Assessing Prevalence and Predictors of Impaired Executive Functioning in Four-Year Stroke Survivors

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Abstract

Stroke is a cerebrovascular accident which may result in long-lasting consequences in the physical, emotional and cognitive wellbeing of a survivor's life. Impaired executive function (EF) is a common form of cognitive impairment following a stroke which often results in the inability to sustain attention, initiate action, control emotions and motor coordination. These types of deficits can significantly impact a stroke survivor's day-to-day living and quality of life. To date, there is a lack of data which examines the long-term effects of stroke on EF. The current study aimed to understand the predictors and prevalence of EF in four-year stroke survivors.

The current four-year follow-up study used a quantitative methodology. The sample (n=132) comprised of previously collected data, obtained from a sub-cohort drawn from a large population-based study, the fourth Auckland Regional Stroke Outcome Study (ARCOS-IV). Baseline data (at time of stroke or within two weeks) was obtained to examine factors which were associated with long-term impaired EF, four years following a stroke. EF was measured using the Comprehensive Trail Making Test (CTMT) at the four-year timepoint. A mean score of < 43 was indicative of impaired EF. Multivariate linear and logistic models were used to identify baseline predictors (reported as Odds Ratio [OR] with 95% confidence intervals [CI]) of impaired EF).

Four years after the stroke, nearly half (48.5%) of the stroke survivors experienced impaired EF (indicated by a score of <43 in the CTMT). Factors such as age, unemployment, a posterior circulation infarct (POCI), stroke in the non-frontal region, stroke in middle cerebral artery (MCA), having a history of previous stroke, history of hypertension, history of coronary artery disease, impaired baseline cognitive function (Montreal Cognitive Assessment [MoCA] scores ≤26) and lower quality of life (EuroQol Quality of Life Scale [EQ-5D] utility scores <0.50) were strongly associated with long-term impaired EF in stroke survivors. Multivariate logistic regression showed

that older age (≥75 years; OR=4.41, CI 1.03-18.86), having a history of hypertension (OR=2.78, CI 1.12-6.88) and impaired cognitive function (MoCA scores ≤ 26; OR=14.24, CI 24.40-84.47) at the baseline (time of stroke) were the significant predictors of impaired EF at four years post-stroke.

This study revealed the prevalence and predictors associated with long-term impaired EF post-stroke. The implication of these findings may be beneficial for clinicians in identifying individuals at the acute phase of stroke who may be at greater risk of having persistent impairment in EF. This information may also assist in informing suitable rehabilitation and treatment strategies for stroke survivors that specifically target EF. In turn, stroke survivors may benefit from improved outcomes such as better functional wellbeing and improved quality of life. Additional research examining the trajectory of EF is warranted in order to determine the natural course of EF within stroke populations.

Keywords: Stroke, Cognitive impairment, Impaired Executive Function, Prevalence, Predictors.

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Attestation of Authorship

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person (except where explicitly defined in the acknowledgements), nor material which to a substantial extent has been submitted for the award of any other degree or diploma of a university or other institution of higher learning.

D.Gopi	4.11.2019
Signature	Date

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Ethics Approval

Ethical approval was obtained from the Northern X Regional Ethics Committee of the Health and Disability Ethics Committee (HDEC) and Auckland University of Technology Ethics Committee (AUTEC) for the studies encompassed in this thesis.

HDEC approval (ref: NTX/10/09/090/AM07) was received on 24th April, 2014 (see Appendix A). AUTEC approval (ref: 11/297) was received on 13th May, 2014 (see Appendix B).

Chapter 1 Introduction

This chapter describes the prevalence of stroke and its economic impact in New Zealand (NZ). The chapter starts by clinically defining a stroke. It also provides an overview of the common disabilities experienced after a stroke, including cognitive impairment and, more specifically, impaired executive function (EF).

Overview of the Study

Stroke is caused when the blood supply to the brain is interrupted, leading to the deprivation of oxygen in the brain (Barton, 2012). Stroke is defined as a clinical condition with acute onset having focal or global cerebral disruption, and is caused predominantly by vascular risk factors; lasting for more than 24 hours, it has the potential to lead to mortality (World Health Organization, 1978). Depending on the nature of the interruption to the blood supply, strokes are classified into two types: ischaemic, in which the artery that supplies blood is obstructed, and haemorrhagic, where the rupture of a blood vessel leads to bleeding in and around the brain (Barton, 2012). Around 85% are ischaemic (Boehme, Esenwa, & Elkind, 2017) and while ischaemic strokes are more prevalent than haemorrhagic strokes, mortality rates for haemorrhagic strokes are considerably higher due to the severity with which it occurs (Andersen, Olsen, Dehlendorff, & Kammersgaard, 2009; Gonzalez-Perez, Gaist, Wallander, McFeat, & Garcia-Rodriguez, 2013; Katan & Luft, 2018).

Stroke is a major cause of disability and the second leading cause of death in adults globally (C. O. Johnson et al., 2019). Strokes affect around 15 million people per annum worldwide (Mozaffarian et al., 2016) with five million stroke survivors living with a post-stroke disability (World Stroke Organization, 2019), resulting in long-term disability in adults (Jankowska et al., 2017). The likelihood of a stroke occurring increases significantly with age; 70% of all strokes occur above the age of 65 (Katan & Luft, 2018; Kelly-Hayes, 2010). In NZ, stroke is the third most significant cause of

mortality and is a leading cause of disability (Hogan & Siddharth, 2018; Stroke Foundation of New Zealand, 2019). Currently, about 57,000 adults in NZ (1.5 % of the population) are living with the after-effects of a stroke (Ministry of Health, 2017). Overall there has been a decline in incidence and mortality rates across all ethnicities in NZ; however, Māori and Pasifika people are more prone to strokes compared to NZ Europeans (Ministry of Health, 2017). While some people may recover after having a stroke, others are prone to permanent disability or death (Ministry of Health, 2018).

For survivors, strokes can cause severe disabilities and negatively impact mobility, functionality (ŞahİN-Onat, Ünsal-DelİalİoğIu, Kulaklİ, & Özel, 2016), mood (Donnellan, Hickey, Hevey, & O'Neill, 2010; Willey Joshua et al., 2010), fatigue levels (Duncan, Wu, & Mead, 2012; Feigin et al., 2015), quality of life (Kreiter et al., 2013) and cognition (Gottesman & Hillis, 2010). These factors are significantly interrelated and can severely impact a patient's life (Ayerbe, Ayis, Crichton, Rudd, & Wolfe, 2015; Haghgoo, Pazuki, Hosseini, & Rassafiani, 2013). Of these factors, cognition plays a central role in orchestrating the day-to-day activities in a patient's life post-stroke (Adrian Wong & Mok, 2015).

Impaired cognition leads to functional and emotional disturbances in stroke survivors (Arsić et al., 2015; Barker-Collo, Feigin, Lawes, Parag, & Senior, 2010). Improvement in cognition post-stroke is also a significant predictor of recovery (Narasimhalu et al., 2011). Moreover, a baseline assessment of cognition soon after a stroke predicts functional and cognitive recovery after stroke (Champod et al., 2019). Strokes have a long-standing effect on patients' cognition (Hayes, Donnellan, & Stokes, 2013). Domains that are commonly affected a stroke includes memory, EF, language, attention, information processing speed and visuospatial function (Broome, Battle, Lawrence, Evans, & Dennis, 2016; Mahon, 2018); of these, the most commonly impaired domain post-stroke is EF (Conti, Sterr, Brucki, & Conforto, 2015; Y. H. Park

et al., 2015). EF includes functions such as problem-solving, decision making, emotional regulation, impulse control, creativity, dealing with complex tasks, and reasoning; these functions are quintessential, and dysfunction in any of the domains can cause difficulties in day-to-day functioning (Diamond, 2013; Lohner, Brookes, Hollocks, Morris, & Markus, 2017).

Around 15-70% of individuals after a stroke experience impaired EF (Leśniak, Bak, Czepiel, Seniów, & Członkowska, 2008; Pinter et al., 2019). Impaired EF reduces the chances of a stroke survivor regaining the ability to function independently (Barker-Collo, Feigin, Parag, et al., 2010; Barker-Collo et al., 2012). Recent research has identified that impaired EF can progress over the years post-stroke (Levine et al., 2018). One of the significant challenges is that, despite the prevalence of impaired EF post-stroke, not many studies have tried to identify the predictors of long-term impaired EF. In addition to this, there are very few population-based studies on long-term domain-specific impairment in stroke survivors (Barker-Collo, Feigin, Parag, et al., 2010). The current study is aimed at examining the prevalence of impaired EF in a cohort of four-year stroke survivors, the factors associated with long-term deficits in EF and the predictors of impaired EF.

To examine impaired EF in four-year stroke survivors, this study utilised the Comprehensive Trail Making Test (CTMT) which is suitable for measuring EF in patients with brain dysfunction (Reynolds, 2002). It is hoped that this work will generate a deeper understanding of the prevalence, associated factors, and predictors of impaired EF long-term post-stroke. This knowledge will guide clinicians in making suitable rehabilitation plans to reduce the degree of impaired EF after a stroke. The high likelihood of impaired EF post-stroke combined with the severe impact it has on a patient's daily life illustrates why it is crucial to identify deficits in EF for stroke survivors.

Chapter 2 Review of Literature

This chapter presents an in-depth literature review on the stroke epidemiology, pathophysiology, stroke-related risk factors, post-stroke cognitive and impaired EF. The chapter identifies existing gaps in the literature.

Epidemiology/ Prevalence and Incidence

Stroke is a leading cause of disability and mortality and causes a substantial financial burden in terms of post-stroke treatment (Rajsic et al., 2019). Global statistics show that 15 million people suffer from stroke every year, with a fatality incidence of approximately 5.8 million, and over 5 million people are disabled (World Stroke Organization, 2019). In NZ, around 9,000 people have a new episode of a stroke every year, with a mortality rate of 2,500 people per annum and approximately 57,000 surviving with its aftermath (Brown, AUT University Auckland/2009; Ministry of Health, 2017).

Nevertheless, stroke incidence and mortality rates are dropping worldwide. In a recent study, a decline of 8.1% was noted in the occurrence of stroke from the year 1990 to 2016; moreover, the global age-standardised disability in adjusted life-years and mortality rate were found to have declined by 36.2% and 34.2% respectively from 1990 to 2016 across all socio-demographic indices (C. O. Johnson et al., 2019). The Global Burden of Disease Study by Feigin, Forouzanfar, et al. (2014) found there was a drop in the mortality rates globally, with the rate of decline being more prominent in high-income countries (37%) than in low-income countries (20%). This trend was also noted in NZ, where there has been a decline in the rate of incidence by 12% over the last 30 years (Feigin et al., 2015). This decline, especially in developed countries, is due to the focus on controlling modifiable risk factors for stroke, better rehabilitation services, and improved treatment facilities. However, the global incidence of stroke is projected to increase due to the aging population (Feigin et al., 2016). The above studies highlight

how crucial it is to provide better rehabilitation and treatment facilities to reduce incidence of stroke.

Pathophysiology of Stroke

Though science has made remarkable advancements in cellular biology, the pathophysiology and neuroprotective mechanisms of stroke are still being studied (Chen, Balami, Esiri, Chen, & Buchan, 2010). It is known that stroke is a heterogeneous syndrome (Boehme et al., 2017) with three predominant pathological subtypes, namely ischaemia, intracerebral haemorrhage, and subarachnoid haemorrhage. Stroke also has various etiological subtypes such as cardioembolism, small vessel disease, large artery atherosclerosis, cryptogenic (stroke with no precise aetiology) and uncommon causes (Mehndiratta & Mehndiratta, 2018). An ischaemic stroke can occur due to thrombosis, embolism or global hypoperfusion (Hui, Patti, Kent, Gondal, & Rebedew, 2019). Studies indicate that ischaemia is determined in about 85% of stroke cases (Musuka, Wilton, Traboulsi, & Hill, 2015) and embolism is the most frequent cause, constituting 75% of the occlusions (Mergenthaler, Dirnagl, & Meisel, 2004). Contrary to the latter finding, earlier studies had identified that cardioembolic and arteroembolic subtypes together constitute only 50% of the causes whereas lacunar stroke is attributed to 25% of cases and the rest are caused by unknown factors (Ay et al., 2005).

Results from the Auckland Regional Community Stroke Study (ARCOS) III and IV, a prominent population-based study in NZ, showed most of the stroke cases fell into the ischaemic sub-type (81%), followed by intracerebral haemorrhage (5%) and subarachnoid haemorrhage (5%) (R. V. Krishnamurthi et al., 2018). The distribution of ischaemic stroke subtypes illustrates that cardioembolic stroke, small-vessel occlusion and large artery stroke contribute 29%, 21% and 15% of cases respectively (R. V. Krishnamurthi et al., 2018). The study also suggests that most stroke survivors fall into the undetermined subtype (31%) of ischaemic stroke. Similarly, the South London

Stroke Study explored the incidence of ischaemic stroke (n=1,181) based on the stroke aetiological subtypes. The results showed that cardioembolism and small-vessel occlusion were the most common aetiological subtypes of stroke with 27% of the total population in each group and a large percentage being of unknown aetiology (Hajat et al., 2011).

It is undisputed that stroke affects different levels of physiological functioning in an individual. The lack of oxygen and glucose delivery to the brain results in severe changes in brain metabolism leading to ischaemic biochemical cascade (Ankarcrona et al., 1995; Zazulia, Markham, & Powers, 2011). Irreversible changes are initiated with the disruption of cellular activities, followed by neuronal activities (William J. Powers, 2016). At a basic cell-based functioning level, functions such as preventing the bleeding (haemostasis) interrupt the flow of components in the circulating blood, brain cellular tissues (blood parenchyma) and blood vessels (Cheon, Kim, Kim, & Koo, 2018). A stroke infarct is characterised by cell death which may be an irreversible loss in the infarct core area and potentially a reversible loss of functionality in the hypoperfused penumbra (the area surrounding the event with reduced blood flow) (Astrup, 1982; Yuan, 2009). Research suggests that, at the functional level, stroke causes dysregulation such as vasomotor paralysis, inability to maintain the cerebral blood flow and alteration to the systems controlling blood circulation (Hoedt-Rasmussen et al., 1967; Kunz & Iadecola, 2009). The location, degree, severity, and duration of the infarct play a vital role in defining long-term functionality post-stroke (N. R. Sims & Muyderman, 2010).

Over the past decade, there have been significant advancements in understanding the underlying biological mechanisms of ischaemic strokes. Evidence from a variety of literature confirms that reduced blood flow to the brain areas triggered by ischaemia can modify the regular cellular functions (Hill et al., 2015; Prakash & Carmichael, 2015). When an ischaemic stroke occurs, there is a fall in the cerebral

blood flow (CBF), an increase in the oxygen extraction fraction levels along with simultaneous reperfusion and hypoperfusion within the initial hours (Hill et al., 2015). Ongoing hypoperfusion can lead to severe damage to the brain cells, resulting in profound disability or death. Moreover, reduced cerebral blood flow (<10mL 100/g/min), reduced blood volume (1.64ml/100 ml) (Marchal et al., 1999), hyper-hypo glycemia (1.1-2.2 mmol/L) (Eckert, Ryding, & Agardh, 1998; Tallroth, Ryding, & Agardh, 1992), and the lowering of regional oxygen cerebral metabolism (CMRO2) levels (0.87 to1.7mL 100/g/min) (Marchal et al., 1999; William J Powers, Grubb Jr, Darriet, & Raichle, 1985) to below the threshold can lead to irreversible damage to brain tissues within the 5–18 hours post-onset of ischaemic stroke (Marchal et al., 1999).

In comparison to ischaemic stroke, around 10-15% of the strokes are due to a haemorrhage (Beal, 2010; Norrving, 2014). Haemorrhage can result in hypoxia (lack of oxygen) due to the rupture of blood vessels, and increased intracranial pressure which leads to interruption of cerebral blood flow. Haemorrhagic strokes are classified into two categories based on the location of blood vessel rupture: intracerebral haemorrhage and subarachnoid haemorrhage (Barton, 2012). An intracerebral haemorrhage is caused by the rupture of a blood vessel and the seepage of blood into the brain tissues and occurs due to hypertension, amyloid angiopathy, vascular malformation, bleeding disorder, or the use of illegal drugs such as amphetamines or cocaine (Rossi & Cordonnier, 2014). Bleeding in the intracranial artery near the pia region is triggered by a rupture of an aneurysm (dilated artery), and this rupture is the common cause of a subarachnoid haemorrhage (Edjlali et al., 2015). The blood which is forced into the subarachnoid space creates a pressure which can cause symptoms such as headache, vomiting, stiffnesses in the neck area and a temporary loss of consciousness, and prolonged pressure can lead to severe brain damage (Nieuwkamp et al., 2009). The

internal bleeding is followed by a biochemical cascade of events which can cause reduced cerebral blood flow, cerebral perfusion pressure and increased intracranial pressure (Parra, 2015). This can lead to delayed vasospasm, a serious complication affecting around 70% of patients and ultimately resulting in severe disability or death (Parra, 2015). Thus, a haemorrhagic stroke is more likely to result in increased mortality, and reduced functional and cognitive outcomes, compared to ischaemic stroke (Perna & Temple, 2015).

