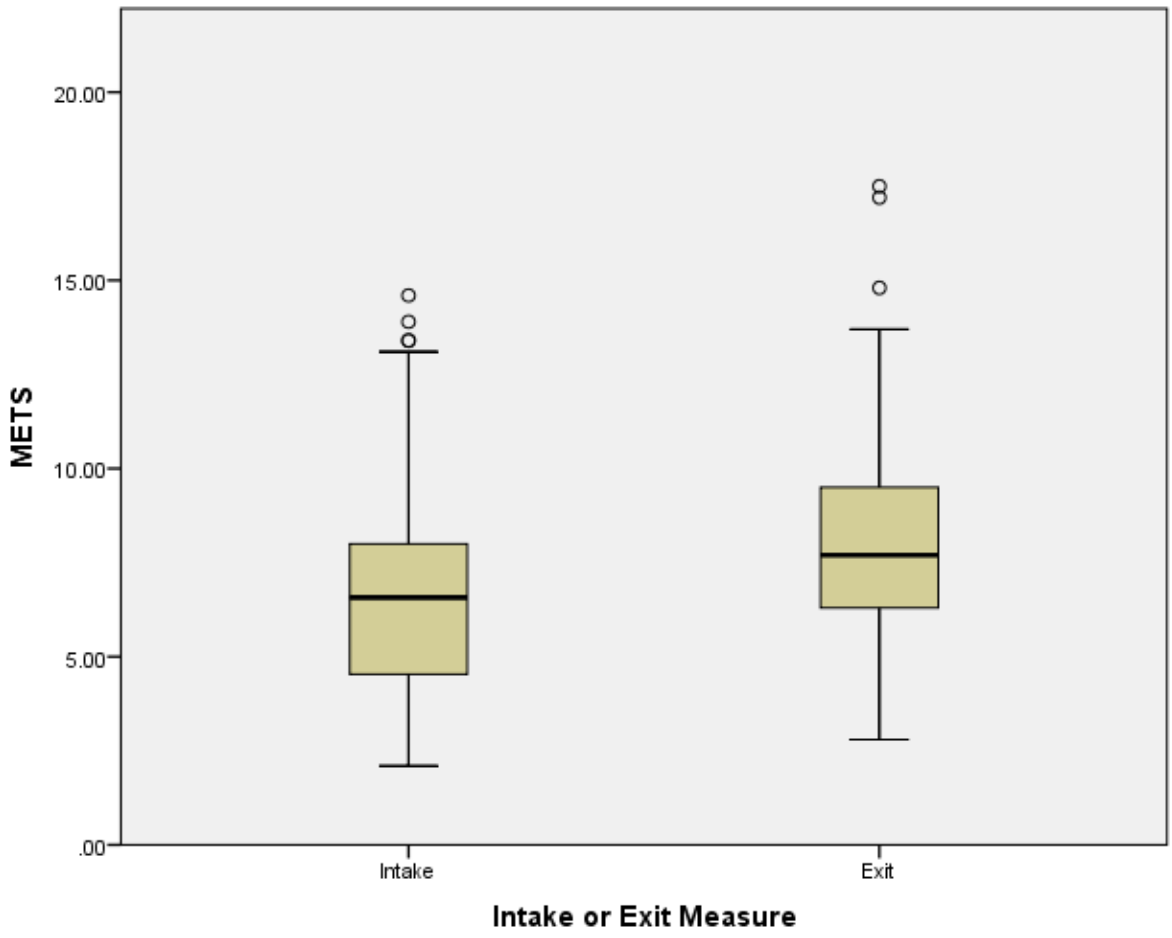

Figure 2. Intake and Exit Distributions for Functional Capacity (METS)

1 MET = 3.5 ml/kg/min O_2 consumption.

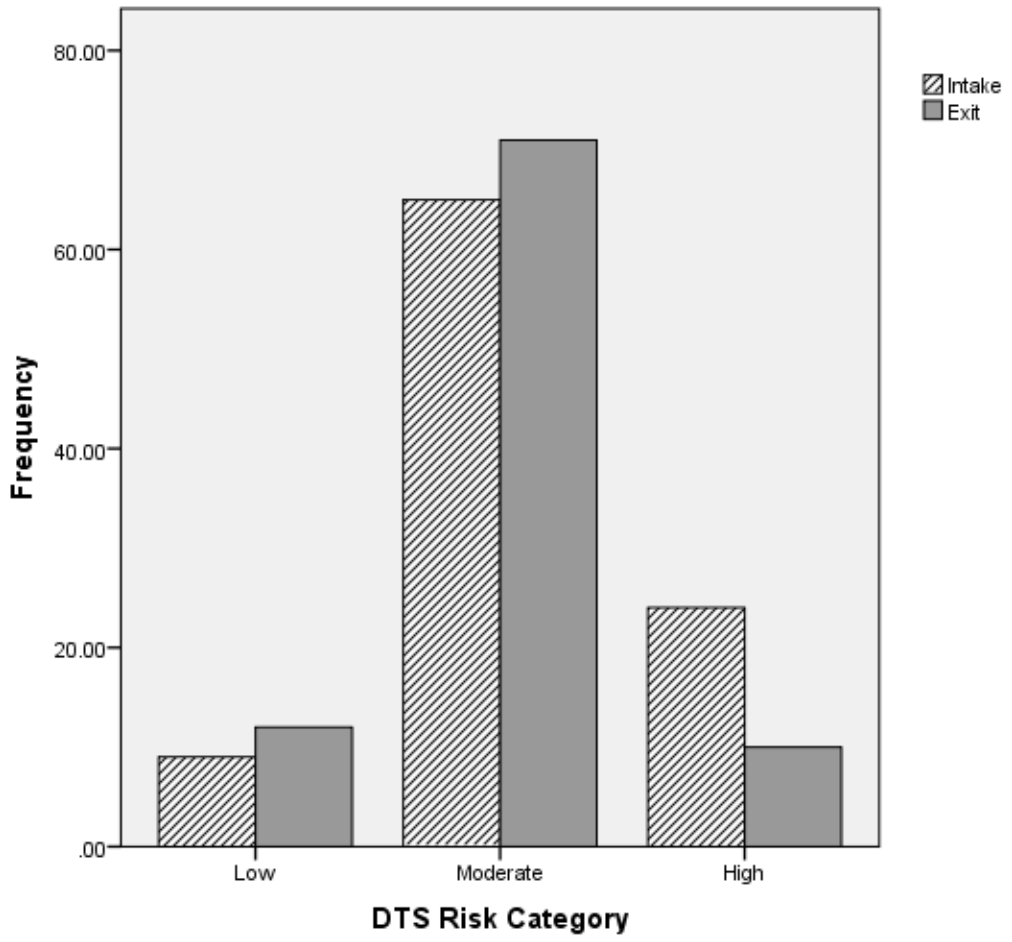

Figure 3. Intake to Exit Changes in Duke Treadmill Score Risk Categories

Chapter 6

6. Discussion

This chapter includes a brief overview in section 6.1 and then section 6.2 provides interpretations for the main study findings. Section 6.3 outlines the study strengths and limitations, while Section 6.4 includes study conclusions and future directives.

6.1 Overview

To the best our knowledge, this is the first study to examine the relationship between exercise adherence and functional capacity among TIA/MNDS stroke survivors in CRSP. The objectives for this study were: 1) quantify the relationship between exercise adherence and functional capacity at CRSP program exit among exercise trained TIA/MNDS patients, 2a) determine whether CRSP programming among exercise trained TIA/MNDS patients results intake to exit improvements in exercise capacity, blood pressure, lipid profile, blood glucose, body measurements and composition; and 2b) determine whether CRSP programming among exercise trained TIA/MNDS patients results in significant intake to exit changes in the following psychometric domains: quality of life and health status, anxiety, depression, general cognitive impairment, attention and working memory, verbal learning and memory, pre-morbid intellectual functioning, and speed/executive/abstraction.