Classification of Ischaemic Stroke

The classification of patients into stroke categories is ideally done to inform treatment, enhance the quality of treatment and improve the therapeutic decision-making process. These classification systems are based on the stroke size of the lesion, location, severity, aetiology and neurological symptoms post-stroke. There are two predominant schemes of classification used in classifying ischaemic stroke: the Trial of Org 10272 in Acute Treatment Subtype Classification (TOAST) (Adams et al., 1993) and the Oxford Community Stroke Project Classification (OCSP) (Bamford, Sandercock, Dennis, Burn, & Warlow, 1991)

The OCSP classification system is based on the initial symptoms of acute ischaemic stroke (Bamford et al., 1991). This simple classification system predicts the size and location of the brain infarct using computerised tomography (CT) or magnetic resonance imaging (MRI) and has previously been analysed to evaluate its accuracy (Kobayashi et al., 2009; Mead, Lewis, Wardlaw, Dennis, & Warlow, 2000; Wardlaw, Dennis, Lindley, Sellar, & Wadaw, 1996). Based on clinical syndromes, there are four subtypes: partial anterior circulation infarcts (PACI), total anterior circulation infarcts (TACI), lacunar infarcts (LACI) and posterior circulation infarcts (POCI) (Bamford et al., 1991).

The symptoms and extent of deficits differ with different subtypes. TACI is associated with a colossal cerebral infarction (Yang et al., 2016); studies have shown that TACI is associated with poor functional outcomes, quality of life, mortality and impaired cognitive performance (Barker-Collo et al., 2016; Paci, Nannetti, D'Ippolito, & Lombardi, 2011; Yang et al., 2016). PACI is involved with an occlusion in the middle cerebral artery (MCA) and anterior cerebral artery (ACA) and is a less severe form of TACI. Compared to anterior circulatory infarcts such as PACI and TACI, LACI and POCI are associated with higher survival rates, less damage, and lesser functional and cognitive disabilities (Barker-Collo et al., 2016; M. T. Smith & Baer, 1999). A major limitation of the OSCP classification is that it fails to address the specific arterial pathology or the aetiology of stroke (Amarenco, Bogousslavsky, Caplan, Donnan, & Hennerici, 2009). However, it helps in understanding the extent of deficits caused post-stroke and their prevalence, which in terms of the present study will give a better understanding of the extent of damage the current population has post-stroke.

Unlike the OSCP, TOAST classifies the ischaemic stroke into five subtypes based on the aetiologies and neuroanatomical characteristics (Adams et al., 1993). The categories consist of large artery atherosclerosis, small artery occlusion, cardio-embolism, other specified aetiologies and other unspecified aetiologies (Adams et al., 1993). Several studies have used this classification system, and recent studies using the TOAST classification have suggested that large artery disease is extremely common (30-60%) in patients with ischaemic stroke (Deleu et al., 2011; Harris et al., 2018; Porcello Marrone et al., 2013). The TOAST classification is useful in identifying aetiology (Hao, Xiao, & Wang, 2013; Kolominsky-Rabas Peter, Weber, Gefeller, Neundoerfer, & Heuschmann Peter, 2001; Shi et al., 2015).

Stroke Risk Factors

Risk factors constitute the factors associated with stroke pathology which are present before the onset of the first episode and could potentially increase the chances of a stroke episode. Taking appropriate steps to keep these factors in control could reduce the chances of a stroke occurrence (Lindgren, 2014). These factors can be classified into modifiable and non-modifiable risk factors.

Modifiable Risk Factors

Stroke is a preventable disease, and about 90% of stroke occurrences are attributed to modifiable risk factors (O'Donnell et al., 2016; O'Donnell et al., 2010; Yusuf et al., 2004) The 'INTERSTROKE' study, an international study with data from 32 countries, highlighted 10 modifiable risk factors associated with the onset of acute stroke: hypertension (high blood pressure), psychological stress, heart disease, ratio of apolipoprotein B to A1, waist-hip ratio, exercise, diet, diabetes mellitus, alcohol consumption, and smoking (O'Donnell et al., 2016).

Hypertension is the most common risk factor for stroke; it contributes to atherosclerosis which can result in ischaemic stroke (Chobanian et al., 2003; Endres, Heuschmann, Laufs, & Hakim, 2011). Hypertension causes immense strain over the blood vessels making them weak and prone to damage (World Heart Federation, 2017). Uncontrolled hypertension can increase the chances of a stroke occurrence five-fold (Vijayan & Reddy, 2016). In NZ, a 15% increase in hypertension has been noted over a span of 30 years, especially in Māori males between the ages of 34 and 75 (Feigin et al., 2015). Hypertension has been found to be very common in stroke survivors below the age of 54 years and is also a significant risk factor for those who are over the age of 60 (Feigin et al., 2015; Miller, Navar, Roubin, & Oparil, 2016). More than two-thirds of the stroke population aged above 65 years are hypertensive (Kobalava & Shavarova, 2017). This trend is due to the increased vascular and structural changes in the brain

with increasing age (Miller et al., 2016). Research has shown that treating hypertension has resulted in a remarkable reduction in stroke instance and mortality (Gaciong, Sinski, & Lewandowski, 2013; Lackland et al., 2014; Moser & Roccella, 2013).

Diabetes mellitus is another significant risk factor, whereby patients with diabetes mellitus are two times more at risk of having a stroke (Banerjee et al., 2012; Sui et al., 2011) and six times more prone to having an ischaemic stroke (R. C. Johnson & Schoeni, 2011). The Northern Manhattan Study found that diabetes mellitus increased the risk of stroke with a hazard ratio of 1.03 (95% CI, 1.02 to 1.04) (Banerjee et al., 2012). Diabetes mellitus increases the risk of having an ischaemic stroke by having degenerating effects on the arterial blood vessels (L. B. Goldstein et al., 2011; Idris, Thomson, & Sharma, 2006).

Migraine is also found to be a risk factor for stroke; however, there is often an interplay between other factors which complicates this relationship. For example, factors such as smoking and contraception increase the risk of migraine in patients with stroke (Kurth, Chabriat, & Bousser, 2012). Studies have shown that patients who suffer from migraine are more at risk compared with individuals who do not have migraine (Etminan, Takkouche, Isorna, & Samii, 2005). Women with migraine are more likely to suffer from an ischaemic stroke (Spector et al., 2010). Research suggests that this sex difference could be due to the fluctuation of hormonal levels, consumption of oral contraception or changes occurring during pregnancy (Allais et al., 2008; Katsarava, Rabe, & Diener, 2008). While the relationship between migraine and haemorrhagic stroke still remains unclear (Gaist, Gonzalez-Perez, Ashina, & Rodriguez, 2014), migraine increases the risk of having an ischaemic stroke due to cerebrovascular hypoperfusion caused by vasospasm, endothelial dysfunction, coagulation abnormalities or genetic factors (Lee, Lee, & Chung, 2016).

People who have a previous history of stroke are also at a higher risk of a recurrent stroke. Reports from the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial showed that 3.5% of stroke survivors with a mean age of 66 years reported a recurrent stroke (Sacco et al., 2008). Similarly, a history of prior or recurrent stroke, older age and lower education double the risk of dementia (Allan et al., 2011; S. T. Pendlebury & Rothwell, 2009). A recent longitudinal study showed that the risk of developing vascular dementia following a history of previous stroke or recurrent stroke is around 50% higher than those who did never had a stroke (Sarah T. Pendlebury & Rothwell, 2019). Preventing the incidence of the first stoke is very important and keeping the above-mentioned modifiable risk factors in check helps significantly to reduce the risk of stroke (Go et al., 2013).

Non-Modifiable Risk Factors

To date, several studies have observed increasing trends in non-modifiable risk factors of stroke such as increasing age (> 55 years), sex, genetic factors and ethnicity (Feigin & Krishnamurthi, 2014; Kelly-Hayes, 2010; Mozaffarian et al., 2016).

Stroke is considered to be the disease of ageing. It is the second leading cause of death for those who are aged 60 years and over (World Stroke Organization, 2019). Research suggests that there is a twofold increase in the incidence of stroke every decade after the age of 55 (Boehme et al., 2017). In terms of gender, results from the Framingham Stroke Risk Profile study showed that the lifetime risk for those who are aged over 56 are as high as one in every five for females and one in every six for males (Rodica et al., 2009; Seshadri et al., 2006). Contradicting to this finding, a study by Appelros, Stegmayr, and Terént (2010) found that the incidence of stroke is more common in men, but the severity of stroke was found to be higher in women. The increased possibility of having a stroke later in life and the social demands placed on women could be the reason for a poor functional outcome, increased severity and

reduced quality of life compared to men of the same age (Dyall et al., 2006; Mozaffarian et al., 2016).

Research suggests that genetic and familial risk factors also increased the risk of stroke. The Framingham Heart Study noted that experiencing a stroke by the age of 65 increased the risk of stroke for the children by three times (Seshadri et al., 2010). A meta-analytic study examining the wide-range genomic data association with ischaemic stroke reported that the genetic susceptibility to stroke differs by age and by sex (increased heritability in women with younger age) (Traylor et al., 2012).

Another major non-modifiable risk factor is ethnicity. African Americans are found to be at higher risk of developing stroke compared to Caucasians and at 1.2 times higher risk for intracranial haemorrhage (Kleindorfer et al., 2006). In NZ, the Māori and Pasifika populations are two to three times more at risk of ischaemic stroke and intra-haemorrhagic stroke in comparison with NZ Europeans (Feigin et al., 2006; Feigin, Krishnamurthi, Barber, & Arroll, 2014). Between 1981 and 2003, while there was a 19% decline in stroke incidence in NZ Europeans, there was an increase of about 19% and 96% in Māori and Pasifika populations respectively (Carter et al., 2006; McNaughton et al., 2011). Moreover, there is a 15 years age difference in the average age of onset of the stroke between the Māori (59.6 years) and Pasifika (61.6 years) groups compared to NZ Europeans (75.3 years) (Feigin et al., 2015). The increased frequency of vascular stroke risk factors (hypertension, diabetes mellitus and coronary heart disease) in Māori and Pasifika populations has significantly increased their risk of stroke (Feigin et al., 2015). Moreover, lower socio-economic status in Māori and Pasifika populations may be attenuating the ethnic differences (Ministry of Health, 2017). Though the factors contributing to this decline is still unknown, genetic and environmental elements have a major role in the increased incidence.

Cognition and Stroke

Cognition is a multifaceted concept which includes memory (retention, retrieval, and recognition of verbal and non-verbal information), visuospatial functioning (visuo-constructive abilities, visual scanning, drawing), language (receptive and expressive), attention (selective, divided, sustained and shifting) and EF (planning, decision making, organising, sensitivity to interference, inhibitory control) (Cumming, Marshall, & Lazar, 2013). Impaired cognitive function is the most common consequence of a stroke, and a decline in any specific cognitive domain is predictive of reduced functional well-being (Adrian Wong & Mok, 2015). The prevalence of cognitive impairment post-stroke is over 20% and remains persistently high even after five years post-stroke (Douiri, Rudd, & Wolfe, 2013). A study by Levine et al. (2015) showed that stroke is strongly associated with a sudden decline in cognitive function, which is observed to steadily accelerate over a span of six years. In addition, a four-year follow-up study in NZ showed that 84% of stroke survivors experienced post-stroke cognitive impairment affecting most of the domains of cognitive functioning, such as memory, attention, EF and information processing speed (Mahon, 2018).

Impaired EF and Stroke

EF is a complex cognitive process that has several subcomponents such as planning, attention, working memory, error detection, correction inhibition, anticipation, initiation, and self-monitoring (Shea-Shumsky, Schoeneberger, & Grigsby, 2019). It refers to the executive skills which enable an individual to behave in accordance with varying situations and act towards future goals by overruling the gratification of immediate need (S. Goldstein, Naglieri, Princiotta, & Otero, 2014).

Over the last few decades, EF has had many definitions provided by many researchers. Luria (1966) defined EF as the process of synthesising one's own action, which enables goal-oriented and purposive behaviour. Stuss and Benson (1984)

described EF as a broad term which consists of skills such as planning, decision making, working memory, goal-directed actions, initiation, and self-monitoring. Barkley (2011) proposed EF to be a self-motivated future-paced action that is intended to alter the outcome in a desirable manner. In short, EF is defined as the aggregate of higher-order skills and functioning which allows an individual to thrive in complex situations (Delis, 2012). Theories hypothesise EF as: (1) a *single system* – an injury to any single domain of EF can lead to impaired EF; (2) *construct led* – fluid intelligence and working memory are the most important domains of EF; and (3) *multiple processes* – day-to-day activities are managed by the optimum functioning of several components of EF, and each component can be studied individually (Burgess & Simons, 2009).

Impaired EF is the common cognitive deficit post-stroke, and impaired EF is reported in 19% to 75 % of the population after a stroke (Laino, 2010; Poulin, Korner-Bitensky, Dawson, & Bherer, 2012). For example, a large population-based study comprising of 2,050 stroke survivors, aged between 70 and 89, reported that impairment in attention and EF were more prominent compared to other cognitive functions (OR, 2.48; 95% CI, 1.73-3.53) (Knopman et al., 2009). Similarly, a study conducted by Sörös, Harnadek, Blake, Hachinski, and Chan (2015) found that EF was the most common cognitive dysfunction in stroke survivors, with nearly 40% of the population showing deficits in the Trail Making Test (TMT) Part B. These studies substantiate that impaired EF is a commonly reported cognitive dysfunction after a stroke.

Despite the prevalence of impaired EF post-stroke, not many studies have investigated the long-term prevalence of impaired EF in stroke survivors. A five-year follow-up study by Barker-Collo, Feigin, Parag, et al. (2010) stated that impaired EF is one of the most common cognitive deficits in long-term post-stroke. Long-term follow-up studies have shown that around 44% to 48% experienced impaired EF even after 12 years post-stroke; and long-term EF impairment is associated with shorter post-stroke

survival rates compared to those with no impaired EF (e.g., 5.8 versus 11.4 years) (Melkas et al., 2010; Oksala et al., 2009). Although a six-year follow-up study by Levine and colleagues (2018) noted a rapid decline in EF after each year post-stroke, this study does not describe the prevalence of long-term impaired EF. These studies point to the importance of monitoring EF to understand the prevalence and degree of impaired EF post-stroke.

Routine evaluation of impaired EF post-stroke is crucial in the stroke population. For example, a study conducted by Ownsworth and Shum (2008) underlined the importance of the periodic evaluation of EF to understand the productivity and employability of individuals post-stroke. The study was based on Lezaks's theory (Lezak, Howieson, & Loring, 1995) which focuses on the understanding of the degree of purposive behaviour and gauging the capacity for goal-directed behaviour. Twenty-seven stroke survivors with a mean age of 47 years were administered a battery of EF tests at 12-month follow-up to assess their level of employment and work productivity. Results showed that individuals' employment and work productivity after stroke was significantly associated with ability to plan, self-monitor and self-regulate (Ownsworth & Shum, 2008). These studies suggest the importance of the periodic evaluation of impaired EF post-stroke and this information can be used to plan EF-specific rehabilitation based on individual needs.

Assessment of EF

To understand the extent of impaired EF post-stroke, researchers have used several neuropsychological measures. A review conducted by Hayes et al. (2013) found TMT, Stroop Colour Word Test (SCWT), Digit Span test (DS), Wisconsin Card Sorting Test (WCST) and Verbal Fluency Test (VFT) to be the most common tests of EF in stroke populations. Similarly, a systematic review by Conti et al. (2015) identified the TMT, SCWT and DS as the most commonly used tests of impaired EF.

TMT is the most popularly used test of EF in individuals with brain damage (Karimpoor et al., 2017) and this could be due to its ease of administration, sensitivity to brain dysfunction and high validity. TMT was first used in the US Army Individual Test Battery in 1944 (Lezak et al., 1995) and was later integrated into various clinical studies and practice due to its sensitivity to brain dysfunction (Rabin, Barr, & Burton, 2005). TMT has two components; Trail A and Trail B. Trail A (TMT A) measures sustained attention and processing speed, whereas Trail B (TMT B) measures divided attention, cognitive set-shifting, cognitive flexibility, working memory and selective attention. For the successful completion of TMT, participants require multifaceted skills such as visual scanning, attention and motor scanning, which makes the test sensitive to identifying brain damage Lezak et al. (1995).

Studies have demonstrated that TMT is capable of assessing EF in stroke survivors, and is a popular test in measuring attention, set-shifting, and information processing speed (Muir et al., 2015). Sörös et al. (2015) illustrated this point clearly by showing that, post-stroke, 40% of the participants had impaired TMT B scores and 31% had impaired TMT A score, indicating deficits in speed of processing, inability to process complex information and cognitive flexibility; by contrast, the Mini-Mental State Examination (MMSE) results noted only 5% impaired EF. In addition to this, a study by Jaywant, Toglia, Gunning, and O'Dell (2018) showed that impaired information processing was identified by TMT B which the Montreal Cognitive Assessment (MoCA) scores failed to detect. These studies have shown the sensitivity of TMT in identifying impaired EF compared to other tools.

Several different trail making tests have been developed since the TMT, for example, the Delis-Kaplan Executive Function System (DKEFS) Trail Test, Connection Trail, and the Comprehensive Trail Making Test (CTMT) (Mayfield, 2017). CTMT is the most recent and comprehensive tool, consisting of five trail tests with increasing

difficulty from Trail 1 to Trail 5 (Reynolds, 2002). Trail 1 is similar to TMT A and measures sustained attention; Trail 2 and Trail 3 measure resistance to distraction, inhibitory control, attentional demands and visual search; Trail 4 measures cognitive set-shifting, working memory and cognitive flexibility; and Trail 5 is similar to TMT B and measures cognitive set-shifting and divided attention (Reynolds, 2002). CTMT Trails 1–3 are called simple sequencing and Trails 4–5 are called complex sequencing (Reynolds, 2002).

CTMT has an extensive normative data for age ranging from 8 years to 74 years and is standardised for clinical and non-clinical populations (Allen, Haderlie, Kazakov, & Mayfield, 2009; Reynolds, 2002). CTMT has robust information on its reliability and validity, and high sensitivity and specificity in diagnosing brain dysfunctions (Armstrong, Allen, Donohue, & Mayfield, 2008; S. R. Smith et al., 2008). During the standardisation process, 28 adults with cerebrovascular accident (CVA) were examined, and the composite index scores (33) were two standard deviations below the mean (Reynolds, 2002). In addition, CTMT was found to have high sensitivity and specificity, in children with TBI (Allen, Thaler, Ringdah, Barney, & Mayfield, 2012; Armstrong et al., 2008).

Although CTMT was standardised in patients with CVA, only a handful of studies have used CTMT to understand the extent of EF post-stroke. In a recent study conducted to understand the short-term cognitive changes in ischaemic stroke (N= 114), CTMT was used to understand the extent of EF and attention deficits (Pinter et al., 2019). The results showed that, at baseline, 46.6% of participants had deficits in attention and 49.5% of participants had deficits in EF; three months post-stroke, a slight improvement in test performance in participants was noted with deficits in attention and EF noted in 30% and 35% of the participants respectively (Pinter et al., 2019). However, the major limitation of the study was that only two CTMT trails (Trail 2 and

Trail 5) were used for this study. Additionally, EF index ratio measuring executive control is usually calculated as the performance of Trail 5/Trail 1 (Arbuthnott & Frank, 2000) but the study by Pinter and colleagues (2019) calculated EF ratio as Trail 2/Trail 5 which does not necessarily give a conclusive result.

A case study used CTMT along with other cognitive tests (such as WCST, SCWT, the Executive Control Battery, the Tower of London Executive Function Test [TLEFT], the Boston Naming Test, Rey's Complex Figure Test [RCFT], and the Rey Auditory Verbal Learning Test [RAVLT]) to evaluate the degree of cognitive deficits following an isolated brain stem stroke (Hoffmann & Malek, 2005). However, the extent of cognitive deficits, the severity of impairment in EF or psychometric data for CTMT were not reported in this study. Therefore, limited sample size and lack of psychometric data in CTMT post-stroke are the major limitations of existing studies.

A recent study was conducted to understand the neurocognitive behaviour of the children with brain dysfunction (N=98) using CTMT and the results showed that the performance of simple and complex sequencing was predicted by motor functions and information processing speed (Mayfield, 2017). Performance in complex sequencing was also predicted by the motor functioning, working memory and information processing speed. However, this study only comprised of a small sample size of participants with stroke (N= 10), and for this reason, these findings have to be interpreted with caution.

To conclude, CTMT has been demonstrated to have strong reliability and validity in stroke. In a sample of elderly stroke survivors, the internal consistency estimate was found to meet or exceed 0.80 (Reynolds, 2002). CTMT was also found to have high sensitivity (0.74) and specificity (0.82), good construct and criterion validity, and classification accuracy (79%) in understanding brain dysfunction in children (Allen et al., 2012). Despite its high utility, specificity, validity supported by external studies in

brain dysfunction, there is a lack of research which has used CTMT in stroke populations. From the review, it is evident that CTMT is sensitive to stroke and brain dysfunction. But, despite the appropriateness of CTMT, limited studies have used CTMT as a measure of EF in the post-stroke population.

Risk Factors and Predictors of Impaired EF

Previous research illustrating the relationship between impaired EF in stroke survivors and sociodemographic characteristics (age, sex, education, employment, ethnicity, marital status), stroke-related characteristics (stroke type, OCSP classification, stroke lateralisation, stroke location, vascular territory, stroke region, and previous stroke) and vascular risk factors (hypertension, diabetes, coronary artery disease, peripheral vascular disease, epilepsy and migraine) are reviewed in the following sections.

Association between Sociodemographic Factors and Impaired EF

Research suggests that elderly stroke survivors with impaired EF were three times more likely to be not working (retired) compared to those who do not have impaired EF (Kim et al., 2011). Older stroke survivors (mean age = 74) with lower academic qualifications (< 6 years of education) were found to have impaired EF post-stroke (Pohjasvaara et al., 2002; Risto Vataja et al., 2005). A six-year follow-up study by Levine and colleagues (2018) found that older stroke survivors (> 75 years) with lower educational qualifications (< high school) are more likely to have impaired EF (measured by the animal fluency test [AFT]) post-stroke compared to stroke survivors who did not have impaired EF. Studies have found that impaired EF is more prevalent in men than in women after a stroke or brain injury; this may be attributed to lower educational qualifications and premorbid functioning of men compared to women of the same age (Hua et al., 2014; Levine et al., 2018; Niemeier, Marwitz, Lesher, Walker, & Bushnik, 2007). Of note is a recent study which has shown that stroke survivors who are

not working have higher levels of impaired EF compared to those who are working (Alex Wong et al., 2019).

A five-year follow-up study on stroke survivors by Feigin and colleagues (2010) showed that ethnicity was found to be associated with impaired EF. For example, EF deficits were more prevalent in non-European compared to NZ European stroke survivors. Additionally, participants of European ancestry were found to perform better than Māori participants when completing the Trail Making Test – Task A (TMT-A) (Barker-Collo, Feigin, Parag, et al., 2010). Despite the association between the prevalence of impaired EF and different socio-economic characteristics, very few longitudinal studies have explored the relationship between sociodemographic characteristics and impaired EF post-stroke.

Association between Stroke-Related Characteristics and Impaired EF

The relationship between impaired EF in stroke survivors and stroke-related characteristics, such as stroke type (ischaemic or haemorrhagic), OCSP classification, stroke lateralisation, stroke location (frontal and non-frontal), vascular territory, stroke region (cortical or subcortical), is reviewed in this section.

Research has shown that the decline in EF following ischaemic and haemorrhagic stroke was similar, but the differences between the two types of stroke were not statistically significant (Levine et al., 2015). Not only the stroke type but also the location of the infarct is associated with impaired EF. According to a five-year post-stroke study in NZ using OCSP classification, EF was the most impaired domain after an ischaemic stroke, and total anterior circulation infarct (TACI) was more strongly associated with the poor performance on tests of EF (TMT A) than all other subtypes of stroke (Barker-Collo et al., 2012). Another five-year follow-up study (n= 121) conducted by Benjamin et al. (2018) have suggested that lacunar infarcts (LACI) were

significantly associated with impaired EF, information processing speed, and global cognitive function.

In the case of hemisphere lateralisation, some studies have argued that left hemisphere damage is more predictive of impaired EF (measured by WCST, SCWT, TMT) than right hemisphere damage in patients with stroke (Nys et al., 2007; R. Vataja et al., 2003), while other studies have suggested that right-hemisphere lesion is more associated with impaired EF (especially in the visuospatial and perceptual tasks of EF) (Lezak, Howieson, Bigler, & Tranel, 2012; Spaccavento et al., 2019). Furthermore, compared to single stroke and no-stroke patients, patients with recurrent stroke had a significant decline in attention, speed, and EF. Recurrence of stroke was also seen to be related to the occurrence of dementia (Srikanth, Quinn, Donnan, Saling, & Thrift, 2006).

EF is often considered to be a frontal lobe mediated function and damage to the frontal lobe is believed to lead to impaired EF. The seminal brain lesion studies by Luria (1966) suggested damage to the frontal lobes led to a 'loss of critical faculty' (i.e. inability to evaluate behaviours and plan actions) causing EF deficits. While some studies have argued that EF is based on the functioning of the frontal lobe (Scheffer et al., 2016; Schiavon, Viola, & Grassi-Oliveira, 2012), others are of the opinion that there are multiple networks, tracts and brain areas that are involved in higher-order functioning such as decision making, problem-solving, attention, and planning (Kolb & Whishaw, 2009). This may be the reason the term "dysexecutive syndrome" has gained popularity more recently, in preference over "frontal syndrome" (Jodzio & Biechowska, 2010).

There is a growing body of evidence which demonstrates that both frontal and non-frontal areas are affected post-stroke. For example, a study conducted by Leskelä et al. (1999) found impairment in EF in both frontal and non-frontal post-stroke groups.

Patients with frontal stroke performed less well than a non-frontal stroke group in tasks involving processing speed (measured by DS, SCWT, TMT A); however, in tasks involving decision making and judgment (WCST), both frontal and non-frontal stroke participants were equally impaired (Leskelä et al., 1999). In contradiction to these findings, there are studies which show that frontal lobe lesions need not necessarily indicate executive dysfunction in stroke patients (Tang et al., 2009). Results from a study conducted by Long et al. (2010) found that children with frontal lobe lesions post-stroke were found to be better at every day EF than children with non-frontal lesions. Similarly, another study has found that extra-frontal lesions (temporal lobe, parietal lobe, cerebellum and subcortical structures) causes impaired EF by having an effect on the attentional networks and inhibitory control (as measured by WCST, Behavioural Assessment of Dysexecutive Syndrome [BADS], Five Digit Test, Go/No-Go Task, and Delay Discounting Task) (Scheffer et al., 2016). These studies emphasise the potential influence of non-frontal areas in EF and, therefore, more research needs to be conducted to investigate its role in impaired EF.

Stroke-related vascular territories are also associated with impaired EF. A study investigating cognitive profiles and their relationship with stroke factors showed that patients with MCA were more likely to have impairments in EF, visuospatial functional and language compared to other vascular territories (W. Zhang, Yun, & Yining, 2014). In addition to this, a longitudinal neuropsychological case study illustrated that MCA infarctions are accompanied by inattention and impaired EF (as measured by MoCA and Wechsler Adults Intelligence Scale [WAIS]) (Shatzman, Mahajan, & Sundararajan, 2016). A relatively recent study on patients with posterior cerebral artery (PCA) stroke showed impaired EF (as measured by DS, SCWT, and phonemic fluency test); impaired EF was also prominent following a lesion in the ventral temporal lobe (fusiform gyrus and parahippocampus) and splenium (K.-C. Park, Yoon, & Rhee, 2011). Although

studies have stated that both cortical and subcortical lesions cause impaired EF (Saczynski et al., 2009), studies have also shown that subcortical lesion alone can lead to impaired EF (Cumming et al., 2013; R. Vataja et al., 2003). In addition, pre-existing white matter lesion is a predictor of EF in the normal elderly population (Carey et al., 2008) and is strongly associated with EF in patients with brain injury (Chuang et al., 2014; Tullberg et al., 2004).

Association between Vascular Risk Factors and Impaired EF

Vascular characteristics are also associated with EF post-stroke. Hypertension, diabetes, coronary artery disease, peripheral vascular disease, epilepsy and migraine are some of the vascular risk factors which are strongly associated with post-stroke impaired cognition and potentially impaired EF (Iadecola & Gottesman, 2019; Lo et al., 2017).

Hypertension is one of the prominent risk factors for impaired cognitive function post-stroke (Lo et al., 2017; Sahathevan, Brodtmann, & Donnan, 2012; Walker, Power, & Gottesman, 2017). Additionally, studies have shown that impaired EF is the most commonly reported cognitive deficit in hypertensive patients following a brain injury (Gąsecki, Kwarciany, Nyka, & Narkiewicz, 2013; He, Du, Ma, Zhang, & Hao, 2017). Several lines of evidence have suggested the prevalence of impaired EF in hypertensive patients (Kim et al., 2011; Vicario, Martinez, Baretto, Casale, & Nicolosi, 2005). Research has suggested that impaired EF could be a consequence of the disruption of blood flow and vascular damage (white matter as well as frontal lobe lesions) triggered by hypertension (Chuang et al., 2014; Iadecola & Gottesman, 2019; X. Li et al., 2015; Sizova et al., 2018; Suzuki et al., 2017; Witkowska et al., 2019). Surprisingly, a study investigating the relationship between hypertension and impaired EF post-stroke noted that people without hypertension had a faster decline in EF over six years (Levine et al., 2018). Despite the prevalence of impaired EF, very few longitudinal studies have

investigated the relationship between impaired EF and hypertension post-stroke in the long term.

According to a four-year follow-up study, diabetes mellitus was found to be associated with the decline in EF (Van den Berg et al., 2010); however, the possible relationship between EF and the combined diagnosis of stroke and diabetes has not been explored in-depth (Kluding, Tseng, & Billinger, 2011). Similarly, a history of coronary artery disease is strongly associated with impaired EF (as measured by TMT, SCWT, and the Controlled Oral Word Association Test [COWAT]); but there is a lack of post-stroke studies illustrating the long-term association between these variables (Burkauskas et al., 2018; Mohammad et al., 2019). The potential explanation is the white matter lesion, brain infarct, hippocampal and cortical grey matter reduction which is associated with the coronary heart disease could lead to impaired EF (M. Zhang, Lange, Chang, Sawchuk, & Rizzo, 2012). Although the association between impaired post-stroke cognition and other vascular variables, such as cholesterol, peripheral vascular disease, epilepsy and migraine, has been previously studied (Alexandrova & Danovska, 2016; Cordonnier, Hénon, Derambure, Pasquier, & Leys, 2007; Lu et al., 2016; Rist & Kurth, 2013; Sahathevan et al., 2012), not many studies have explored the relationship between these variables and impaired EF in long-term stroke survivors.

To summarise, the evidence from the literature suggests that some of the sociodemographic factors, stroke-related characteristics, and stroke-related risk factors are associated with EF after a stroke. However, not many studies have been conducted to understand what predicts EF post-stroke, and there are very few longitudinal studies exploring the same.

EF and Stroke-Related Outcome Measures

Impaired EF can impose a significant toll on individuals' functionality post-stroke, and its coexistence with conditions such as depression (Bour, Rasquin, Limburg,

& Verhey, 2011; Melkas et al., 2010; Narushima, Paradiso, Moser, Jorge, & Robinson, 2007; Sobreiro et al., 2014), impairments in motor functioning (Hayes et al., 2013; Kluding et al., 2011; Liu-Ambrose & Eng, 2015; Rand, Eng, Liu-Ambrose, & Tawashy, 2010), and ability to drive (Motta, Lee, & Falkmer, 2014) lead to reduced quality of life. The cognitive decline along with severe impaired EF increases the risk of dementia (Clark et al., 2009) and reduced functional well-being (Ankolekar et al., 2014) which may result in dependent living. Furthermore, the ability to adapt to a new environment is particularly difficult for stroke survivors, especially with an impaired EF (Conti et al., 2015). The relationship between long-term impaired EF and stroke-related outcomes, such as cognition, functional wellbeing, mood, fatigue, degree of disability and quality of life, are reviewed in this section.