6.2 Interpretation of Main Study Findings

6.2.1 Baseline Characteristics, Risk Factors and Health Status Measures

Our selected sample was at high risk of recurrent vascular events due their index event as well as most of them being overweight, having a sedentary lifestyle, a history of smoking, as well as being hypertensive and hyperlipidemic. About 53% of our sample reported their highest level of education as less than high school or graduated high school. Educational attainment is a commonly used measure of SES suggesting that the majority of our sample had low SES - an important risk factor for TIA, stroke, and CVD. Only a small subset (8%) of our sample were in the DTS low risk category, suggesting most of our sample had a predicted five-year mortality rate of 10% (moderate risk) or 35% (highest risk category).

The average participant age for our selected sample was 66 years which was similar to other studies with TIA/MNDS samples that also had an average age over 60 years (15,57–60,64). From the 155 participants that enrolled in the facility-based exercise program, 115 (74.2%) participants completed CRSP which is slightly greater than reported CRSP completion rates for TIA (65) and cardiac patients (118). The 115 participants enrolled in the facility-based exercise option attended on average 66% of the standard 50 sessions, which is slightly lower than other studies that have reported exercise session attendance rates of 73% (65), 84% (64), 94% (16) but those studies had smaller sample sizes and some of them were of shorter duration (e.g. 8 weeks). It is possible due to our mean time spent in our CRSP program being 8.5 months, participant adherence may have decreased over time.

At intake, 15.7% and 25.2% of the participants screened positive for depression and anxiety respectively, illustrating the clinical importance of screening for depression and anxiety after TIA/MNDS. Our findings and other findings in the literature (49,50,52,53) suggest that 8% to 17% and 14% to 23% of patients would screen positively for depression and anxiety post TIA/MNDS. Our findings confirm the high risk of post TIA depression and anxiety and justifies the greater need to pay attention to these psychological outcomes in this patient population. This patient population had a lower physical health status compared to the average score of 50 (10) in the US population (94). Specifically, at intake, the participants average SF-12 physical composite score was 43.6, while the mental composite score was 51.3. A lower intake physical composite score would suggest that our sample may have had issues in physical functioning, role functioning, bodily pain, and general health vitality. These limitations could have influenced CRSP participation. Furthermore, their mental health status was comparable to the average national norm of 50 (10) in the US population.

6.2.3 Objective One

The results of the present study showed there is a “dose-response-like” relationship between the number of exercise classes attended and functional capacity at exit. Specifically, for every 10 exercise classes, there was a predicted increase of 0.6 METS. The Canadian Cardiovascular Society developed quality indicators for CRSP, and one of the top 5 quality indicators is an ‘increase in exercise capacity’ (118). Specifically, an increase of 0.5 METS in the participants exercise capacity from the initial to the final exercise session (119). Our study was unique in that it investigated the number of exercise classes attended in CRSP and

how they relate to functional capacity in TIA/MNDS patients and our findings demonstrate the potential benefits of TIA/MNDS patients completing a CRSP exercise program and achieving the CCS quality indicator exercise capacity increase of > 0.5 METS. Our findings have potential implication on exercise prescription guidelines and informing "dose" in CRSP for TIA/MNDS patients. Additionally, they demonstrate that the quality indicators developed for assessing the quality of CRSP programming for other cardiovascular diseases may also be used in this patient population.

On average, the participants attended 33 (12.0) exercise sessions or 66% of the 50 typically prescribed sessions. Post hoc analysis of the difference in the number of exercise classes attended between subjects that achieved a 0.5 MET increase vs subjects that did not, found that subjects that achieved a 0.5 MET increase had a mean of 35 (9.6) exercise classes attended, compared to subjects that did not achieve a 0.5 MET increase that had a mean attendance of 25 (14.9) classes attended – a significant difference. This finding is similar to a recent real-world CRSP outcome study of cardiac patients where CRSP completers that achieved at least a 0.5 MET increase in exercise capacity attended a median of 32 supervised exercise sessions (IQR = 21-41) compared to 25 (5-37) exercise training sessions for CRSP completers who did not achieve a 0.5 MET increase (120). These findings suggest that exercise attendance is integral in the improvement of functional capacity in CRSP.

6.2.4 Objective Two

From CRSP intake to exit, this sample demonstrated improvements in functional capacity and other key risk-mediating outcomes. For functional capacity, we observed a mean increase during cardiac rehabilitation programming of 1.8 METS (28%) which is greater than 0.5 METS (CCS quality indicator). Our results align with other studies having reported significant improvements in functional capacity measured in METS (63) and peak VO_2 (16,64–66,68)(16,63–65,67)(15,62–64,66). Specifically, only 37% of the subjects met the METS target of ≥7.0 METS at intake, which improved to 65% of subjects meeting this target at exit. Overall, we found improvements in the participants lipid profile (TC, non-HDL-C, and TG), a protective effect (18). More subjects met the LDL-C, non-HDL-C, and TG targets from intake to exit. For lipid profile, there is inconsistency in the literature with regards to improvement in participant's lipid profiles. Faulkner et al., (2013) found that

TIA/MNDS patients enrolled in an 8-week health enhancing physical activity program had significant baseline to post-intervention decrease in TC as well, but other studies did not find improvements in participants lipid profiles (TC, LDL, HDL, TG) for participants enrolled in a CRSP 10-week program (72).

Further, we found improvements in blood pressure, specifically DBP. These findings are also inconsistent in the literature with studies demonstrating improvements in SBP but not DBP (16,65), and no improvements in either SBP or DBP (72). Additionally, we observed favorable improvements in BMI, WC, and weight. Although, the changes were small (~2% reduction), these are usually the more difficult risk factors to improve in CRSP, but have also been observed in other studies with stroke patients (65,72). Considering, approximately 81% of our sample was overweight, weight loss is likely to lead to clinically important health benefits (121). Lastly, we did not observe a change in FBG, this is likely due to having a small subset of our sample being diabetic. Overall, the inconsistencies across studies are likely due to the variability in the CRSP program components (study type, duration, number of prescribed exercise sessions, and completion rates). Overall, our findings show an overall improvement in the participants cardiovascular disease risk profile.

Additionally, mean depression and anxiety scores decreased significantly, suggesting improved emotional functioning in this sample. Screening for depression decreased from 16% to 7% of participants screening positive for depression. A similar trend was observed for anxiety with a decrease from 25% to 15%. Improvements in depression post TIA/MNDS and stroke have also been reported (65,66). Average PCS (physical health status) improved from intake to exit suggesting fewer physical limitations at exit. Other studies also reported improved physical functioning as part of the SF-36-PCS (70), and also observed improvements in subjects' PCS (69). Mean RAVLT, A6, and A7 increased from intake to exit suggesting improvements in verbal learning and memory. Additionally, improvements in executive functioning were observed from the increase in FAS-OVF. These favourable results work towards resolving some deficits of cognitive functioning after TIA that could impact one's ability to learn, understand new information, and apply health behaviours to their lives intended to reduce vascular risk factors.

We did not observe improvements in mental health status, general cognitive impairment, attention, and working memory. For general cognitive impairment, it is possible that the observed results were influenced by the measurement tool used. A systematic review investigating, prevalence of cognitive impairment following TIA and minor stroke reported variable increasing prevalence of 17%, 39%, and 54% using MMSE, NTB, and MoCA respectively (38). Our neutral findings regarding CRSP and mental health status are inconsistent with other findings in the literature. A RCT found significant improvements in mental health and MCS summary score (70), while another RCT did not observe such improvements (69). Our hypothesis that CRSP would improve all psychometrics cannot be fully supported with our findings, and the inconsistencies in these psychometric domains merit further study.