Baseline Cognition

Studies have previously shown that impaired cognition in the acute phase post-stroke is predictive of long-term cognitive impairment (Mahon, 2018; Nys et al., 2007; Nys et al., 2005). Similarly, long-term follow-up studies have noted the consistent decline of impaired cognition over increasing years post-stroke, and the decline is prominent in the domain of EF (Barker-Collo, Feigin, Parag, et al., 2010; Levine et al., 2015). In addition to this, recent studies have shown that impaired cognition at the baseline is associated with long-term impaired EF after stroke (measured using TMT-B and the Digit Symbol Substitution Test [DSST]) (Delavaran et al., 2017; Douven et al., 2018). A study by Kapoor and colleagues (2019) explained the relationship between impaired baseline cognition, impaired EF and functional recovery after stroke. The study found that impaired baseline cognition was associated with reduced functional recovery; and impaired EF (as measured by COWAT, TMT, DS) was strongly associated with lower functional independence post-stroke (Kapoor et al., 2019). Although many long-term studies have focused on baseline cognition and long-term

impaired cognition, there have not been many longitudinal studies that have explored the predictive relationship between impaired baseline cognition and long-term impaired EF post-stroke.

Functional Recovery and Level of Independence

Functional wellbeing and level of independence are understandably compromised in patients who have survived stroke. EF is a reliable indicator of functional prognosis following stroke (Nys et al., 2005) and has been demonstrated to be a reliable indicator for long-standing improvement (S. H. Park, Sohn, Jee, & Yang, 2017). Results from a follow-up study on 80 stroke patients by Leśniak et al. (2008) indicated that older age, low score in the tests of functional recovery (as measured by the Barthel Index [BI]) and impaired EF predicted poor functional outcome. Similarly, a one-year follow-up study conducted by Park and colleagues (2017) in subacute stroke patients (n=104) found that 83% had post-stroke impaired EF which was significantly associated with reduced functional outcome. The authors reported that those patients with impaired EF (60.5%) were more likely to have a longer duration of hospital stay compared to those with no impaired EF. In addition, a recent follow-up study of patients with subacute stroke (n=50) reported that EF deficits were significantly associated with functional dependence in day-to-day activities, one year post-stroke (Lipskaya-Velikovsky, Rozental-Iluz, Rand, Zeilig, & Weingarden, 2018). These studies highlight the importance of monitoring impaired EF over time in stroke survivors.

A recent study on 182 acute stroke survivors by Y. H. Park et al. (2015) confirmed that EF is a potential predictor for the improvement of post-stroke disability. A large-sample five-year follow-up study on healthy elderly participants also supports the long-standing effects of EF on functional wellbeing (Willis et al., 2006). While deficits in global cognitive function and domains such as memory, language, visuospatial abilities have a significant relationship with and affect functional

improvement, EF is the strongest predictor of functional well-being (Y. H. Park et al., 2015). The importance of EF, which is a valuable determinant in understanding subjective well-being, is often undervalued in clinical research (Toh, Yang, & Hartanto, 2019). In short, EF plays a vital role in functional recovery, but little is known about whether lower functional recovery predicts long-term impairment in EF.

Mood

Anxiety and depression are the most common conditions post-stroke. However, post-stroke depression is well researched when compared to post-stroke anxiety, which has received little attention (Hackett, Yang, Anderson, Horrocks, & House, 2010). A Cochrane systematic review stated 20% of post-stroke survivors experienced notable levels of anxiety (Knapp et al., 2017). Female stroke survivors below the age of 65, with a history of depression and after experiencing severe strokes, were at a higher risk of developing anxiety (Ayerbe, Ayis, Rudd, Heuschmann, & Wolfe, 2011). Some studies have shown that post-stroke anxiety is not associated with impaired cognitive function (Ferro, Caeiro, & Santos, 2009; Shimoda & Robinson, 1998). In the same vein, results from the South London Stroke Register study showed that anxiety did not predict impairment in cognitive function even up to ten years post-stroke (Ayerbe et al., 2011). From the above, it is evident that not many studies have analysed the relationship between anxiety and EF post-stroke, and future studies are needed to understand this relationship.

The relationship between EF and depression post-stroke is well-established. Depression is common stroke survivors, with up to 75% of them suffering from depression (Taylor-Piliae, Hepworth, & Coull, 2013). Impaired EF usually coexists with depression and is a significant predictor of post-stroke depression (Terroni et al., 2012). The classic characteristics of vascular depression (a subtype of late-life depression, associated with a CVA) is the markedly impaired EF characterised by reduced

sequencing, planning, organising, initiation, coordination of complex goal-directed behaviour and management of day-to-day activities (Butters et al., 2000; Nebes et al., 2000), especially in the geriatric population (Lockwood, Alexopoulos, & van Gorp, 2002; Melkas et al., 2010). A review by Conti et al. (2015) claimed that this partnership between impaired EF and depression often leads to a poor functional outcome post-stroke.

Longitudinal studies have been conducted on stroke survivors to understand the relationship between depression and impaired EF. A 12-year follow-up study by Melkas et al. (2010) found that impaired EF is a reliable and strong predictor of depression, post-stroke survival and poor outcomes in general. A Finland based 12-year follow-up study on patients with ischaemic stroke revealed that depressed patients have a shorter span for the recurrence of stroke; but, at the same time, patients with both impaired EF and depression have an even shorter span of stroke recurrence compared to those who were not depressed (Sibolt et al., 2013). This study also showed that patients with depression-executive dysfunction (DES) were much older compared to the patients who did not have DES.

Taken together, these studies suggest that impaired EF is strongly related to depression and functional disability, especially in the elderly population. However, most of the studies evaluating impaired EF excluded participants with post-stroke depression (Sundar & Adwani, 2010). Another gap in the current understanding of depression and impaired EF in stroke survivors is whether depression can predict impaired EF in long-term stroke survivors.

Fatigue

Post-stroke fatigue (PSF) is common in stroke survivors and has a strong association with impaired EF (Hubacher et al., 2012). It is one of the frequently stated and debilitating difficulties experienced after stroke (Ozyemisci-Taskiran, Batur,

Yuksel, Cengiz, & Karatas, 2019). Previous studies have claimed that fatigue is related to impaired EF skills such as reduced attention span, impaired planning, organising, complex tasks and functional dependence (Joyce, Blumenthal, & Wessely, 1996; Patel, Coshall, Rudd, & Wolfe, 2002). In a study by Pihlaja, Uimonen, Mustanoja, Tatlisumak, and Poutiainen (2014), patients with PSF had decreased information processing speed and PSF was also found to be associated with increased depressive symptoms and reduced work performance.

A study by Radman et al. (2012) showed similar results wherein stroke survivors with fatigue have critically low alertness, impaired EF, and higher levels of anxiety and depression compared to those who did not experience fatigue; and this trend continued at both six months and one year post-stroke. In contrast, some studies have stated that there is no relationship between PSF and impaired EF (Schepers, Visser-Meily, Ketelaar, & Lindeman, 2006). Nevertheless, recent studies have suggested that PSF affects different components of EF, and its effects can even last up to 10 years post-stroke (Maaijwee et al., 2015; Pihlaja et al., 2014).

From the studies analysed above, it is apparent that fatigue affects different facets of EF and daily functioning post-stroke. However, only a few studies have been conducted to evaluate the relationship between PSF and EF (Ponchel, Bombois, Bordet, & Hénon, 2015). The direction of causality of PSF with cognitive impairment is still debatable (Choi-Kwon & Kim, 2011). Finally, it is essential to demarcate the effects of PSF from depression (Johansson & Rönnbäck, 2012) to understand how cognitive fatigue predicts impaired EF. Despite the prevalence of PSF, it is understudied and not well researched in neurological disorders (Penner & Paul, 2017).

Degree of Disability

Evidence suggests that stroke causes severe disability, and over half of stroke survivors are either functionally dependent or disabled (Royal College of Physicians,

2011). Several studies have argued that disability, handicap and health-related quality of life are associated with impaired EF (Barker-Collo, Feigin, Parag, et al., 2010; Barker-Collo et al., 2012). For example, results from the long-term Helsinki Stroke Aging Memory study showed that impaired EF (5.8 vs 10.1 years, $p<0.0001$) and a poor modified Rankin Scale (mRS) score (3.9 vs 9.7 years, $p<0.0001$) are factors predictive of disability and reduced survival after an episode of stroke (Oksala et al., 2009). A 21-year follow-up study on post-stroke participants showed impaired inhibition control was strongly associated with risk of the early institutionalisation of stroke survivors (as measured by mRS and Instrumental Activities of Daily Living (IADL) (Laakso et al., 2019).

In contrast to the studies presented above, though around 60% of the post-stroke population experience disability (mRS scores ≥ 3), no association was found between functional disability and impaired EF (Ojagbemi & Owolabi, 2013). The results could be due to the good cognitive recovery in participants over two years post-stroke. Collectively, these studies provide a critical evaluation of the possible factors that explain the association between EF and degree of disability.

Quality of Life

Quality of life is recognised to be one of the most critical outcomes in almost all health conditions (Megari, 2013). After a stroke, the quality of life of a survivor is usually compromised due to the degree of functional disability, stroke severity, emotional well-being, cognitive deficits and health-related outcomes (Katona, Schmidt, Schupp, & Graessel, 2015; Ramos-Lima, Brasileiro, Lima, & Braga-Neto, 2018). Cognitive deficits, specifically impaired EF, are significantly associated with the quality of life; impaired EF also determines a person's ability to return to work (Conti et al., 2015). Since impaired EF leads to depression, motor impairments and disability (Liu-Ambrose & Eng, 2015; Rand et al., 2010; Sobreiro et al., 2014) after a stroke, these

factors automatically may worsen a patient's quality of life (Carvalho-Pinto & Faria, 2016; Terrill, Schwartz, & Belagaje, 2018) .

Previous research findings have suggested that impaired EF is associated with reduced quality of life, and this has the potential to impact other cognitive functions (Crawford & Henry, 2005; Leśniak et al., 2008). A London-based study examined this trend and results showed that improved health-related quality of life is contributed to by high EF, lower stress level, higher self-esteem and lower stroke severity (O'Keeffe, Ganesan, King, & Murphy, 2012). Similarly, a study conducted on stroke survivors demonstrated that impaired EF was linked to reduced functional well-being, mood, and weakness in upper and lower limbs (Theeke et al., 2014). The evidence reviewed shows that there is a clear association between impaired EF, reduced quality of life and well-being post-stroke.

Identifying the Gaps in the Literature

The major limitation of most of the studies reviewed in this chapter is that results did not examine the long-term predictors of impaired EF. Other studies focused on evaluating the predictability of the effect of impaired EF on the functional wellbeing, mood, quality of life, and fatigue after a stroke, but very few studies focus on understanding what factors predict EF post-stroke. Another important question which needs to be answered is whether factors such as sociodemographic characteristics, stroke-related characteristics, vascular risk factors, and physical and psychological condition post-stroke continue to be a significant independent predictor of impaired EF in the presence of multiple predictors (Y. H. Park et al., 2015). Although there are studies showing the association between cognitive functioning and impaired EF in patients with stroke, not many studies have explored the longitudinal relationship (Counsell & Dennis, 2001). Moreover, very few longitudinal studies have explored the relationship between impaired EF and outcome measures; and not many have explored

the factors that predict long-term impaired EF in stroke survivors. These findings demonstrate that further studies are warranted to understand the predictors of long-term impaired EF.

Some authors claim that the authenticity of the early evaluation of physical and psychological factors post-stroke, especially of cognitive variables, must be treated with caution as the acute effects of stroke can impact these measures; while others are of the opinion that these early evaluations are robust and valid predictors of long-term cognitive status (Larson et al., 2003; Patel et al., 2002; Tatemichi et al., 1994; van Zandvoort, Kessels, Nys, de Haan, & Kappelle, 2005). The current study has used an early evaluation of the stroke-related physical and psychological factors post-stroke to understand their effects on long-term post-stroke status. Since EF is the seat of high-order complex functioning, identifying its predictors would help in future rehabilitation measures focusing on cognitive, functional and psychological rehabilitation processes which would enhance the activities of daily living, functional recovery, mood and the quality of life of a stroke survivor.

Conclusion

To summarise, there are several factors which influence EF in patients after a stroke. Rarely do these factors seem to have a stand-alone influence on EF. As seen from the review of the literature, these factors tend to have a compounded effect on EF by their interplay with each other. Thus, understanding these factors is vital in making informed decisions, and in formulating rehabilitation strategies and interventions for stroke survivors with impaired EF.

Chapter 3 Methodology

From the literature review, it is evident that there is a gap in understanding the predictors and the prevalence of long-term impaired EF in stroke survivors. This chapter describes the research design of the current study by analysing the techniques, strategies and tools used for this research.

Rationale

The objective of this study is to examine the prevalence and predictors of EF four years after the occurrence of stroke. This study utilised previously collected data by Mahon (2018) to explore the predictors and prevalence of impaired cognitive function in long-term stroke survivors. EF was assessed using the CTMT four years after a stroke. CTMT is designed to detect impaired EF as well as attentional deficits after brain injury. By identifying the predictors of impaired EF, this study will provide an understanding as to how the different factors affect impaired EF four-years after their first stroke. Understanding these predictors is of high relevance where the quality of life and functional independence of these survivors are concerned.

Research Questions

1) What is the prevalence of impaired EF four years after a stroke?
2) What are the factors associated with impaired EF in stroke survivors after four years?
3) What are the predictors of impaired EF in stroke survivors after four years?

Hypothesis

The overall hypothesis is that impaired EF is prevalent in long-term stroke survivors; it is also hypothesised that sociodemographic factors, stroke characteristics, vascular risk factors and older age contribute to the decline in EF.

Hypothesis 1: To identify the prevalence of impaired EF four years after a stroke. The hypothesis is that impaired EF is present in a significant number of stroke survivors four years post-stroke.

Hypothesis 2: To identify factors associated with impaired EF four years after a stroke. The hypothesis is that baseline stroke-related characteristics are associated with greater impaired EF.

Hypothesis 3: To identify the predictors of impaired EF four-years after a stroke. The hypothesis is that baseline stroke-related characteristics predict the impaired EF of stroke survivors four years post-stroke.

Design

The current study is a retrospective cohort study using a quantitative research methodology. This study is a sub-study of the PhD research conducted by Mahon (2018). Participants had previously taken part in the "Auckland Regional Community Stroke Study" (ARCOS-IV, the original population-based study) and were selected based on their consent given for a four-year follow-up study.

Participant Recruitment in the Original Study

The ARCOS-IV study is one of the very few population-based studies conducted until now and is acknowledged both nationally and internationally. The detailed methodology has been described elsewhere (R. Krishnamurthi et al., 2014). ARCOS is an incidence and outcome study conducted on patients who had their first-ever stroke and recurrent strokes in Auckland. The participants for this study were selected based on the following primary criteria:

1) occurrence of stroke was between March 1, 2011, and February 29, 2012,

2) living in the Greater Auckland region, and

3) aged older than 16-years.

Case ascertainment of the original study was based on the "hot pursuit" method. Information on stroke-related cases was gathered from both clinical and non-clinical data. The data was collected by qualified researchers at Auckland public hospitals using strategic searches, regular checks of information from hospital emergency departments, outpatient departments, private clinics, non-hospitalised cases and nursing homes (R. Krishnamurthi et al., 2014). Cases which did not have sufficient computerised brain imaging scans or confirmation of data were classified as undetermined (R. Krishnamurthi et al., 2014). Information on each patient's current medical condition, health-related risk factors and previous medical conditions were obtained from the hospital records with consent.

The original study consisted of 2,096 participants. Only 821 consented to follow-ups, from whom the information was collected within two weeks post-stroke, and/or at one-, six- and twelve-months post-stroke. Consent was obtained from each participant before the data was collected. The baseline information was collected from medical records and via online hospital workstation-based software called Concerto. The baseline data included: sociodemographic data, previous medical history, diagnosis of neurological conditions, history of family illness, and recent laboratory test results. The assessment used for the baseline assessment included cognitive measures such as the Computerized Neuropsychological Vital Signs test (CNS-VS) (Gualtieri & Johnson, 2006), and the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). To understand functional wellbeing, mood and quality of life, measures such as the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983), the Visual Analogue Fatigue Scale (VAFS) (Tate, 2010), the European Quality of Life Questionnaire- 5 Dimension (EQ-5D) (The EuroQol Group, 1990), the Barthel Index

(BI) (Sulter, Steen, & Keyser, 1999) and the Modified Rankin Rating Scale (mRS) (Rankin, 1957) were used.