6.2.5 Exploratory Analyses

The exploratory analyses to assess whether there was a relationship between exit DTS risk category and number of exercise sessions attended, did not find an association between the two variables. Interestingly, it was observed that the proportion of individuals in the high risk DTS category improved significantly from CRSP intake to exit into lower mortality risk categories, suggesting that some subjects' prognosis changed quite favourably during cardiac rehabilitation programming.

6.3 Study Strengths and Limitations

One of the main strengths of this study is that it is the first to our knowledge to investigate CRSP exercise class attendance and its effects on functional capacity in TIA/MNDS patients. Thus, this research addressed a gap in the literature by exploring dose-response relationships for exercise attendance after TIA/MNDS. This provides useful guidance for policy makers interested in providing CRSP services for patients post TIA/MNDS. Additionally, the present study provides real-life participation of TIA/MNDS patients that are not typically represented in established CRSP programs which is likely due to issues with funding. This research is highly relevant for the current stroke prevention strategies as it provides further evidence of how TIA/MNDS patients could benefit from CRSP. Our research adds to the body of knowledge that could help support a mandate to include this patient population in this established community-based program. Further, this study had nearly equal sex

representation, and it comprehensively assessed key CRSP risk factors, psychological profiles, and outcomes. These analyses were made possible by the London CRSP clinical database that included numerous variables for assessment. Further this study exhibits temporality, which makes it possible to suggest that the outcomes were impacted by the intervention. Despite the positive aspects of this research, the present study does have some limitations.

One of the main limitations of this study was the absence of a control group, therefore we cannot make causal inferences. With this study design, there is no control over other non-CRSP elements that may have also been changing throughout the duration of the intervention. Further limitations included missing data due to collection methods. Specifically, some demographic characteristics were missing from the Ottawa sample, but data for the primary objective had little missing data, therefore it likely had no influence on those results. Missing psychometric data was of greater concern for analyses of the secondary objective and this may have influenced the results obtained for these variables. Additionally, our sample was largely Caucasian (96%), therefore our findings would not be generalizable to non-Caucasian populations. Lastly, sample size was pre-determined due to the retrospective nature of the study design, therefore it was not possible to calculate an optimal sample size required for scientifically valid results.

6.4 Conclusions and Future Directives

To our knowledge, this is the first report to explore the effect of exercise attendance on functional capacity for TIA/MNDS patients in CRSP. The results of this study demonstrated a dose-response-like relationship between exercise attendance and functional capacity which reached a clinically significant change. Further, exercise-trained TIA/MNDS patients had significant improvements in key cardiovascular risk factors, depression, anxiety, physical health, verbal learning, memory and executive functioning.

Future work should replicate these findings through a randomized controlled trial both within London, Ottawa and within other CRSP programs to improve generalizability. Longer-term impact of CRSP for these patients as well as cost-effectiveness analyses would also be relevant and would add to the body of knowledge. Post-stroke psychological outcomes are fairly under researched and the measures used are often variable, which merits further

consistent study in this subject area. Additionally, neuro-psychological outcomes should be employed after TIA as they may aid in the identification of cognitive deficits in this patient population. Further research should also explore different aspects of exercise attendance such as exercise type, duration, and intensity.

Additional work in this subject area could potentially have treatment relevance that would have important implications for TIA/MNDS secondary prevention strategies. If we are able to significantly mitigate the risk of recurrent stroke, measures to help improve participants adherence will be integral for future stroke prevention plans. If future work illustrates that enrolment in CRSP for this patient population is better than current stroke practice, that could shift the allocation of resources for CRSP programs to revise the criteria for enrolment in these programs. This research presents a unique and productive collaboration between Cardiac Rehabilitation and Stroke Prevention Clinics. Being able to connect TIA/MNDS patients to existing cardiac rehabilitation programs presents an opportunity to improve overall service provision without having to reform Stroke Prevention Clinics to include "CRSP-like" programming, a duplication of services which would likely be associated with additional and unnecessary costs. Our findings suggest that breaking down the silos of cardiac and stroke rehabilitation while implementing a "vascular rehabilitation" program might be a more effective means of secondary disease prevention for cardiac and cerebrovascular patients.

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Appendices

Appendix A: Attendance Breakdown

Table 10: Exercise Attendance Breakdown

Number of Classes Attended	Frequency	Percent
1	2	1.7
5	1	0.9
8	2	1.7
9	2	1.7
12	2	1.7
13	1	0.9
15	2	1.7
17	2	1.7
18	2	1.7
19	2	1.7
20	1	0.9
21	1	0.9
23	4	3.5
24	2	1.7
25	3	2.6
27	2	1.7
28	3	2.6
29	3	2.6
30	2	1.7

Table 10: Exercise Attendance Breakdown Continued

Number of Classes Attended	Frequency	Percent
31	3	2.6
32	4	3.5
33	2	1.7
34	5	4.3
35	5	4.3
36	1	0.9
37	5	4.3
38	6	5.2
39	6	5.2
40	5	4.3
41	4	3.5
42	2	1.7
43	1	0.9
44	6	5.2
45	4	3.5
46	3	2.6
48	4	3.5
50	2	1.7
54	1	0.9
60	1	0.9

Appendix B: Bonferroni Adjustments

Table 11: Bonferroni Adjustments for Key CRSP Outcomes

Domain	Variables	Calculation	P value
Functional capacity	METS	0.05 ÷ 1	0.05
Lipid profile	TC, LDL-C, HDL-C, non-HDL-C, TG	0.05 ÷ 5	0.01
Glucose	FBG	0.05 ÷1	0.05
Blood pressure	SBP, DBP	0.05 ÷ 2	0.03
Body composition	WC, BMI, weight	0.05 ÷ 3	0.02

Table 12: Bonferroni Adjustments for Psychometric Domains

Domain	Variables	Calculation	P value
Depression and Anxiety	HADS-T, HADS-D, HADS-A	0.05 ÷ 3	0.02
Quality-of-life	SF12-PCS, SF12-MCS	0.05 ÷ 2	0.03
General cognitive impairment	MMSE	0.05 ÷ 1	0.05
Attention and working memory	Digits-Fwd, Digits Back, Trails A	0.05 ÷ 3	0.02
Verbal learning and memory	RAVLT sum, A6, A7	0.05 ÷ 3	0.02
Speed, executive, abstraction	Digit-Sym, Trails B, CDT, FAS-OVF, Similarities	0.05 ÷ 5	0.01
Pre-morbid intellectual functioning	NAART	0.05 ÷ 1	0.05

Appendix C: Regression Models

Table 13: Primary Objective Regression Models

	Model 1			Model 2		
Variable	B	SE	95% CI	B	SE	95% CI
Attendance	-0.00	0.03	-0.06, 0.05	0.05	0.02	0.03, 0.08
Intake METS				0.96	0.06	0.83, 1.08
R^2	0.00			0.71		
	Model 3			**Model 4**		
Variable	B	SE	95% CI	B	SE	95% CI
Attendance	0.05	0.02	0.02, 0.08	0.06	0.01	0.03, 0.09
Intake METS	0.95	0.06	0.83, 1.08	0.87	0.07	0.74, 1.01
Sex (male)	-0.20	0.33	-0.86, 0.46	-0.29	0.32	-0.93, 0.35
Age (years)				-0.05	0.02	-0.08, -0.01
R^2	0.71			0.73		

	Model 5		
Variable	B	SE	95% CI
Attendance	0.06	0.01	0.03, 0.09
Intake METs	0.90	0.07	0.77, 1.03
Sex (male)	-0.33	0.32	-0.97, 0.30
Age (years)	-0.05	0.02	-0.08, -0.01
Sedentary Lifestyle	0.72	0.32	0.08, 1.36
R^2	0.75		

Appendix D: Assessment of Potential Selection Bias

Assessment of Potential Selection Bias

To compare the differences between participants that completed CRSP (completers) vs. participants that did not complete CRSP (non-completers), Pearson chi-square test was used for categorical variables, Fisher's exact test was used when expected cell counts were small, and independent samples t-test was used for continuous variables. Additionally, variables NYHA and CCS were collapsed to increase cell counts. Tables 14 to Table 16 outline these comparisons.

Table 14: Baseline Characteristics - Completers vs. Non-completers

Characteristic at Baseline	Completers N = 115	Non-Completers N = 40	P value
	Mean (SD) or Frequency N (%)		
Site			
London	98 (85.2)	29 (72.5)	0.072*
Ottawa	17 (14.8)	11 (27.5)	
Study			
1 – Observational Study	62 (53.9)	19 (47.5)	0.203*
2 – 1st RCT	13 (11.3)	1 (2.5)	
3 – 2nd RCT	40 (34.8)	20 (50.0)	
Age (years)	66 (10.2)	67 (12.7)	0.731•
Sex			
Male	65 (56.5)	24 (61.5)	0.584*
Female	50 (43.5)	15 (28.5)	
Ethnicity			
White/Caucasian	110 (95.7)	37 (92.5)	1.00∼
Other	5 (4.3)	1 (0.0)	
Missing		2 (0.1)	
Highest Level of Education			
Less than high school	31 (27)	12 (35.3)	0.697*
Graduated high school	30 (26.1)	12 (35.3)	
Some post-secondary	16 (13.9)	2 (5.9)	
Graduated university/college	33 (28.7)	8 (23.5)	
Not obtained/missing	5 (4.3)	6 (15.0)	
Employment Status			0.142*
Employed	43 (37.3)	6 (15.0)	
Unemployed/Disability/Retired	70 (60.1)	16 (40.0)	
Not obtained/missing	19 (16.5)	18 (45.0)	
Living Situation			
Alone	26 (22.6)	7 (17.5)	0.747*
With spouse/partner/others	70 (60.8)	16 (40.0)	
Not obtained/missing	19 (16.5)	17 (42.5)	
NYHA Functional Classification			
Class I	81 (70.4)	16 (40.0)	0.345*
Class II	13 (11.3)	4 (20.0)	
Class III	5 (4.3)	2 (5.0)	
Class IV	0 (0.0)	0 (0.0)	
Not obtained/missing	16 (13.9)	18 (45.0)	
CCS Grading System of Angina Pectoris			
Class 0	94 (81.7)	19 (47.5)	0.529*
Class I	4 (3.5)	2 (5.0)	
Class II	1 (0.9)	1 (2.5)	
Class III	0 (0.0)	0 (0.0)	
Class IV	0 (0.0)	0 (0.0)	
Not obtained/missing	16 (13.9)	22 (55.0)	

*Pearson Chi-Square | ∼ Fisher's Exact test | • Independent Samples T-test

Table 15: Risk Factors at Intake - Completers vs. Non-completers

Risk Factor	Completers (n = 115) Mean (SD) or Frequency N (%)	Non-Completers (n=40) Mean (SD) or Frequency N (%)	P value
Sedentary lifestyle	67 (58.3)	19 (47.5)	0.238 *
Dyslipidemia Missing	91 (79.1) 2 (1.7)	22 (55.0) 0 (0.0)	0.002*
Hypertension	89 (77.4)	23 (57.5)	0.016*
Family CVD history	48 (41.7)	12 (30.0)	0.189*
Diabetes Type 1 Type 2	30 (26.1) 2 (0.1) 28 (93.3)	10 (25.0)	0.892* 0.224~
Smoking history Current smoker Former smoker Non-smokers Not obtained/missing	 17 (14.8) 55 (47.8) 42 (36.5) 1 (0.9)	 6 (15.0) 13 (32.5) 15 (37.5) 6 (15.0)	0.589*
Post-menopausal Syndrome Females (n=49; n=15) Missing	27 (23.5) 27 (55.1) 1 (0.9)	8 (20.0) 8 (53.3) 0 (0.0)	0.632*
Mean BMI (n = 114) BMI > 25 Missing	29.8 (4.9) 93 (80.9) 1 (0.9)	28.9 (5.3) 24 (72.7) 0 (0.0)	0.369• 0.267*

*Pearson Chi-Square | ~ Fisher's Exact test | • Independent Samples T-test

Table 16: Baseline Health Status Measures - Completers vs. Non-completers

Psychometric / Characteristic	Completers N = 115	Non-completers N = 40	P value
	Mean (SD) or Frequency N (%)		
Depression and Anxiety at intake			
HADS-D ≥ 8	18 (15.7)	4 (10.0)	0.652*
Missing	4 (3.5)	9 (22.5)	
HADS-A ≥ 8	29 (25.2)	15 (38.5)	0.129*
Missing	2 (1.7)	1 (0.0)	
HADS-Total ≥ 14	23 (20.0)	11 (27.5%)	0.089*
Missing	4 (3.5)	9 (22.5)	
Quality of Life			
SF-12 PCS	43.6 (9.8)	42.8 (9.0)	0.703•
Missing	10 (8.7)	9 (22.5)	
SF-12 MCS	51.4 (8.9)	46.7 (13.1)	0.237•
Missing	10 (8.7)	9 (22.5)	
Duke Treadmill Score	-5.8 (7.3)	-7.8 (6.3)	0.265•
Duke Treadmill Score Risk Category			0.216*
Low Risk	9 (7.8)	1 (0.0)	
Moderate Risk	65 (56.5)	9 (22.5)	
High Risk	24 (20.9)	8 (20.0)	
Missing	17 (14.8)	22 (55.0)	

*Pearson Chi-Square | • Independent Samples T-test

Appendix E: Assessment of Potential Non-Response Bias

Assessment of Potential Non-Response Bias

To compare the differences between participants that had a known variable vs. participants that did not respond, Pearson chi-square test was used for categorical variables, Fisher's exact test was used when expected cell counts were small, and independent samples t-test was used for continuous variables. For comparisons where one of the groups had a sample size of less than 30, the Welch's t-test for independent means was used. Additionally, variables NYHA and CCS were collapsed to increase cell counts. Table 17 to Table 28 outline these comparisons.

Table 17: Comparison Between Participants with Known Employment Status vs. Unknown Employment Status

Characteristic	Known Employment Status N = 96	Unknown Employment Status N = 19	P value
	Mean (SD) or Frequency N (%)		
Site			
London	96 (100)	2 (10.5)	**<0.001**~
Ottawa	0 (0.0)	17 (89.5)	
Study			
1 – Observational Study	62 (64.6)	0 (0.0)	**<0.000***
2 – 1st RCT	12 (12.5)	1 (5.3)	
3 – 2nd RCT	22 (22.9)	18 (94.7)	
Age (years)	66 (10.5)	67 (8.9)	0.482∞
Sex			
Male	50 (52.1)	15 (78.9)	**0.031**~
Female	46 (47.9)	4 (21.1)	
Ethnicity			
White/Caucasian	92 (95.8)	1 (5.3)	**0.000**~
Other	4 (4.0)	18 (94.7)	
Highest Level of Education			
Less than high school	31 (32.3)	0 (0.0)	0.304*
Graduated high school	22 (22.9)	8 (42.1)	
Some post-secondary	14 (14.6)	2 (10.5)	
Graduated university/college	25 (26.0)	8 (42.1)	
Not obtained/missing	4 (4.2)	1 (5.3)	
Living Situation			
Alone	25 (26.0)	3 (15.8)	**0.022**~
With spouse/partner/others	70 (72.9)	0 (0.0)	
Not obtained/missing	1 (1.0)	16 (84.2)	
NYHA Functional Classification			
Class I	78 (81.3)	3 (15.8)	**0.005**~
Class II	13 (13.5)	0 (0.0)	
Class III	5 (5.2)	0 (0.0)	
Class IV	0 (0.0)	0 (0.0)	
Not obtained/missing	0 (0.0)	16 (84.2)	
CCS Grading System of Angina Pectoris			
Class 0	91 (94.8)	3 (15.8)	1.00~
Class I	4 (4.2)	0 (0.0)	
Class II	0 (0.0)	0 (0.0)	
Class III	1 (1.0)	0 (0.0)	
Class IV	0 (0.0)	0 (0.0)	
Not obtained/missing	0 (0.0)	16 (84.2)	