Participants in the PhD Study

In the PhD study, 499 stroke survivors who had consented to a follow-up study were contacted after four years. Statistics obtained from the Ministry of Health (MoH) database showed that seventy-five patients passed away after the 12-month follow-up. Thirty-one participants were excluded as they could not be contacted after repeated attempts. From the remaining pool of 393 candidates, 84 patients declined participation. Fifty-two were hospitalised or severely ill, which led to a further reduction in the number in the participant pool. Finally, the remaining participant pool consisted of 257 participants out of the 499 participants who initially consented for the study (12 months post-stroke). Of these 257, 83% (n=214) had suffered just one stroke (their first ever), and the remaining 17% (n=43) had suffered recurrent strokes since their last follow-up at 12 months.

Participants in the Current Study

In the current study, 132 patients were chosen from the total sample of 257 patients from the PhD study. The current sample was selected based on the availability of their CTMT scores. In the original study, the CTMT test was not conducted in the baseline assessment but was conducted only at four years post-stroke. Loss of participants was due to participant attrition, severe fatigue, poor MoCA scores and functional disability post-stroke.

The sampling technique used was non-probability sampling – purposive-maximum variation. A purposive sampling technique is where the sample was not randomly chosen but chosen based on the availability of the CTMT scores. Participant information included sociodemographic characteristics, stroke characteristics, vascular risk factors, cognition, functioning level, mood, fatigue, disability and quality of life.

These variables help in gaining a better understanding of the factors predicting and moderating impaired EF.

The participants' baseline characteristics and performance in the outcome measures was assessed at the time of stroke. Four years after their stroke, their EF was assessed using CTMT. During the baseline assessment (for example, at the time of stroke or within two weeks of the stroke event), some of the outcome measures were missing due to the inability to conduct evaluations. Participant attrition was also due to the lack of follow-up, and led to missing data. For this study, the data on the participants who were unable to participate were included in the analysis. This data inclusion is to understand the sample characteristics of the participants who were unable to do the baseline assessment.

Procedure

Data for this study was obtained from previously collected data at a four-year follow-up time point and extracted from a database. In brief, informed consent was obtained from the participants prior to data collection for the four-year follow-up. A researcher conducted a face-to-face interview at a location suitable to the participant. Data was also collected at baseline (or within two weeks of the stroke event) which included: sociodemographic factors, stroke-related characteristics and vascular risk factors. The baseline assessments also included cognition, level of independence, mood, fatigue, disability and quality of life (Table 1) The four-year assessment was comprised of a number of questions on current health since the last stroke and an assessment of EF (using the CTMT). The total test administration time for the CTMT ranged from five to twelve minutes.

Data Collection

Baseline data on the measures of sociodemographic characteristics, stroke characteristics, vascular risk factors, cognition, functioning level, mood, fatigue,

disability and quality of life were taken from the ARCOS-IV 2011-2012 (R. Krishnamurthi et al., 2014). Data on EF was collected from the follow-up study (Mahon, 2018) on the scores of CTMT, which was administered to four-year stroke survivors.

Ethical Approval

The study has received approval from both the New Zealand Northern Regional Ethics Committee (NTX/10/90/090/AM07) and the Auckland University of Technology Ethics Committee (AUTEC 11/297).

Sociodemographic Characteristics and Stroke-related Characteristics

To examine the predictors of impaired EF in post-stroke patients, the following variables are included: sociodemographic factors such as age, sex, education, ethnicity employment status and marital status; stroke characteristics such as stroke subtype, OCSP classification, hemisphere of lesion, stroke location (frontal and non-frontal), vascular territory (MCA, PCA, PICA, ACA), stroke region (cortical and subcortical stroke) and history of previous stroke; and vascular risk factors such as cholesterol, hypertension, diabetes mellitus, coronary artery disease, peripheral vascular disease, epilepsy and migraine.

Outcome Measures

To examine the predictors of impaired EF in post-stroke patients, the following outcome measures are included: cognition (Montreal Cognitive Assessment: MoCA), functional recovery/level of independence (Barthel Index), mood (Hospital Anxiety and Depression Scale), fatigue (Fatigue Severity Scale), degree of disability (Modified Rankin Scale) and quality of life (Euro Qol Quality of Life Scale: EQ-5D).

Montreal Cognitive Assessment (MoCA)

MoCA is a short screening tool for assessing global cognitive impairment (Appendix A), which is commonly used in longitudinal studies (Nasreddine et al., 2005; Toglia, Fitzgerald, O'Dell, Mastrogiovanni, & Lin, 2011). Though the initial version of this assessment had ten domains, the final version covers eight domains, which are attention, concentration, language, memory, orientation, constructive abilities, orientation and conceptual thinking (Nasreddine et al., 2005). Higher the scores better the cognitive functioning; the highest score is 30 and the cut off is any score ≤26, for which the participant is considered to have an impairment, and for any score >26 the participant is considered not impaired (Nasreddine et al., 2005).

Previous studies revealed that cut-off for MoCA is inadequate for the stroke population, and is optimized at a lower threshold scores ranging from 19 to 24 (Godefroy, Bugnicourt, & Fickl, 2011; Salvadori et al., 2013; Stolwyk, O'Neill, McKay, & Wong, 2014). A systematic review showed that MoCA had high sensitivity 0.95, but a lower specificity with a cut-off score of ≤26, compared with a sensitivity 0.84 and specificity 0.78 with a cut-off score of ≤22 (Lees, Broomfield, & Quinn, 2014). Nevertheless, using a conservative score of ≤24 have shown to reduce the sensitivity of MoCA to detect post-stroke cognitive impairment (Cumming et al., 2013). As there has been no consensus on the optimum cut-off score for MoCA post-stroke, a recommended cut-off score of ≤26 is used consistently in research; and a cut-off score of ≤26 is reported to have adequate sensitivity to detect cognitive impairment post-stroke (Larouche et al., 2016; Mijajlović et al., 2017; Toglia et al., 2011). In a recent study, MoCA was found to be highly sensitive to identifying EF deficits in stroke survivors (Fu et al., 2017). For the purpose of the current study, a total MoCA of ≤26 were defined to be have impaired baseline cognition versus those with a total MoCA score >26 were defined to have no cognitive impairment.

Barthel Index (BI)

BI measures functional recovery and level of independence after stroke (Appendix E) (López-Espuela, 2016). This index evaluates the activities of daily living and mobility (Sulter et al., 1999). It has ten items, and the scores on each item range from 0 to 3; the higher the scores, the better the level of independence. The scores from the BI are classified into five levels: A BI score of 20 indicates that the participant is "totally independent"; ratings between 15 and 19 indicate "mild dependency"; ratings between 10 and 14 indicate "moderate dependency"; ratings ranging from 5 to 9 indicate "severe dependency"; and ratings ranging from 0 to 4 indicate "very severe dependency" (Wade & Collin, 1988). BI showed excellent interrater reliability in a metanalytic study (95% CI, 0.90-0.96) (Duffy, Gajree, Langhorne, Stott, & Quinn, 2013). BI is validated and is widely used in the stroke population (López-Espuela, 2016; Quinn, Langhorne, & Stott, 2011). Several longitudinal studies used BI to investigate the functional recovery in stroke (Janssen et al., 2010; Kunkel, Fitton, Burnett, & Ashburn, 2015; López-Espuela, 2016).

Hospital Anxiety and Depression Scale (HADS)

HADS is a psychometric tool developed by Zigmond and Snaith (1983) to measure anxiety and depression (Appendix F). It has 14 items with scores falling between 0 and 21; scores between 0 and 7 indicate no anxiety or depression, scores between 8 and 10 indicate a mild level of anxiety or depression, scores between 11 and 14 indicate a moderate level of anxiety or depression, and scores between 15 and 12 indicate a severe level of anxiety or depression (Herrmann, 1997; Zigmond & Snaith, 1983). Any score ≥ 8 indicates the presence of anxiety or depression. HADS has high internal consistency for the subscales of anxiety and depression (Cronbach's alpha 0.83 and 0.82) (Zigmond & Snaith, 1983). It is validated in the population with TBI (Whelan-Goodinson, Ponsford, & Schönberger, 2009). HADS has been reported to be

sensitive to the changes in mood during an illness (Zigmond & Snaith, 1983). However, an early study in stroke patients noted a poor specificity for anxiety (0.46) and depression (0. 44) with a cut off scores of 4 and 5 respectively (G. Johnson et al., 1995). But a more recent study identified post-stroke depression with high sensitivity (91.7%) and moderate specificity (65.3%) with a cut off of 11 in the depression scale (Aben, Verhey, Lousberg, Lodder, & Honig, 2002). Though HADS is commonly used to understand the levels of anxiety in a clinical population, the sensitivity of the anxiety measure in the stroke population is still debated, which is not the case for other tests of anxiety (Kneebone, Fife-Schaw, Lincoln, & Harder, 2016). Many longitudinal studies have used HADS to understand the effect of mood on impaired cognition (Barker-Collo, Feigin, Parag, et al., 2010; Mahon et al., 2017).

Visual Analogue Fatigue Scale (VAFS)

VAFS assesses the level of fatigue at an individual level (Appendix G)(Tseng, Gajewski, & Kluding, 2010). The scores can range from 0 to 100 measured in millimetres on a 10 cm long vertical line (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989). The scores range from the point of no fatigue (0) to severe fatigue (100); a higher score thus indicates more fatigue (Tate, 2010; Tseng, Billinger, Gajewski, & Kluding, 2010). The vertical measure eliminates visual neglect or visual-spatial neglects in stroke patients (Tseng, Gajewski, et al., 2010). VAFS has excellent reliability and validity in identifying the post-stroke fatigue (Lerdal et al., 2009; Nadarajah, Mazlan, Abdul-Latif, & Goh, 2015; Tseng, Gajewski, et al., 2010).

Modified Rankin Scale (mRS)

mRS is a reliable to tool to gauge the degree of disability or the level of dependency experienced by a stroke survivor (Appendix H)(Banks & Marotta, 2007; Rankin, 1957). It is a six-item scale with scores ranging from 0 (having no residual symptoms at all) to 5 (being bedridden), with 6 being deceased (Rankin, 1957). The administration time for mRS is less than six minutes. mRS has demonstrated high validity, reliability and clinical sensitivity to detect clinical change following

stroke (Banks & Marotta, 2007). Long-term and short-term dependency is caused by lesion volume, stroke subtype and the degree of damage caused by stroke, and are measured using mRS. The scale is validated in several studies (Derex et al., 2004; Petty et al., 2000; Schiemanck et al., 2005). Studies have shown that performance in mRS and MoCA can together predict the post-stroke functional outcome, and mRS individually predicts the social cost and consequences of future post-stroke trials (Broderick, Adeoye, & Elm, 2017; Ferreira, Moro, & Franco, 2015; Ganesh, Luengo-Fernandez, Wharton, & Rothwell, 2018).

EuroQol Quality of Life Scale (EQ-5D)

EQ-5D is one of the most popular generic scales for evaluating the health index in patients with stroke (Appendix I) (Quinn, Dawson, Walters, & Lees, 2009). EQ-5D is designed to understand the patient's wellbeing using five questions with three levels of responses. The administration time for EQ-5D is less than five minutes. The five dimensions assessed in the scale are mobility, self-care, usual activities, pain/discomfort, anxiety and depression (The EuroQol Group, 1990). An individual response can range from 1-3 in increasing degree of severity; a score of 1 is assigned when the participant experiences no or some problems, a score of 2 when there are moderate problems, and a score of 3 when there are severe problems (The EuroQol Group, 1990). It also uses EQ Visual Analogue Fatigue Scale (VAS) in which the participants respond from 0-100 depending on their current health index, where a response of zero indicates the worst possible health and 100 indicates best possible health. The test has been standardised on populations from different countries, including NZ; there is cut-off for each dimension based on the norms from a population-based sample (The EuroQol Group, 1990).

Several studies have been done assessing the quality of life in stroke using EQ-5D (Marilyn et al., 2018). It has excellent reliability and validity, according to the

cardiovascular studies (Dyer, Goldsmith, Buxton, & Sharples, 2010). From robust studies on patients with stroke, EQ-5D has reasonable construct, concurrent and discriminant validity, and also has a precision in predicting the health-related quality of life in stroke survivors (Hunger, Sabariego, Stollenwerk, Cieza, & Leidl, 2012; Pinto, Maso, Vilela, Santos, & Oliveira-Filho, 2011). According to a recent study on the acute stroke population, the validity of EQ- 5D-5L as a health index has some psychometric advantages when compared to EQ-5D-3L (Golicki et al., 2015). Though it is one of the most commonly used questionnaires to measure the health index (Brooks & Group, 1996; Quinn et al., 2009), a limitation with a health-related quality of life measure such as EQ-5D in the stroke population is that it is a self-reported measure (van Exel, Scholte op Reimer, & Koopmanschap, 2004).

Comprehensive Trail Making Test (CTMT)

CTMT measures EF and processing speed in individuals aged 8 to 74 years with neurological disorders using five trails of increasing difficulty (Reynolds, 2002). CTMT helps to identify brain dysfunction specific to the frontal lobe. The test is sensitive in measuring the processing speed, visual search, set-shifting abilities, and sustained and divided attention (Reynolds, 2002). Unlike its predecessor, TMT, which had two trails, CTMT has five trails sensitive to different measures of EF.

Trail 1 measures sustained attention where the participant has to join numbers in serial order; no distractors present in the first trail task. Trail 1 is analogous to TMT-Part A. Trail 2 and Trail 3 measure the resistance to distraction, visual scanning, attention and inhibitory control (Reynolds, 2002). Trail 4 measures cognitive flexibility, working memory and set-shifting abilities. Finally, Trail 5, which is analogous to TMT-B, measures divided attention, cognitive set-shifting and flexibility (Reynolds, 2002). Trail 1 has numbers which the participant has to join sequentially. Trail 2 and Trail 3 are distractor tasks; Trail 2 has empty circles, and Trail 3 has figures inside the circle.

Trail 4 contains both numbers and words – it has circles with numbers and words denoting numbers in the boxes. Trail 5 is similar to TMT Part B, where the participant has to alternate between the number and the letter. Unlike TMT Part B, some circles are empty, which acts as a distractor. The task requires participants to connect the stimuli (numbers and letters) as quickly as possible. Based on the complexity of the trails, Trail 1-3 are classified as simple sequencing, and Trail 4 and Trail 5 are categorised as complex sequencing (Reynolds, 2002).

The test takes from 5 to 12 minutes for completion. The scoring process takes about five minutes. A score higher than 70 is indicative of superior functioning, scores less than 43 are suggestive of impaired EF and any score less than 30 is suggestive of severe impairment (Reynolds, 2002). Raw scores are converted to T-scores, and a Composite Index Score is obtained. The Composite Index is also accompanied by the percentile ranks. From the available norms, the average T-score is 50 with a standard deviation of 10. However, in adults with CVA, the mean Composite Index Score was 33 which was two standard deviations below the mean (Armstrong et al., 2008). The internal consistency for the five trails ranges from 0.70 to 0.77, with reliability value of 0.92 for the Composite Index (Reynolds, 2002).

During the standardisation process, Composite Index Scores were obtained for 28 adults with CVA, with an internal consistency estimate of 0.80 or above for the group of participants who are elderly, belonged to ethnic minority and suffered from stroke (Reynolds, 2002, p. 27). Moreover, the coefficient alpha for the CTMT Composite Index Score was 0.90 or above for both clinical and non-clinical participants. CTMT has high test-retest and interrater reliability. Furthermore, the classification accuracy of CTMT is high (79%), which is similar to TMT. The CTMT has notable construct and criterion validity (Allen et al., 2009; S. R. Smith et al., 2008)

and high sensitivity and specificity (0.74 and 0.82 respectively) in predicting impaired EF in individuals with brain injury (Allen et al., 2012).

Statistical Analysis

Profile analyses have been used for the descriptive statistics to summarise the demographic, sociodemographic and stroke-related characteristics and stroke-related risk factors. The categorical variables were reported as frequencies and percentages. The continuous variables were reported as means and standard deviations. For the statistical analysis, SPSS software version 25 was used.

Chi-square analysis was conducted to understand the degree of difference between the samples used for the study (n=132; participants with CTMT scores) and those not used (n=125; participants with no CTMT scores). Bivariate analysis was done to understand the relationship between impaired EF and the baseline stroke-related variables (such as sociodemographic factors, stroke-related characteristics and vascular risk factors) and psychological factors (cognitions, functionality, disability, fatigue, quality of life and mood), with EF being assessed at four years post-stroke using CTMT. The outcome variable (CTMT; dependent variable) was converted into binary categories (impaired versus not-impaired) based on cut-offs from previous research. Cross-tabulation was used to understand the difference in occurrence between the categorical outcome variable and the predictor variables. An exploratory analysis was conducted to understand the relationship between each component of CTMT and the mean CTMT scores. The level of significance was set to an alpha level of 0.05.

A binary logistic regression was designed to assess the relationship between impaired EF and the sociodemographic characteristics, stroke-related factors, vascular risk factors and outcome measures ($p<0.05$). Multicollinearity was assessed to understand the degree of association between the psychological outcome measures

(independent variables) and the significant predictors were retained in the final regression model.

A multivariate logistic regression model was designed to assess the contribution of predictor variables to impaired EF. Covariates were retained in the multivariate regression model based on a threshold of $p<0.25$ in the individual bivariate models. Stepwise selection was used on the full model, with the likelihood ratio tests used to determine the significance of the variable's contribution to the model. The significance level for the final multivariate logistic regression model was set to $p<0.05$ to signify the statistical significance. Potential confounders in the regression analysis included age, sex, education, employment, ethnicity, stroke type, hemisphere, recurrent stroke, vascular territory, stroke region, location of the stroke, coronary artery disease, epilepsy and migraine.

Sample Size Estimation

A formal sample size estimation was not done because the sample was drawn from a more extensive population study.

Chapter 4 Results

This study is aimed at understanding the predictors and prevalence of impaired EF in four-year survivors of stroke. This chapter provides an overview of the statistical analysis and results along with its tabulation and interpretation.

Descriptive Statistics

Table 1 below provides a summary of the demographic characteristics, stroke-related characteristics and the risk factors. From a total number of 257 participants, 132 participants have completed CTMT in the fourth year since their stroke. The mean age of these 132 participants was found to be M = 63.99 ± 13.47 (age ranging from 24.72 to 90.08 years). The average time since the stroke was 3.24 years ± 0.20 (ranging from 2.5 to 3.8 years). Chi-square analysis determined that participants who were included in the analysis (participants with CTMT scores; n=132) compared with those who were not included in the study (participants without CTMT scores; n=125) did not differ in terms of sex, ethnicity, stroke type, stroke location, vascular territory and stroke region ($p>0.05$). Participants who were included in this study (n=132) were more likely to be older (65-74 years; n=43, 32%), educated (over 12 years of education; n=108 81.8%), unemployed/retired (n=91,68.9%), married (n=90, 69.7%) with significant group difference in the OCSP category compared to those who were not included in the study (n=125; at all $p<0.05$).

The sample for the current study consisted of a majority of NZ Europeans (n=106, 80.3%). Most of the participants had an ischaemic stroke (n=110, 83.3%), stroke in non-frontal region (n=73, 59.8%), stroke in MCA (n=69, 52.3%), stroke in the subcortical region (n=78, 59.1%) or had a history of previous stroke or TIA (n=108, 81.8%).

Several diseases were found to be co-existing in post-stroke patients. Results showed nearly half of the participants chosen for this study suffered from high

cholesterol (n=67, 50.8%) and hypertension (n= 73, 55.3%), and a high proportion had diabetes (n=109, 82.6%). However, only few stroke survivors had coronary artery disease (n=23, 17.4 %), peripheral vascular disease (n=7, 5.3%), epilepsy (n= 5, 3.8%) or migraine (n=23, 17.4%).

Table 1 Demographic and Clinical Features of Sample with CTMT scores (n=132) Compared Sample without CTMT scores(n=125)

Descriptive	**CTMT n (%)**	**Non-CTMT n (%)**	**Test of Difference Value**
Age			
<50	23 (17.4%)	11 (8.8%)	X^2= 21.30, **p<0.01***
51-64	38 (28.8%)	19 (15.2%)	
65-74	43 (32.6%)	37 (29.6%)	
75+	28 (21.2%)	58 (46.6%)	
Sex			
Female	57 (43.2%)	62 (49.6%)	X^2=1.06, p=0.30
Male	75 (56.8%)	63 (50.4%)	
Ethnicity			
NZ European	106 (80.3%)	100 (80%)	X^2=0.00, p=0.95
Non-European	26 (19.7%)	25 (20%)	
Education			
Did not complete school	22 (16.7%)	46 (36.8%)	X^2=21.00, **p<0.01***
Completed school	26 (19.7%)	26 (20.8%)	
Degree	38 (28.8%)	13 (10.4%)	
Diploma/Certificate	26 (19.7%)	22 (17.6%)	
Other post-school education	18 (13.6%)	16 (12.8%)	
Not specified	2 (1.5%)	2 (1.6%)	

Descriptive	CTMT n (%)	Non-CTMT n (%)	Test of Difference Value
Employment Status			
Employed	41 (31.1%)	9 (7.2%)	X^2=23.32, **p<0.01***
Unemployed/retired	91 (68.9%)	116 (92.8%)	
Marital Status			
Married	92 (69.7%)	68 (54.4%)	X^2=6.39**, p<0.01***
Not married	40 (30.3%)	57 (45.6%)	
Stroke Type			
Ischaemic stroke	110 (83.3%)	114 (91.2%)	X^2=3.33, p=0.06
Haemorrhagic stroke	22 (16.7%)	11 (8.8%)	
OCSP			
PACI	42 (31.8%)	38 (30.4%)	X^2=11.70, **p=0.02***
TACI	5 (3.8%)	13 (10.4%)	
LACI	32 (24.2%)	41 (32.8%)	
POCI	39 (29.5%)	29 (23.3%)	
Unknown	14 (10.6%)	4 (3.2%)	
Hemisphere Lateralisation			
Left	56 (42.4%)	56 (47.2%)	X^2=6.06, p=0.11
Right	59 (44.7%)	60 (48%)	
Brainstem	7 (5.3%)	1 (0.8%)	
Both/Uncertain	10 (7.6%)	5 (4%)	
Stroke Location			
Frontal	23 (10%)	15 (68.8%)	X^2=2.45, p=0.29
Non-Frontal	79 (59.8%)	86 (12%)	
Unknown	30 (22.7%)	24 (19.2%)	

Descriptive	CTMT n (%)	Non-CTMT n (%)	Test of Difference Value
Vascular territory			
MCA	69 (52.3%)	69 (55.2%)	X^2=1.06, p=0.79
PCA	25 (18.9%)	26 (20.8%)	
PICA	19 (14.4%)	13 (10.4%)	
ACA/SCA/Unknown	19 (14.4%)	17 (13.6%)	
Stroke Region			
Subcortical	78 (59.1%)	74 (59.2%)	X^2=2.74, p=0.25
Cortical	40 (30.3%)	30 (24%)	
Unknown	14 (10.6%)	21 (16.8%)	
Previous Stroke			
No	108 (81.8%)	106 (84.8%)	X^2=0.41, p=0.52
Yes	24 (18.2%)	19 (15.2%)	
Previous TIA			
No	108 (81.8%)	92 (73.6%)	X^2=3.87, p=0.14
Yes	23 (17.4%)	33 (26.4%)	
Missing	1 (0.8%)	0 (%)	
Cholesterol			
No	64 (48.5%)	52 (42.3%)	X^2=1.10, p=0.29
Yes	67 (50.8%)	71 (57.7%)	
Missing	1 (0.8%)	0 (0%)	
Hypertension			
No	59 (44.7%)	31 (24.8%)	X^2=11.16, **p<0.01***
Yes	73 (55.3%)	94 (75.2%)	
Diabetes			
No	109 (82.6%)	99 (79.2%)	X^2=0.474, p=0.49
Yes	23 (17.4%)	26 (20.8%)	

Descriptive	CTMT n (%)	Non-CTMT n (%)	Test of Difference Value
Coronary Artery Disease			
No	109 (82.6%)	93 (75%)	X^2=2.20, p=0.14
Yes	23 (17.4%)	31 (25%)	
Peripheral Vascular Disease			
No	125 (94.7%)	110 (90.2%)	X^2=1.882, p=0.17
Yes	7 (5.3%)	12 (9.8%)	
Epilepsy			
No	127 (96.2%)	118 (95.9%)	X^2=0.01, p=0.91
Yes	5 (3.8%)	5 (4.1%)	
Migraine			
No	108 (81.8%)	98 (79.7%)	X^2=0.317, p=0.57
Yes	23 (17.4%)	25 (20.3%)	
Missing	1 (0.8%)		
Age: Mean and SD	63.99 (13.47)	71.78 (12.59)	
Time Since Stroke: Mean and SD	3.25 (0.21)	3.32 (0.25)	

*p value of <0.05 represents significance.
Note: PACI=partial anterior circulatory infarct, TACI=total anterior circulatory infarct, LACI=lacunar infarct, POCI=posterior circulatory infarct, MCA=middle cerebral artery, PCA=posterior cerebral artery, PICA=posterior inferior cerebral artery, ACA=anterior cerebral artery, SCA=superior cerebellar artery.

Outcome Measure at Baseline

Table 2 below shows the number of participants who have completed the outcome measures at the baseline, the mean outcome scores (M) and standard deviations (SD). Cognitive impairment was indicated as present at the baseline as measured by MoCA (M=23.56 ±4.37); a MoCA score of ≤26 indicates cognitive impairment. The average self-reported fatigue as measured by the VAFS was obtained (M=47.26 ±28.50). A score of 0 indicates no fatigue and a score of 100 represents

severe fatigue; a mean score of 47.26 in this sample suggests mild to moderate fatigue was present in the participants in the acute stage post-stroke.

Results from the remaining outcome measures assessed at baseline indicated minimal impairment after a stroke. The BI (M=18.69 ±3.10) measured minimal functional disability in stroke survivors within a month after their stroke. Lower BI scores (0-20) indicate greater disability. At the time of stroke, anxiety (M=5.15 ±4.14) or depression (M=4.22 ±2.62) was not present in the current sample as measured by HADS, where any score ≤7 indicates normal mood. The degree of disability, as measured by mRS, was found to be minimal (M=1.67 ±1.02). The health index for domains such as mobility (M=1.45 ±0.50), self-care (M=1.24 ±0.47), usual activities (M=1.69 ±0.65), pain and discomfort (M=1.41 ±0.53), anxiety and depression (M=1.39 ±0.49) measured using EQ-5D shows mild to moderate disabilities. While EQ-5D domain scores of 1, 2 and 3 indicate mild, moderate and severe disabilities respectively, an EQ-5D Utility Score of 0 indicates worst possible heath and a score of 1 indicates best possible health. The Utility Scores (M=0.63 ±0.19) of the current sample indicate mild to moderate health-related problems following a stroke.

Table 2. Outcome measures at baseline

Variables	N	Mean (M)	Median	SD	IQR	Missing
MoCA	61	23.56	24	4.37	7	71
BI	68	18.69	20	3.10	1	64
HADS						
Anxiety	62	5.15	4	4.14	5	70
Depression	60	4.22	4	2.62	4	72
VAFS	57	47.26	60	28.50	50	75
mRS	70	1.67	2	1.02	1	62
EQ-5D						
Mobility	58	1.45	1	0.50	1	74
Self-Care	58	1.24	1	0.47	0	74
Usual activities	58	1.69	2	0.65	1	74
Pain and Discomfort	58	1.41	1	0.53	1	74
Anxiety and Depression	57	1.39	1	0.49	1	75
EQ-5D Utility Score	57	0.68	0.63	0.19	0.13	75

*Scores of the baseline outcome measures are represented as means (M) and standard deviations (SD), with interquartile range (IQR) also given.
Note: MoCA=Montreal Cognitive Assessment, BI=Barthel Index, HADS=Hospital Anxiety and Depression Scale, VAFS=Visual Analogue Fatigue Scale, mRS=Modified Rankin Scale, EQ-5D=EuroQol Quality of Life Scale.

Prevalence of Impaired EF

A CTMT score of <43 is considered to indicate a patient is impaired. In Table 3, below, it can be seen that 48.48% of the participants had impaired EF at four years post-stroke. Table 3 also shows the composite index score of CTMT indicating deficits in EF (M=42.67 ±11.30). Figure 1, below, shows the impaired EF over the five trails of CTMT. A decline in mean scores was noted in the performance of individual trails from Trail 1 (M=42.94, SD=10.701) to Trail 5 (M= 37.68, SD=12.250). Table 3 below, shows the mean (M) and standard deviation (SD) of individual trails and composite index scores. Table 3 also shows the percentage of participants impaired in each trail.

Table 3 indicates that the participants' performance in Trail 1 showed sustained attention of the participants was within the low average-average limits (M=42.94 ±10.70). Performance in Trail 2 and Trail 3 was within the average limits (M=46.80 ±12.40 and M=44.36 ±12.95 respectively) indicating no deficits in inhibitory control, resistance to distraction, attentional demands and visual search (Table 3, below). Performance in Trail 4 showed the mean performance of the participants was bordering on the average in the limits (M=43.58 ±14.55), indicating marginal average performance in the tasks of cognitive flexibility, cognitive set-shifting and working memory. Finally, the mean performance in Trail 5 suggests mild to moderate impairment in cognitive set-shifting and divided attention (M=37.68 ±11.30).

Table 4 illustrates the association of sociodemographic characteristics, stroke characteristics and vascular risk factors with post-stroke impaired EF. Table 4 indicates that impaired EF was found to be more prevalent in stroke survivors who are over 75 years of age (78.6%), not working (57.1%), had a previous stroke (70.8%) and have a history of hypertension (57.5%).

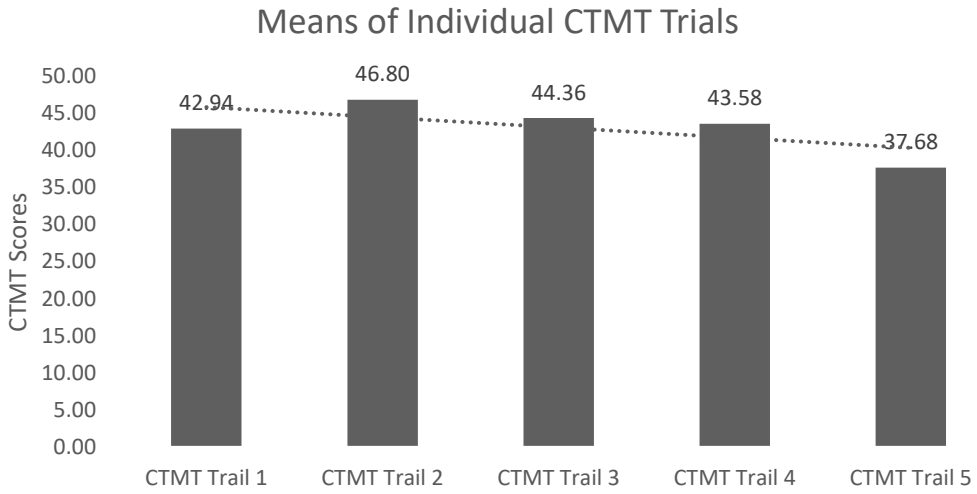

Figure 1. Performance of individuals on each CTMT trail

Table 3 Means of Individual Trail Scores of CTMT

Trails Scores	N	Mean (M)	SD	Impaired CTMT n (%)
CTMT Composite Index Scores	132	41.67	11.30	64 (48.48%)
CTMT Trail 1	132	42.94	10.70	58 (43.94%)
CTMT Trail 2	132	46.80	12.40	48 (36.36%)
CTMT Trail 3	132	44.36	12.96	63 (47.73%)
CTMT Trail 4	132	43.58	14.55	61 (46.21%)
CTMT Trail 5	132	37.68	12.25	91 (68.94%)

*Scores of the outcome variable are represented as means (M) and standard deviations (SD).
Note: CTMT=Comprehensive Trail Making Test.