*Pearson Chi-Square | ~ Fisher's Exact test | • Independent Samples T-test
Statistically significant values are **bolded.**

Table 18: Comparison Between Participants with Known Living Situation vs. Unknown Living Situation

Characteristic at Baseline	Living Situation Known N = 97	Living Situation Unknown N = 18	P value
	Mean (SD) or Frequency N (%)		
Site			
London	97 (100.0)	1 (5.6)	**<0.000**~
Ottawa	0 (0.0)	17 (94.4)	
Study			
1 – Observational Study	62 (63.9)	0 (0.0)	**<0.000**~
2 – 1st RCT	12 (12.4)	1 (5.6)	
3 – 2nd RCT	23 (23.7)	17 (94.4)	
Age (years)	65 (10.5)	68 (8.5)	0.240∞
Sex			
Male	51 (52.6)	14 (77.8)	0.048*
Female	46 (47.4)	4 (22.2)	
Ethnicity			
White/Caucasian	91 (95.9)	14 (94.4)	0.527~
Other	4 (4.0)	1 (5.6)	
Highest Level of Education			
Less than high school	31 (31.9)	0 (0.0)	**0.006**~
Graduated high school	23 (23.7)	7 (38.9)	
Some post-secondary	14 (14.4)	2 (11.1)	
Graduated university/college	1 (1.0)	8 (44.4)	
Not obtained/missing	4 (4.1)	1 (5.6)	
Employment Status			
Employed	45 (46.4)	0 (0.0)	< **0.000**~
Unemployed/Disability/Retired	51 (52.6)	0 (0.0)	
Not obtained/missing	1 (1.0)	18 (100.0)	
NYHA Functional Classification			
Class I	79 (81.4)	1 (5.6)	< **0.000**~
Class II	13 (13.4)	0 (0.0)	
Class III	5 (5.2)	0 (0.0)	
Class IV	0 (0.0)	0 (0.0)	
Not obtained/missing	0 (0.0)	17 (94.4)	
CCS Grading System of Angina Pectoris			
Class 0	92 (94.8)	2 (11.1)	< **0.000**~
Class I	4 (4.1)	0 (0.0)	
Class II	0 (0.0)	0 (0.0)	
Class III	1 (1.0)	0 (0.0)	
Class IV	0 (0.0)	0 (0.0)	
Not obtained/missing	0 (0.0)	16 (88.9)	

*Chi-Square test | ~ Fisher's Exact test | ∞ Welch's t-test for independent means
Statistically significant values are **bolded.**

Table 19: Comparison Between Participants with Known SF12 vs. Unknown SF-12

Characteristic at Baseline	SF-12 Known N = 95	SF-12 Unknown N = 20	P value
	Mean (SD) or Frequency N (%)		
Site			
London	80 (84.2)	18 (90.0)	0.733∼
Ottawa	15 (15.8)	2 (10.0)	
Study			
1 – Observational Study	51 (53.7)	11 (55.0)	0.979*
2 – 1st RCT	11 (11.6)	2 (10.0)	
3 – 2nd RCT	33 (34.7)	7 (35.0)	
Age (years)	65 (9.7)	70 (11.9)	0.055∞
Sex			
Male	53 (55.8)	12 (60.0)	0.730*
Female	42 (44.2)	8 (40.0)	
Ethnicity			
White/Caucasian	91 (95.8)	19 (95.0)	1.00∼
Other	4 (4.4)	1 (5.0)	
Highest Level of Education			
Less than high school	25 (26.4)	6 (30.0)	0.420 *
Graduated high school	25 (26.3)	5 (25.0)	
Some post-secondary	13 (13.7)	3 (15.0)	
Graduated university/college	31 (32.7)	2 (10.0)	
Not obtained/missing	1 (1.1)	4 (20.0)	
Employment Status			
Employed	40 (42.1)	11 (55.0)	0.170*
Unemployed/Disability/Retired	40 (42.2)	5 (25.0)	
Not obtained/missing	15 (15.8)	4 (20.0)	
Living Situation			
Alone	19 (23.8)	7 (35.0)	0.232∼
With spouse/partner/others	57 (71.3)	10 (50.0)	
Not obtained/missing	4 (5.1)	3 (15.0)	
NYHA Functional Classification			
Class I	65 (68.4)	16 (80.0)	0.575*
Class II	12 (12.6)	1 (5.0)	
Class III	4 (4.2)	1 (5.0)	
Class IV	0 (0.0)	0 (0.0)	
Not obtained/missing	14 (14.7)	2 (10.0)	
CCS Grading System of Angina Pectoris			
Class 0	77 (81.0)	17 (85.0)	0.840*
Class I	3 (3.2)	1 (5.0)	
Class II	0 (0.0)	0 (0.0)	
Class III	1 (1.0)	0 (0.0	
Class IV	0 (0.0)	0 (0.0)	
Not obtained/missing	14 (14.7)	2 (10.0)	

*Chi-Square test | ∼ Fisher's Exact test | ∞ Welch's t-test for independent means
Statistically significant values are **bolded.**

Table 20: Comparison Between Participants with Known HADS-T vs. Unknown HADS-T

Characteristic at Baseline	HADS-T Known N = 99	HADS-T Unknown N = 16	P value
	Mean (SD) or Frequency N (%)		
Site			
London	85 (85.9)	13 (81.3)	0.704 ~
Ottawa	14 (14.1)	3 (18.8)	
Study			
1 – Observational Study	53 (53.5)	9 (56.3)	
2 – 1st RCT	13 (13.1)	0 (0.0)	
3 – 2nd RCT	33 (33.3)	7 (43.8)	
Age (years)	65 (10.4)	68 (9.3)	0.254∞
Sex			
Male	58 (58.6)	7 (43.8)	0.267 *
Female	41 (41.4)	9 (56.3)	
Ethnicity			
White/Caucasian	94 (94.9)	16 (100.0)	1.00 ~
Other	5 (5.0)	0 (0.0)	
Highest Level of Education			
Less than high school	27 (27.3)	4 (25.0)	0.198*
Graduated high school	24 (24.2)	6 (37.5)	
Some post-secondary	15 (15.2)	1 (6.3)	
Graduated university/college	30 (30.3)	3 (18.3)	
Not obtained/missing	3 (3.0)	2 (12.5)	
Employment Status			
Employed	42 (42.5)	3 (18.8)	0.105*
Unemployed/Disability/Retired	42 (42.5)	9 (56.3)	
Not obtained/missing	15 (15.2)	4 (25.0)	
Living Situation			
Alone	24 (24.2)	2 (12.5)	0.504~
With spouse/partner/others	59 (59.6)	11 (68.8)	
Not obtained/missing	1 (1.0)	3 (18.8)	
NYHA Functional Classification			
Class I	74 (74.7)	5 (31.3)	0.073*
Class II	5 (5.1)	5 (31.3)	
Class III	0 (0.0)	0 (0.0)	
Class IV	0 (0.0)	0 (0.0)	
Not obtained/missing	14 (14.1)	6 (37.5)	
CCS Grading System of Angina Pectoris			
Class 0	80 (80.8)	10 (62.5)	**0.033**~
Class I	5 (5.1)	0 (0.0)	
Class II	0 (0.0)	0 (0.0)	
Class III	0 (0.0)	0 (0.0)	
Class IV	0 (0.0)	0 (0.0)	
Not obtained/missing	14 (14.1)	6 (37.5)	