Table 4 Sociodemographic Characteristics, Stroke-related Characteristics and Vascular Risk Factors associated with Impaired EF

Descriptive	Not Impaired n (%)	Impaired n (%)	Number of Participants
Age			
<50	15 (65.2%)	8 (34.8%)	23
51-64	26 (68.4%)	12 (31.6%)	38
65-74	21 (48.8%)	22 (51.2%)	43
75+	6 (21.4%)	22 (78.6%)	28
Sex			
Female	32 (56.1%)	25 (43.9%)	57
Male	36 (48%)	39 (52%)	75
Ethnicity			
NZ European	54 (50.9%)	52 (49.1%)	106
Non-European	14 (53.8%)	12 (46.2%)	26

Descriptive	Not Impaired n (%)	Impaired n (%)	Number of Participants
Education			
Did not complete school	10 (45.5%)	12 (54.5%)	22
Completed school	14 (53.8%)	12 (46.2%)	26
Degree	22 (57.9%)	16 (42.1%)	38
Diploma/Certificate	11 (42.3%)	15 (57.7%)	26
Other post-school education	11 (61.1%)	7 (38.9%)	18
Employment Status			
Employed	29 (70.7%)	12 (29.3%)	41
Unemployed/retired	39 (42.9%)	52 (57.1%)	91
Marital Status			
Married	46 (50%)	46 (50%)	92
Not married	22 (55%)	18 (45%)	40
Stroke Type			
Ischaemic stroke	53 (48.2%)	57 (51.8%)	110
Haemorrhagic stroke	15 (68.1%)	7 (31.8%)	22
OCSP			
PACI	22 (53.7%)	20 (46.3%)	41
TACI	2 (40%)	3 (60%)	5
LACI	20 (62.5%)	12 (37.5%)	32
POCI	15 (38.5%)	24 (61.5%)	39
Unknown	9 (64.3%)	5 (35.7%)	14
Hemisphere Lateralisation			
Left	30 (53.6%)	26 (46.4%)	56
Right	28 (47.5%)	31 (52.5%)	59
Brainstem	4 (57.1%)	3 (42.9%)	7
Both/Uncertain	6 (60%)	4 (10%)	10

Descriptive	Not Impaired n (%)	Impaired n (%)	Number of Participants
Stroke Location			
Frontal	17 (73.9%)	6 (26.1%)	23
Non-Frontal	37 (46.8%)	42 (53.9%)	79
Unknown	14 (46.7%)	16 (53.3%)	30
Vascular territory			
MCA	33 (47.8%)	37 (52.2%)	69
PCA	15 (60%)	10 (40%)	25
PICA	14 (73.8%)	5 (26.2%)	19
ACA/SCA/Unknown	7 (36.8%)	12 (63.2%)	19
Stroke Region			
Subcortical	40 (51.3%)	38 (48.7%)	78
Cortical	20 (50%)	20 (50%)	40
Unknown	8 (57.1%)	6 (42.9%)	14
Previous Stroke			
No	61 (56.5%)	47 (43.3%)	108
Yes	7 (29.2%)	17 (70.8%)	24
Previous TIA			
No	56 (51.9%)	52 (48.1%)	108
Yes	11 (47.8%)	12 (52.2%)	23
Cholesterol			
No	37 (57.9%)	27 (42.1%)	64
Yes	30 (44.8%)	37 (37.2%)	67
Hypertension			
No	37(62.7%)	22 (37.3%)	59
Yes	31 (42.5%)	42 (57.5%)	73

Descriptive	Not Impaired n (%)	Impaired n (%)	Number of Participants
Diabetes			
No	57 (52.3%)	52 (47.7%)	109
Yes	11 (47.8%)	12 (52.2%)	23
Coronary Artery Disease			
No	61 (55.9%)	48 (22.1%)	109
Yes	7 (30.4%)	16 (69.6%)	23
Peripheral Vascular Disease			
No	66 (52.8%)	59 (47.2%)	125
Yes	2 (28.6%)	5 (71.4%)	7
Epilepsy			
No	65 (51.2%)	62 (48.8%)	127
Yes	3 (60%)	2 (40%)	5
Migraine			
No	53 (49%)	55 (51%)	108
Yes	15 (65.2%)	8 (34.8%)	23

Note: PACI=partial anterior circulatory infarct, TACI=total anterior circulatory infarct, LACI=lacunar infarct, POCI=posterior circulatory infarct, MCA=middle cerebral artery, PCA=posterior cerebral artery, PICA=posterior inferior cerebral artery, ACA=anterior cerebral artery, SCA=superior cerebellar artery.

Bivariate Logistic Regression: Sociodemographic, Stroke-related and Vascular Risk Factors with Impaired EF

A bivariate logistic regression was performed to understand the relationship between the sociodemographic characteristics and the clinical factors (independent variables) and the impaired EF. From the bivariate logistic regression model (Table 5, below), age was found to be significantly associated with impaired EF (β=1.9279, *p*-value=0.0024). Participants who were 75 years or above were more likely to have impaired EF compared to younger adults. Similarly, being unemployed or retired were

found to be significantly associated with impaired EF compared to those who were employed (β=1.1701, *p*-value=0.0037).

Stroke-related characteristics such as OCSP subtype, stroke location, vascular territory and history of previous stroke were found to be associated with impaired EF (Table 5). OCSP subtype POCI was more strongly associated with impaired EF compared to the stroke in other OCSP subtypes (β=0.9808, *p*-value=0.0460). Surprisingly, compared to frontal lobe strokes, non-frontal lobe strokes were found to be more strongly associated with the impaired EF at four years post-stroke (β=-1.1682, *p*-value=0.0263). Stroke in the MCA circulation was more strongly associated with impaired EF compared to the stroke in the ACA/SCA/Unknown circulation (β=-1.1748, *p*-value=0.0408). A history of previous stroke was associated with impaired EF four-years after stroke (β=-1.1480, *p*-value=0.0189). Moreover, the presence of vascular characteristics such as hypertension (β=0.8236, *p*-value=0.0216) and coronary artery disease (β=1.0664, *p*-value=0.0304) were also strongly associated with the impaired EF four years post-stroke.

Table 5 Bivariate Logistic Regression Models showing the Relationship between Impaired EF and Sociodemographic, Stroke-Related and Vascular Risk Factors

Variables	**Categories**	**Estimate (β)**	**Std. Error**	**z-value**	**df**	***p*-value**
Intercept		-0.6286	0.4378	2.0616	1.0000	0.1510
	51-64	-0.1446	0.5599	0.0667	1.0000	0.7962
Age (ref= <50 years old)	56-74	0.6751	0.5336	1.6008	1.0000	0.2058
	75+	1.9279	0.6354	9.2047	1.0000	**0.0024***
Intercept		-0.2469	0.2669	0.8553	1.0000	0.3551
Sex	Male	0.3269	0.3531	0.8572	1.0000	0.3545
Intercept		0.1823	0.4282	0.1813	1.0000	0.6702
Education	Completed school	-0.3365	0.5815	0.3349	1.0000	0.5628
(ref=Did not complete	Degree	-0.5008	0.5397	0.8609	1.0000	0.3535
education)	Diploma/ Certificate	0.1278	0.5839	0.0479	1.0000	0.8267
	Other post-school education	-0.6343	0.6458	0.9646	1.0000	0.3260
Intercept		-0.0377	0.1943	0.0377	1.0000	0.8460
Ethnicity	Non-European	-0.1164	0.4388	0.0704	1.0000	0.7908

Variables	Categories	Estimate (β)	Std. Error	z-value	df	*p*-value
Intercept		-0.8824	0.3432	6.6087	1.0000	**0.0101***
Employment	Unemployed/ retired	1.1701	0.4033	8.4153	1.0000	**0.0037***
Intercept		0.0000	0.2085	0.0000	1.0000	1.0000
Married status	Not married	-0.2007	0.3801	0.2787	1.0000	0.5976
Intercept		0.0728	0.1908	0.1454	1.0000	0.7030
Stroke type	Haemorrhagic	-0.8349	0.4959	2.8343	1.0000	0.0923
Intercept		-0.5108	0.3651	1.9571	1.0000	0.1618
	PACI	0.4155	0.4783	0.7546	1.0000	0.3850
OCSP stroke subtype	TACI	0.9163	0.9832	0.8685	1.0000	0.3514
(ref=LACI)	POCI	0.9808	0.4916	3.9808	1.0000	**0.0460***
	Unknown	-0.0770	0.6667	0.0133	1.0000	0.9081
Intercept		-0.1431	0.2679	0.2852	1.0000	0.5933
Hemisphere of lesion	Right	0.2449	0.3739	0.4291	1.0000	0.5125
(ref=Left)	Brainstem	-0.1446	0.8094	0.0319	1.0000	0.8582
	Both/Uncertain	-0.2624	0.6989	0.1409	1.0000	0.7074

Variables	**Categories**	**Estimate (β)**	**Std. Error**	**z-value**	**df**	***p*-value**
Intercept		0.1268	0.2255	0.3160	1.0000	0.5740
Stroke location	Frontal	-1.1682	0.5257	4.9387	1.0000	**0.0263***
(ref=Non-frontal)	Unknown	0.0068	0.4298	0.0002	1.0000	0.9874
Intercept		0.1452	0.2414	0.3617	1.0000	0.5476
Stroke vascular territory	PCA	-0.5506	0.4743	1.3479	1.0000	0.2456
(ref=MCA)	ACA/SCA/Unknown	-1.1748	0.5742	4.1860	1.0000	**0.0408***
	PICA	0.3938	0.5334	0.5452	1.0000	0.4603
Intercept		-0.0513	0.2265	0.0513	1.0000	0.8209
Stroke region	Cortical	0.0513	0.3890	0.0174	1.0000	0.8951
(ref=Subcortical)	Unknown	-0.2364	0.5856	0.1629	1.0000	0.6865
Intercept		-0.2607	0.1941	1.8046	1.0000	0.1792
Previous Stroke	Yes	1.1480	0.4892	5.5064	1.0000	**0.0189***
Intercept		-0.0741	0.1926	0.1481	1.0000	0.7004
Previous TIA	Yes	0.1611	0.4597	0.1228	1.0000	0.7260
Intercept		-0.3151	0.2531	1.5496	1.0000	0.2132
Cholesterol	Yes	0.5248	0.3527	2.2135	1.0000	0.1368

Variables	Categories	Estimate (β)	Std. Error	z-value	df	*p*-value
Intercept		-0.5199	0.2692	3.7288	1.0000	**0.0535***
Hypertension	Yes	0.8236	0.3585	5.2762	1.0000	**0.0216***
Intercept		-0.0918	0.1918	0.2292	1.0000	0.6321
Diabetes	Yes	0.1788	0.4594	0.1515	1.0000	0.6971
Intercept		-0.2397	0.1929	1.5431	1.0000	0.2142
Coronary artery disease	Yes	1.0664	0.4925	4.6875	1.0000	**0.0304***
Intercept		-0.1121	0.1792	0.3916	1.0000	0.5315
Peripheral vascular disease	Yes	1.0284	0.8556	1.4446	1.0000	0.2294
Intercept		-0.0473	0.1775	0.0709	1.0000	0.7901
Epilepsy	Yes	-0.3582	0.9300	0.1484	1.0000	0.7001
Intercept		0.0370	0.1925	0.0370	1.0000	0.8474
Migraine	Yes	-0.6656	0.4782	1.9373	1.0000	0.1640

*A value of $p<0.05$ represents statistical significance.
Note: PACI=partial anterior circulatory infarct, TACI=total anterior circulatory infarct, LACI=lacunar infarct, POCI=posterior circulatory infarct, MCA=middle cerebral artery, PCA=posterior cerebral artery, PICA=posterior inferior cerebral artery, ACA=anterior cerebral artery, SCA=superior cerebellar artery.

Bivariate Logistic Regression between impaired EF and Outcome Measures

The results in Table 6 show that there exists a strong association between impaired baseline cognitive functioning measured by MoCA and impaired EF at four years post-stroke assessed by CTMT (β=2.1059, *p*-value=0.0094). Also, the bivariate regression analysis from Table 6 reveals a significant association between those patients who were unable to do the MoCA assessment and impaired EF (β=2.2127, *p*-value=0.0051). Different dimensions of EQ-5D were also found to be associated with impaired EF. The health index for mobility, as measured by EQ-5D, shows that scores indicating moderate mobility problems were found to have an association with impaired EF (β=1.7429, *p*-value=0.0030). Also, participants who were not assessed during the baseline assessment were found to have impaired EF (β=0.8118, *p*-value=0.0371). Similarly, those who were not assessed for EQ-5D usual activities (β =1.1044, *p*-value=0.0292) were also found to have a significant association with impaired EF.

Table 6 Bivariate Logistic Regression showing the outcome measures of participants who completed CTMT

Variables	**Categories**	**Estimate (β)**	**Std. Error/SE**	**z-value/Wald**	**df**	***p*-value**
Intercept		-2.0149	0.7528	7.1644	1.0000	**0.0074***
MoCA	Impaired	2.1059	0.8110	6.7421	1.0000	**0.0094***
(ref=Not impaired)	Not assessed	2.2127	0.7897	7.8520	1.0000	**0.0051***
Intercept		-0.1671	0.2897	0.3326	1.0000	0.5642
BI	Dependent	-0.0336	0.5347	0.0040	1.0000	0.9499
(ref=functionally independent)	Not assessed	0.2296	0.3827	0.3598	1.0000	0.5486
Intercept		-0.2136	0.2934	0.5299	1.0000	0.4666
HADS Anxiety	Anxious	-0.4796	0.6214	0.5957	1.0000	0.4402
(ref=Not anxious)	Not assessed	0.3854	0.3790	1.0342	1.0000	0.3092
Intercept		-0.2318	0.2792	0.6892	1.0000	0.4064
HADS Depression	Depressed	-0.8668	0.8629	1.0090	1.0000	0.3151
(ref=Not depressed)	Not assessed	0.3989	0.3659	1.1880	1.0000	0.2757
Intercept		-0.3102	0.3970	0.6105	1.0000	0.4346
VAFS	Fatigued	-0.2877	0.5463	0.2773	1.0000	0.5985
(ref=Not fatigued)	Not assessed	0.5513	0.4601	1.4358	1.0000	0.2308

Variables	Categories	Estimate (β)	Std. Error/SE	z-value/Wald	df	*p*-value
Intercept		-0.3483	0.2666	1.7068	1.0000	0.1914
mRS	Moderate- Severe Disability	0.6848	0.6434	1.1328	1.0000	0.2872
(ref= Mild disability)	Not assessed	0.4775	0.3686	1.6783	1.0000	0.1951
Intercept		-0.5878	0.5578	1.1105	1.0000	0.2920
EQ-5D Utility Score	Worst possible health	0.8109	0.8724	0.8640	1.0000	0.3526
(ref= Best possible health)	Moderate quality of health	-0.0183	0.6632	0.0008	1.0000	0.9779
	Not assessed	0.8289	0.6043	1.8815	1.0000	0.1702
Intercept		-1.2730	0.4276	8.8618	1.0000	**0.0029***
EQ-5D Mobility	Moderate problems	1.7430	0.5877	8.7965	1.0000	**0.0030***
(ref= No problems)	Not assessed	1.4900	0.4874	9.3462	1.0000	**0.0022***
Intercept		-0.5947	0.3114	3.6468	1.0000	0.0562
EQ-5D Self-Care	Severe problems	21.7976	40192.9695	0.0000	1.0000	0.9996
(ref=No problems)	Moderate problems	0.5947	0.6560	0.8219	1.0000	0.3646
	Not assessed	0.8118	0.3895	4.3446	1.0000	**0.0371***

Variables	Categories	Estimate (β)	Std. Error/SE	z-value/Wald	df	*p*-value
Intercept		-0.8873	0.4491	3.9037	1.0000	**0.0482***
EQ-5D Usual Activities	Severe problems	1.5805	0.9755	2.6246	1.0000	0.1052
(ref=No problems)	Moderate problems	0.5996	0.5895	1.0346	1.0000	0.3091
	Not assessed	1.1044	0.5063	4.7572	1.0000	**0.0292***
Intercept		-0.2877	0.3416	0.7094	1.0000	0.3996
EQ-5D Pain and Discomfort	Severe problems	21.4906	40192.9695	0.0000	1.0000	0.9996
(ref=No problems)	Moderate problems	-0.4745	0.5711	0.6901	1.0000	0.4061
	Not assessed	0.5047	0.4140	1.4867	1.0000	0.2227
Intercept		-0.1719	0.3393	0.2565	1.0000	0.6125
EQ-5D Anxiety and Depression	Moderate problems	-0.8090	0.5868	1.9008	1.0000	0.1680
	Not assessed	0.4130	0.4114	1.0079	1.0000	0.3154

*A value of $p<0.05$ represents statistical significance.
Note: MoCA=Montreal Cognitive Assessment, BI=Barthel Index, HADS=Hospital Anxiety and Depression Scale, VAFS=Visual Analogue Fatigue Scale, mRS=Modified Rankin Scale, EQ-5D=EuroQol Quality of Life Scale.

Multicollinearity

Multicollinearity was tested between the variables to understand the degree of association between outcome measures in the current sample (Appendix J). For example, the EQ-5D Utility Score is negatively correlated with all five sub-domains of EQ-5D such as EQ-5D Mobility ($r=-0.543$, $p<0.01$**), EQ-5D Self-Care ($r=-0.535$, $p<0.01$**), EQ-5D Usual Activities, ($r=-0.708$, $p<0.01$**), EQ-5D Pain and Discomfort ($r=-0.624$, $p<0.01$**) and EQ-5D Anxiety and Depression ($r=-0.466$, $p<0.01$**), and hence only the EQ-5D Utility Score has been added into the final multivariate model. The negative correlation is because the increase in Utility Score indicates better health, whereas an increase in the sub-scores indicates poorer quality of life. Similarly, VAFS was found to be correlated with the HADS Anxiety ($r=0.429$, $p<0.01$**) and mRS ($r=0.356$, $p<0.01$**). Therefore, the variables to be included in the multivariate logistic regression model were chosen based on the significance of the level of multicollinearity as well as the significance of the individual bivariate logistic regression models.