*Chi-Square test | ~ Fisher's Exact test | ∞ Welch's t-test for independent means
Statistically significant values are **bolded.**

Table 21: Comparison Between Participants with Known MMSE vs. Unknown MMSE

Characteristic at Baseline	MMSE Known N = 97	MMSE Unknown N = 18	P value
	Mean (SD) or Frequency N (%)		
Site			
London	83 (85.6)	15 (83.3)	0.729∼
Ottawa	14 (14.4)	3 (16.7)	
Study			
1 – Observational Study	54 (55.7)	8 (44.4)	
2 – 1st RCT	11 (11.3)	2 (11.1)	
3 – 2nd RCT	32 (33.0)	8 (44.4)	
Age (years)	66 (10.2)	65 (10.8)	0.977∞
Sex			
Male	53 (54.6)	12 (66.7)	0.344*
Female	44 (45.4)	6 (33.3)	
Ethnicity			
White/Caucasian	93 (95.9)	17 (94.4)	0.580∼
Other	4 (4.0)	1 (5.6)	
Highest Level of Education			
Less than high school	24 (24.7)	7 (38.9)	0.287∼
Graduated high school	26 (26.8)	4 (22.2)	
Some post-secondary	13 (13.4)	3 (16.7)	
Graduated university/college	31 (31.9)	2 (11.1)	
Not obtained/missing	3 (3.1)	2 (11.1)	
Employment Status			
Employed	40 (41.3)	5 (27.8)	0.365*
Unemployed/Disability/Retired	42 (43.3)	9 (50.0)	
Not obtained/missing	15 (15.5)	4 (22.2)	
Living Situation			
Alone	21 (21.6)	5 (27.8)	0.541∼
With spouse/partner/others	60 (61.9)	10 (55.6)	
Not obtained/missing	16 (16.5)	3 (16.7)	
NYHA Functional Classification			
Class I	69 (71.1)	8 (44.4)	0.103 ∼
Class II	11 (11.3)	4 (22.2)	
Class III	4 (4.1)	0 (0.0)	
Class IV	0 (0.0)	0 (0.0)	
Not obtained/missing	13 (13.4)	6 (33.3)	
CCS Grading System of Angina Pectoris			
Class 0	79 (81.4)	11 (61.1)	0.499
Class I	4 (4.1)	1 (5.6)	
Class II	0 (0.0)	0 (0.0)	
Class III	1 (1.0)	0 (0.0)	
Class IV	0 (0.0)	0 (0.0)	
Not obtained/missing	13 (13.4)	6 (33.3)	

*Chi-Square test | ∼ Fisher's Exact test | ∞ Welch's t-test for independent means
Statistically significant values are **bolded.**

Table 22: Comparison Between Participants with Known RAVLT Sum vs Unknown RAVLT

Characteristic at Baseline	RAVLT Sum Known N = 97	RAVLT Sum Unknown N = 18	P value
	Mean (SD) or Frequency N (%)		
Site			
London	83 (85.6)	15 (83.3)	0.729
Ottawa	14 (14.4)	3 (16.7)	
Study			
1 – Observational Study	54 (55.7)	8 (44.4)	
2 – 1st RCT	11 (11.3)	2 (11.1)	
3 – 2nd RCT	32 (33.0)	8 (44.4)	
Age (years)	66 (10.2)	65 (10.8)	0.977∞
Sex			
Male	53 (54.6)	12 (66.7)	0.344*
Female	44 (45.4)	6 (33.3)	
Ethnicity			
White/Caucasian	93 (95.9)	17 (84.4)	0.580~
Other	4 (4.0)	1 (5.6)	
Highest Level of Education			
Less than high school	24 (24.7)	7 (38.9)	0.287~
Graduated high school	26 (26.8)	4 (22.2)	
Some post-secondary	13 (13.4)	3 (16.7)	
Graduated university/college	31 (31.9)	2 (11.1)	
Not obtained/missing	3 (3.1)	2 (11.1)	
Employment Status			
Employed	40 (41.3)	4 (27.8)	0.365*
Unemployed/Disability/Retired	42 (43.3)	9 (50.0)	
Not obtained/missing	15 (15.5)	4 (22.2)	
Living Situation			
Alone	21 (21.6)	5 (27.8)	0.541~
With spouse/partner/others	60 (61.9)	10 (55.6)	
Not obtained/missing	1 (1.0)	3 (16.7)	
NYHA Functional Classification			
Class I	69 (71.1)	8 (44.4)	0.103 ~
Class II	11 (11.3)	4 (22.2)	
Class III	4 (4.1)	0 (0.0)	
Class IV	0 (0.0)	0 (0.0)	
Not obtained/missing	13 (13.4)	6 (33.3)	
CCS Grading System of Angina Pectoris			
Class 0	79 (81.4)	11 (61.1)	0.499
Class I	4 (4.1)	1 (5.6)	
Class II	3 (1.0)	0 (0.0)	
Class III	0 (0.0)	0 (0.0)	
Class IV	0 (0.0)	0 (0.0)	
Not obtained/missing	3 (13.4)	6 (33.3)	

*Pearson Chi-Square test | ~ Fisher's Exact test | ∞ Welch's t-test for independent means
Statistically significant values are **bolded.**

Table 23: Comparison Between Participants with Known Similarities vs Unknown Similarities

Characteristic at Baseline	Similarities Known N = 83	Similarities Unknown N = 32	P value
	Mean (SD) or Frequency N (%)		
Site			
London	83 (100.0)	15 (46.9)	**<0.001***
Ottawa	0 (0.0)	17 (53.1)	
Study			
1 – Observational Study	43 (51.8)	8 (25.0)	**<0.001***
2 – 1st RCT	50 (48.2)	2 (6.3)	
3 – 2nd RCT	0 (0.0)	22 (68.8)	
Age (years)	66 (10.6)	66 (9.4)	0.903•
Sex			
Male	43 (51.8)	22 (68.8)	0.100*
Female	40 (48.2)	10 (31.3)	
Ethnicity			
White/Caucasian	80 (86.4)	30 (93.8)	0.617 ~
Other	3 (3.6)	2 (6.2)	
Highest Level of Education			
Less than high school	24 (28.9)	7 (21.9)	0.784*
Graduated high school	21 (25.3)	9 (28.1)	
Some post-secondary	12 (14.5)	4 (12.5)	
Graduated university/college	23 (27.7)	10 (31.3)	
Not obtained/missing	3 (3.6)	2 (6.3)	
Employment Status			
Employed	40 (48.2)	5 (15.6)	**<0.001***
Unemployed/Disability/Retired	42 (50.6)	9 (28.2)	
Not obtained/missing	1 (1.2)	18 (56.3)	
Living Situation			
Alone	21 (25.3)	5 (15.6)	**<0.001***
With spouse/partner/others	60 (72.3)	10 (31.3)	
Not obtained/missing	1 (1.2)	17 (53.1)	
NYHA Functional Classification			
Class I	69 (81.9)	8 (25.0)	**<0.001***
Class II	11 (13.3)	4 (12.5)	
Class III	4 (4.8)	0 (0.0)	
Class IV	0 (0.0)	0 (0.0)	
Not obtained/missing	0 (0.0)	20 (62.5)	
CCS Grading System of Angina Pectoris			
Class 0	78 (94.0)	11 (34.4)	**<0.001***
Class I	4 (4.8)	1 (3.1)	
Class II	1 (1.2)	0 (0.0)	
Class III	0 (0.0)	0 (0.0)	
Class IV	0 (0.0)	0 (0.0)	
Not obtained/missing	0 (0.0)	20 (62.5)	

*Pearson Chi-Square | ~ Fisher's Exact test | • Independent Samples T-test
Statistically significant values are **bolded.**

Table 24: Comparison Between Participants with Known Digits vs Unknown Digits

Characteristic at Baseline	Digits Known N = 97	Digits Unknown N = 18	P value
	Mean (SD) or Frequency N (%)		
Site			
London	83 (85.6)	15 (83.3)	0.729∼
Ottawa	14 (14.4)	3 (16.7)	
Study			
1 – Observational Study	51 (55.7)	8 (44.4)	0.691*
2 – 1st RCT	11 (11.3)	2 (11.1)	
3 – 2nd RCT	32 (33.0)	8 (44.4)	
Age (years)	66 (10.2)	66 (10.8)	0.978 ∞
Sex			
Male	53 (54.6)	12 (66.7)	0.344*
Female	44 (45.4)	6 (33.3)	
Ethnicity			
White/Caucasian	93 (95.9)	17 (94.4)	0.580∼
Other	4 (4.0)	1 (5.6)	
Highest Level of Education			
Less than high school	24 (24.7)	7 (38.9)	0.437*
Graduated high school	26 (26.8)	2 (22.2)	
Some post-secondary	13 (13.4)	3 (16.7)	
Graduated university/college	31 (31.9)	2 (11.1)	
Not obtained/missing	3 (3.1)	2 (11.1)	
Employment Status			
Employed	40 (41.3)	5 (27.8)	0.365*
Unemployed/Disability/Retired	42 (43.3)	9 (50.0)	
Not obtained/missing	15 (15.5)	4 (22.2)	
Living Situation			
Alone	21 (21.6)	5 (27.8)	0.327*
With spouse/partner/others	78 (80.4)	10 (55.6)	
Not obtained/missing	16 (16.5)	3 (16.7)	
NYHA Functional Classification			
Class I	69 (71.1)	12 (66.7)	0.714*
Class II	11 (11.3)	2 (11.1)	
Class III	4 (4.1)	1 (5.6)	
Class IV	0 (0.0)	0 (0.0)	
Not obtained/missing	13 (13.4)	3 (16.7)	
CCS Grading System of Angina Pectoris			
Class 0	79 (81.4)	15 (83.3)	0.716∼
Class I	4 (4.1)	0 (0.0)	
Class II	0 (0.0)	0 (0.0)	
Class III	1 (1.0)	0 (0.0)	
Class IV	0 (0.0)	0 (0.0)	
Not obtained/missing	13 (13.4)	3 (16.7)	

*Pearson Chi-Square test | ∼ Fisher's Exact test | ∞ Welch's t-test for independent means
Statistically significant values are **bolded.**

Table 25: Comparison Between Participants with Known CDT vs. Unknown CDT

Characteristic at Baseline	CDT Known N = 97	CDT Unknown N = 18	P value
	Mean (SD) or Frequency N (%)		
Site			
London	83 (85.6)	15 (83.3)	0.729∼
Ottawa	14 (14.4)	3 (16.7)	
Study			
1 – Observational Study	51 (55.7)	8 (44.4)	0.691*
2 – 1st RCT	11 (11.3)	2 (11.1)	
3 – 2nd RCT	32 (33.0)	8 (44.4)	
Age (years)	66 (10.2)	66 (10.8)	0.978∞
Sex			
Male	53 (54.6)	12 (66.7)	0.344*
Female	44 (45.4)	6 (33.3)	
Ethnicity			
White/Caucasian	93 (95.9)	17 (94.4)	0.580∼
Other	4 (4.0)	1 (5.6)	
Highest Level of Education			
Less than high school	24 (24.7)	7 (38.9)	0.437*
Graduated high school	26 (26.8)	2 (22.2)	
Some post-secondary	13 (13.4)	3 (16.7)	
Graduated university/college	31 (31.9)	2 (11.1)	
Not obtained/missing	3 (3.1)	2 (11.1)	
Employment Status			
Employed	40 (41.3)	5 (27.8)	0.365*
Unemployed/Disability/Retired	42 (43.3)	9 (50.0)	
Not obtained/missing	15 (15.5)	4 (22.2)	
Living Situation			
Alone	21 (21.6)	5 (27.8)	0.327*
With spouse/partner/others	78 (80.4)	10 (55.6)	
Not obtained/missing	16 (16.5)	3 (16.7)	
NYHA Functional Classification			
Class I	69 (71.1)	12 (66.7)	0.714*
Class II	11 (11.3)	2 (11.1)	
Class III	4 (4.1)	1 (5.6)	
Class IV	0 (0.0)	0 (0.0)	
Not obtained/missing	13 (13.4)	3 (16.7)	
CCS Grading System of Angina Pectoris			
Class 0	79 (81.4)	15 (83.3)	0.716∼
Class I	4 (4.1)	0 (0.0)	
Class II	0 (0.0)	0 (0.0)	
Class III	1 (1.0)	0 (0.0)	
Class IV	0 (0.0)	0 (0.0)	
Not obtained/missing	13 (13.4)	3 (16.7)	

*Pearson Chi-Square test | ∼ Fisher's Exact test | ∞ Welch's t-test for independent means
Statistically significant values are **bolded.**

Table 26: Comparison Between Participants with Known Trails vs. Unknown Trails

Characteristic at Baseline	Trails Known N = 96	Trails Unknown N = 19	P value
	Mean (SD) or Frequency N (%)		
Site			
London	82 (85.4)	16 (84.2)	1.00~
Ottawa	14 (14.6)	3 (15.8)	
Study			
1 – Observational Study	54 (56.3)	8 (42.1)	0.441*
2 – 1st RCT	11 (11.5)	2 (10.5)	
3 – 2nd RCT	31 (32.3)	9 (47.4)	
Age (years)	66 (10.1)	65 (11.0)	0.772∞
Sex			
Male	53 (55.2)	12 (63.2)	0.523*
Female	43 (44.8)	7 (36.8)	
Ethnicity			
White/Caucasian	92 (95.8)	18 (94.7)	1.00 ~
Other	4 (4.0)	1 (5.3)	
Highest Level of Education			
Less than high school	24 (25.0)	7 (36.8)	0.404*
Graduated high school	26 (27.1)	4 (21.1)	
Some post-secondary	12 (12.5)	4 (21.1)	
Graduated university/college	31 (32.3)	2 (10.5)	
Not obtained/missing	3 (3.1)	2 (10.5)	
Employment Status			
Employed	39 (40.6)	6 (31.6)	0.561*
Unemployed/Disability/Retired	42 (42.7)	9 (47.4)	
Not obtained/missing	15 (15.6)	4 (21.1)	
Living Situation			
Alone	21 (21.9)	5 (26.3)	0.760~
With spouse/partner/others	59 (61.5)	11(57.9)	
Not obtained/missing	16 (16.6)	3 (15.8)	
NYHA Functional Classification			
Class I	68 (70.8)	13 (68.4)	1.00 ~
Class II	11 (11.5)	2 (10.5)	
Class III	4 (4.2)	1 (5.3)	
Class IV	0 (0.0)	0 (0.0)	
Not obtained/missing	13 (13.5)	3 (15.8)	
CCS Grading System of Angina Pectoris			
Class 0	78 (81.3)	16 (84.2)	0.727~
Class I	4 (4.2)	0 (0.0)	
Class II	0 (0.0)	0 (0.0)	
Class III	1 (1.0)	0 (0.0)	
Class IV	0 (0.0)	0 (0.0)	
Not obtained/missing	13 (13.5)	3 (15.8)	

*Pearson Chi-Square test | ~ Fisher's Exact test | ∞ Welch's t-test for independent means
Statistically significant values are **bolded.**

Appendix F: Alternative Analyses for Secondary Objectives

Table 27: Objective 2A – Analyses Using Listwise Deletion (n = 97)

Outcome	Target	Intake Mean (SD)	Exit Mean (SD)	Change Units (%)	P Value
METs	≥7.0	6.43 (2.8)	8.40 (3.1)	1.97	<0.001*
TC, mmol/L	<4.0	4.27 (1.2)	4.00 (1.1)	-0.27	0.006*
LDL-C, mmol/L	<2.0	2.22 (1.0)	2.01 (0.9)	-0.21	0.010
HDL-C mmol/L	>1.0	1.34 (0.4)	1.39 (0.4)	0.05	0.082
Non-HDL-C	<4.0	3.36 (1.0)	3.03 (0.9)	-0.33	<0.001*
TG, mmol/L	<1.8	1.56 (1.3)	1.32 (0.7)	-0.24	0.005*
FBG, mmol/L	<6.0	5.92 (1.6)	5.93 (1.3)	0.01	0.947
SBP, mm Hg	<140	132.82 (17.1)	130.96 (15.5)	-1.87	0.331
DBP, mm Hg	<90	79.02 (9.0)	76.28 (8.0)	-2.74	0.007*
WC, cm	Males <102; Females <88	101.58 (12.6)	99.03 (11.8)	-2.55	<0.001*
BMI, kg/m^2	<25	29.98 (4.9)	29.30 (4.7)	-0.68	<0.001*
Body weight, kg	n/a	84.38 (14.6)	82.48 (14.5)	-1.90	<0.001*

*****Statistically Significant

Table 28: Objective 2B – Analyses Using Listwise Deletion (n = 53)

Outcome	**Intake Mean (SD)**	**Exit Mean (SD)**	**Change Units**	**P Value**
HADS-D, points	3.53 (3.3)	2.17 (2.9)	-1.36	<0.001*
HADS-A, points	5.75 (3.6)	4.23 (3.3)	-1.52	<0.001*
HADS-T, points	9.28 (6.0)	6.40 (5.5)	-2.89	<0.001*
SF12 - MCS	50.33 (10.4)	54.7 (7.6)	4.34	<0.000*
SF12 - PCS	44.30 (9.18)	47.83(10.2)	3.52	0.011*
MMSE, points	28.26 (1.3)	28.49 (1.7)	0.23	0.376
NAART, corr	35.84 (11.2)	36.38 (11.3)	0.53	0.221
Dig-Fwd, raw points	8.28 (2.1)	8.43 (2.5)	0.15	0.575
Dig-Back, raw points	6.55 (2.4)	6.25 (2.6)	-0.30	0.231
Dig-Sym, raw points	45.77 (12.7)	49.53 (11.6)	3.76	<0.001*
Similarities	18.00 (5.1)	18.47 (5.6)	0.47	0.391
Trails-A, s	35.17 (17.6)	31.55 (12.1)	-3.62	0.026
Trails-B, s	87.00 (46.9)	83.58 (43.1)	-3.40	0.435
RAVLT, words; sum A1-5	43.13 (8.6)	47.28 (10.2)	4.15	<0.001*
A6	8.26 (2.9)	9.04 (3.4)	0.77	0.021
A7	8.09 (2.8)	9.28 (3.5)	1.19	<0.001*
Clock-drawing, points	3.19 (0.9)	3.09 (1.0)	-0.09	0.489
FAS-OVF, words	38.62 (10.7)	41.92 (12.9)	3.30	0.010

*****Statistically Significant

Appendix G: Curriculum Vitae

MELISSA MAJONI

EDUCATION

Western University | London, ON 2019
Master of Science
Epidemiology and Biostatistics Candidate
Thesis Title: The Relationship Between Exercise Training Adherence and Improvement in Functional Capacity Among Transient Ischemic Attack and Mild Non-disabling Stroke Survivors in Cardiac Rehabilitation
Supervisors: Dr. Saverio Stranges and Dr. Neville Suskin

University of Waterloo | Waterloo, ON 2017
Bachelor of Science
Major: Honours Health Studies
Specialization: Health Research Specialization
Thesis Title: Behaviours in Alzheimer's Disease and Health-Related Quality-of-life of Retired and Near-retired Caregivers
Supervisor: Dr. Mark Oremus

HONORS AND AWARDS

Western Graduate Research Scholarship ($4,200)	2017
Graduating Dean's Honours List	2017
RBC Retirement Research Undergraduate Fellowship ($2,200)	2016
Crawford and Company Sons and Daughters Scholarship Award ($10,000)	2013
University of Waterloo President's Scholarship ($2,000)	2013

RESEARCH EXPERIENCE

Graduate Research Assistant, Western University	2017 to 2019
Research Assistant, University of Waterloo	2016 to 2016
Research Assistant, University of Waterloo	2015 to 2016

ACADEMIC/TEACHING EXPERIENCE

Graduate Teaching Assistant, Western University	2019 to 2019
Marker, Western University	2018 to 2019
Teaching Assistant, University of Waterloo	2017 to 2017

SCHOLARLY PUBLICATIONS

MANUSCIPTS

1. **Majoni M**, Oremus M. Does being a retired or employed caregiver affect the association between behaviours in Alzheimer's disease and caregivers' health-related quality-of-life? BMC Res Notes. 2017 Dec;10(1).
2. Fernandes M, **Majoni M**, Garg AX, Dubois L. Systematic review and meta-analysis of preventative strategies for acute kidney injury in patients undergoing abdominal aortic aneurysm repair. [In Press].

PUBLISHED ABSTRACTS

1. **Majoni M**, Suskin N, Unsworth K, Stranges S, Prior P. Cardiac Rehabilitation as Secondary Prevention Among Survivors of Transient Ishaemic Attacks: A Pilot Randomized Controlled Trial. Can J Cardiol. 2018 Oct;34(10):S26.

PRESENTATIONS

ORAL PRESENTATIONS

1. **Majoni M**, Stranges S, Prior P, Klar N, Suskin N. Relationship Between Exercise Adherence and Functional Capacity Among Transient Ischemic Attack and Mild Non-Disabling Stroke Survivors in Cardiac Rehabilitation. Canadian Society for Epidemiology and Biostatistics Biennial National Conference, May 2019. Ottawa, ON, Canada.
2. **Majoni M,** Stranges S, Prior P, Klar N, Suskin N. Relationship Between Exercise Adherence and Functional Capacity Among Transient Ischemic Attack and Mild Non-Disabling Stroke Survivors in Cardiac Rehabilitation. London Health Research Day, April 2019. London, ON, Canada.
3. **Majoni M**, Suskin N, Unsworth K, Stranges S, Prior P. Cardiac Rehabilitation as Secondary Prevention Among Survivors of Transient Ischemic Attacks: A Pilot Randomized Controlled Trial. Canadian Cardiovascular Congress, Oct 2018. Toronto, ON, Canada.

POSTER PRESENTATIONS

1. **Majoni M**, Oremus M. Does being a retired or employed caregiver affect the association between behaviours in Alzheimer's disease and caregivers' health-related quality-of-life? Canadian Society for Epidemiology and Biostatistics Biennial National Conference, May 2017. Banff, AB, Canada.

GRADUATE COURSES

Analytic Epidemiology | Clinical Epidemiology | Clinical Trials | Foundations of Epidemiology | Health Services Research Methods | Multivariable Methods in Biostatistics | Principles of Biostatistics | Systematic Reviews | Meta-Analyses

PROFESSIONAL DEVELOPMENT

WORKSHOPS

- GIS Workshop: Introductory Geospatial Data Visualization for Health Research, May 2019
- SAS Intermediate Workshop, SAS Institute, Western University, November 2018
- Introduction to R, Department of Statistical & Actuarial Sciences, October 2017
- Intermediate R, Department of Statistical & Actuarial Sciences, October 2017