From the bivariate regression (Table 6, above), EQ-5D Mobility, EQ-5D Self-Care and EQ-5D Usual Activities were found to be significant ($p<0.05$). Since all the EQ-5D domains are significantly correlated with the EQ-5D Utility Score, the EQ-5D Utility Score is inserted into the final multivariate logistic regression model instead of adding individual sub-domains of EQ-5D (EQ-5D Mobility, EQ-5D Self-Care and EQ-5D Usual Activities).

Multivariate Logistic Regression

Covariates were retained in the multivariate regression model based on a threshold of $p<0.25$ in the individual bivariate models. Stepwise selection was used on the full model, with the likelihood ratio tests to determine the significance of the variable's contribution to the model. Results from the multivariate model show that older age, hypertension and poor baseline cognition are significant predictors of

impaired EF. Compared to the stroke survivors who were under 50, the stroke survivors over the age of 75 were four times more at risk of having impaired EF (p=0.045*, OR=4.41, CI 1.03-18.86). In contrast to those who did not have hypertension, those who had hypertension were at three times more at risk of having impaired EF at four years post-stroke (p=0.028*, OR=2.78, CI 1.12-6.88). In contrast to the participants who were screened to be not cognitively impaired (MoCA scores >26), the participants who had poor MoCA scores were over ten times more at risk of having an impaired EF at four years post-stroke (p=0.003*, OR=10.34, CI 1.74-61.49). A marginal significant association was found between vascular territory and impaired EF post-stroke. Compared to a stroke in other vascular territories, especially in ACA, SCA and other unknown territories, a stroke in the MCA region indicate that the stroke survivors are at a 72.2% higher risk of having an impaired EF (p=0.061, OR=0.27, CI 0.07-1.06).

Table 7 Multivariate Analysis Illustrating the Predictors of Impaired EF

Variable	Category	Estimate (β)	Std. Error	z-value	df	p-value	OR	95% CI	
Intercept				12.457	3	**0.006***			
Age	51-64	-0.768	0.670	1.313	1	0.252	0.464	0.125	1.726
	56-74	0.094	0.659	0.020	1	0.886	1.099	0.302	4.002
(Ref= <50 years old)	75+	1.484	0.741	4.010	1	**0.045***	4.411	1.032	18.855
Intercept				7.298	3	0.063			
Stroke vascular territory	PCA	-0.874	0.554	2.490	1	0.115	0.417	0.141	1.236
(ref=MCA)	ACA/SCA/Unknown	-1.281	0.684	3.509	1	0.061	0.278	0.073	1.061
	PICA	0.642	0.675	0.903	1	0.342	1.900	0.506	7.139
Hypertension	Yes	1.019	0.464	4.826	1	**0.028***	2.771	1.116	6.881
Intercept				8.549	2	**0.014***			
MoCA	Impaired	2.656	0.908	8.547	1	**0.003***	14.237	2.400	84.466
(ref=Not impaired)	Not assessed	2.336	0.910	6.596	1	**0.010***	10.340	1.739	61.486
Constant		-2.760	1.006	7.534	1	**0.006***	0.063		

*A value of $p<0.05$ represents statistical significance.
Note: MCA=middle cerebral artery, PCA=posterior cerebral artery, PICA=posterior inferior cerebral artery, ACA=anterior cerebral artery, SCA=superior cerebellar artery, MoCA=Montreal Cognitive Assessment.

Conclusion

Impaired EF was prevalent in four-years stroke survivors. The hypothesis that impaired EF is present in a significant number of stroke survivors at four years post-stroke is accepted. The second hypothesis, that stroke-related characteristics are associated with greater impaired EF, is partially accepted. Sociodemographic characteristics such as age and employment, vascular risk factors such as hypertension and coronary artery disease, and baseline outcome measures such as cognition and health-related quality of life were associated with impaired EF, in addition to stroke-related risk factors such as OCPS stroke-subtype (POCI), stroke location (non-frontal), stroke vascular territory (MCA), and a history of previous stroke. The third hypothesis, that baseline stroke-related characteristics predict the impaired EF of stroke survivors at four years post-stroke, is rejected. None of the stroke-related factors predicted impaired EF at four years post-stroke. Covariates such as older age (sociodemographic factor), history of hypertension (vascular risk factor) and cognitive impairment (outcome measure) at baseline predicted impaired EF at four years post-stroke.

Chapter 5 Discussion

This chapter provides an in-depth discussion of the findings from this study. This study aims to understand the prevalence and predictors of EF in four-year survivors of stroke. The significance of the study, limitations, and suggestions for future research and practice are also discussed in this chapter.

Brief Overview of Results

The current study examined the prevalence and predictors of impaired EF four years after a stroke using a quantitative methodology. Impaired EF was measured using CTMT. A total of 132 participants completed the CTMT four years after a stroke, and results indicate that 48.5% of participants had impaired EF (indicated by a score <43 on the CTMT). The results from the bivariate logistic regression analysis showed that significant impairment in EF was noted in participants over the age of 75 (78.6%), those not working (57.1%), those who experienced stroke subtype-POCI (60%), those who experienced strokes in the MCA region (52.2%), and those who had experienced a previous stroke (70.8%). Additionally, participants with a history of hypertension (57.5%), coronary artery disease (69.6%), impaired baseline cognition (72.1%; MoCA ≤26) and lower health-related quality of life (48.8%; EQ-5D Utility score <0.50) were found to have impaired EF four years after the stroke. From the multivariate logistic regression analysis, older age (above 75+), a history of hypertension and poor baseline cognition (MoCA scores ≤26) were found to be significant predictors of impaired EF.

Prevalence of Impaired EF

Nearly half of the stroke survivors (48.5%) experienced impaired EF four years after the stroke. Consistent with our findings, research has found that impaired EF is the most common cognitive deficit affecting up to 75% of stroke survivors (Chung, Pollock, Campbell, Durward, & Hagen, 2013; Conti et al., 2015; Leśniak et al., 2008).

Participants in the current study showed deficits in EF domains such as sustained attention (CTMT- Trail 1; M=42.94 ±10.70) and divided attention and cognitive set-shifting (CTMT Trail 5; M=37.68 ±11.30), as measured by the individual CTMT trails, where individual trail scores <43 indicate impairment (Reynolds, 2002). In support of our findings, long-term studies have shown deficits in attention (divided and selective) and cognitive set-shifting after stroke (as measured by the Test of Attention and Performance, the Star Cancellation Test [SCT], and the Test of Everyday Attention) (Hyndman & Ashburn, 2003; Hyndman, Pickering, & Ashburn, 2008; Spaccavento et al., 2019)

Consistent with our study, a five-year NZ follow-up study by Barker-Collo and colleagues (2010) on patients post-stroke (n=307) revealed that impaired EF was shown to be one of the most common cognitive deficits. Another study reported 50% of stroke survivors were found to have impaired EF (as measured by SCWT and the Concept Shifting Test) even after two years post-stroke (Bour et al., 2011). In addition to this, a six-year follow-up study by Levine and colleagues (2015) found that there is a significant decline in EF (measured by AFT) after each year post-stroke. Although Levine et al.'s study described the rate of EF decline across six years, it does not describe the prevalence of long-term impaired EF.

Understanding the long-term prevalence of impaired EF is beneficial in gauging the complications that can accompany a stroke. Several studies have shown that long-term impaired EF is associated with shorter survival compared with no impaired EF. For example, a 12-year post-stroke follow-up study by Oksala and colleagues (2009) showed stroke survivors who had no impaired EF survived on average six years longer than those who had impaired EF (5.8 versus 11.4 years) (Oksala et al., 2009). Similarly, a 12-year follow-up study found that 44.4% of stroke survivors had impaired EF and that it was associated with shorter survival compared to those with no impaired EF (6.4

versus 10.6 years) (Melkas et al., 2010). A consistent finding that emerged from these studies is the association between impaired EF post-stroke and lower survival rates (Wiberg, Kilander, Sundström, Byberg, & Lind, 2012).

From the studies described above, it is clear that deficits in EF play a vital role in quality of life and longevity, and therefore it is crucial to evaluate and manage impaired EF post-stroke. Lower survival rates are potentially due to impaired judgement, crucial decision-making abilities and functional dependence, which accompanies impaired EF post-brain injury (Libin et al., 2015). For instance, a study that reviewed the neurobehavioral abnormalities in TBI illustrated that impaired EF is associated with difficulty in adapting to daily life, tackling real-life problems, making appropriate decisions on safety, maintaining functional and emotional well-being (Wood & Worthington, 2017). An impaired EF-specific management and rehabilitation programme will reduce the long-term adverse consequences experienced by stroke survivors (Shea-Shumsky et al., 2019). The following sections provide an in-depth discussion of the factors associated with impaired EF.

Factors Associated with Impaired EF

Impaired EF was found to be strongly associated with sociodemographic factors such as age and not working; stroke-related characteristics such as POCI (OCSP stroke subtype), non-frontal strokes (stroke location), stroke in MCA (vascular territory) and history of previous stroke; vascular risk factors such as hypertension and a history of coronary artery disease; and outcome measures such as reduced quality of life and low MoCA scores (≤26).

Association between Sociodemographic Factors and Impaired EF

From the bivariate analysis, sociodemographic factors such as age and unemployment or retirement are shown to be associated with impaired EF, while no

association was found between sex, level of education, ethnicity and marital status, and impaired EF.

Consistent with the findings from the present study, previous research has suggested that sociodemographic variables such as age and unemployment or retirement were strongly associated with impaired EF (Kim et al., 2011; Nakling et al., 2017). However, very limited long-term studies have been conducted to investigate the relationship between age and impaired EF post-stroke. For example, a longitudinal study by Levine and colleagues (2018) suggested that older stroke survivors who are over the age of 75 are more likely to have faster rates of EF decline (as measured by AFT) over six years. However, data within TBI populations have yielded similar results, showing older participants are more likely to be vulnerable to having persistent impaired EF in the long term after brain injury (Rabinowitz, Hart, Whyte, & Kim, 2018; Senathi-Raja, Ponsford, & Schonberger, 2010), resulting in deleterious effects to overall cognitive and functional prognoses (Dikmen et al., 2009). Similarly, another TBI five-year follow-up study found that increasing age (>50) was strongly associated with impaired EF and information processing speed (measured by TMT and the Digit Symbol Coding Test respectively) (Fraser, Downing, Biernacki, McKenzie, & Ponsford, 2019). Salthouse (2010) also substantiated similar age-related changes in impaired EF, where increased age was strongly associated with less accurate and slower performance in tasks of inhibition (Flankers-based inhibition tasks), and, therefore, the findings of the present study are not surprising.

Findings from this study are consistent with previous studies indicating the association between unemployment/retirement and impaired EF after a stroke (Culler, Wang, Byers, & Trierweiler, 2011; Fride et al., 2015). Concordant with our study, a strong association was found between non-working long-term stroke survivors and impairment in self-regulation, multi-tasking and the ability to concentrate (impaired EF

as reported by qualitative evaluation) (Wang, Kapellusch, & Garg, 2014). Although there are very limited long-term post-stroke follow-up studies investigating the relationship between impaired EF and participants' employment status, studies have investigated this relationship in TBI and other neurological injuries population (Wood & Worthington, 2017). A recent study noted that impaired EF could lead to unemployment, as measured by the Executive Function Performance Test and the Flanker Inhibitory Control and Attention Test in National Institutes of Health Toolbox Cognitive Battery, in people with long-term neurological injury (Alex Wong et al., 2019).

A study by Ownsworth and Shum (2008) examined how impaired EF (low scores in the Tinkertoy test; norms not known) results in a detrimental effect on productivity and employability after a stroke. The detrimental effects are primarily due to the inability to multitask, plan goals, self-monitor and sustain attention (Lezak et al., 1995; van der Kemp et al., 2019). These higher-order skills are critical to reintegrating into the workforce, meeting the demands of the role and thereby improving the employment outcome (National Research Council, 2011). Previous studies have pointed out that improvement in EF is predictive of better employment outcomes (McGurk, Mueser, & Pascaris, 2005). In light of the evidence from the present study and existing literature, periodic evaluation of impaired EF can guide future cognitive rehabilitation post-stroke. This rehabilitation potentially improves the employability and productivity of stroke survivors.

In the present study, sociodemographic variables such as sex, ethnicity, level of education and marital status were not found to be associated with post-stroke impaired EF. Contrary to our findings, other studies have found that participants who are male and have lower educational qualification (<high school education) were more likely to have impaired EF after a brain injury (Jokinen et al., 2016; Levine et al., 2015;

Niemeier et al., 2007; Oksala et al., 2009). In these studies, male participants had lower educational qualifications and lower premorbid functioning compared to female participants (Niemeier et al., 2007); and participants with less than high school qualification had a lower quality of life (Levine et al., 2015) which may affect their EF test performance. These differences are not noted in the participants of the present study; this may have contributed to no association being observed between impaired EF and sex, education or marital status.

A five-year follow-up study on stroke survivors illustrated that impaired EF was more prevalent in Non-European (especially Māori) participants than NZ European participants as measured by the TMT-A time of completion (Barker-Collo, Feigin, Parag, et al., 2010). A note of caution is that the study by Barker-Collo and colleagues (2010) consisted of a small number of Māori participants. Similarly, in the present study, the sample was over-represented by NZ-European stroke survivors (80.3%), and only 3.8% of the participants were Māori. Therefore, further studies with equal representation of ethnicities have to be conducted for conclusive results.

Association between Stroke-Related Characteristics and Impaired EF

Stroke related-characteristics such as a history of MCA lesion, previous stroke, non-frontal stroke and POCI (OCSP stroke subtype) were found to be associated with impaired EF at four years post-stroke ($p<0.05$). No association was found between stroke type, the hemisphere of lesion, or stroke region (cortical and subcortical region) and impaired EF long-term post-stroke.

A neuropsychological case study indicated the presence of MCA infarction and subsequent impairment in attention and EF three years post-stroke (MoCA and WAIS) (Shatzman et al., 2016). However, these findings cannot be generalised to our study, as the results of the study are based on a single case. Other research has shown that after an MCA infarction, patients experience impaired attention and EF (as measured by SCT

and a behavioural inattention test) (K. Li & Malhotra, 2015), attributed to the visual neglect that accompanies an MCA lesion (Kwasnica, 2002). In our study, visual neglect was not measured, and therefore the presence of visual neglect may have contributed to poor performance in CTMT (score <43). Therefore, future studies are required to understand the association between MCA lesion and impaired EF, while also assessing for the presence of visual neglect.

The relationship between a history of previous stroke and impaired EF has been studied previously and is consistent with our findings. For example, patients with a history of prior stroke had a significant decline in attention, speed of processing and EF two years post-stroke (Srikanth et al., 2006). However, unlike our study, not many population-based long-term studies have explored the relationship between previous stroke and post-stroke impaired EF.

Contrary to the previous literature, our study has found that people with non-frontal stroke and POCI were more prone to having impaired EF. Previous studies have highlighted the effects of a frontal lobe lesion on long-term impaired EF (Lezak et al., 2012; Mataró et al., 2001). The literature also suggests a link between impaired EF (low score on SCWT) and TACI (anterior) region in five-year stroke survivors (Barker-Collo et al., 2012). The variation in findings in the present study could be attributed to skewed sample in both non-frontal region stroke (n=79) and frontal region stroke (n=23) as well as POCI (n=39) and TACI region (n=5). Although there are studies which highlight the importance of non-frontal regions in impaired EF post-stroke (Leskelä et al., 1999; Long et al., 2010), population-based studies are needed to gain a conclusive result.

A plausible explanation for the present findings is that the lesion in posterior areas such as occipital lobe, which extends to the posterior ventral temporal lobe and splenium, can potentially lead to impaired EF (K.-C. Park et al., 2011). A lesion in these areas can cause diverse neuropsychological impairments such as visual agnosia,

amnesia and alexia, which is evidenced by decreased performance on SCWT, decreased verbal fluency, and decreased working memory (DS), suggesting impaired EF (Kumral, Bayulkem, Ataç, & Alper, 2004; K.-C. Park et al., 2011; Pillon, Bakchine, & Lhermitte, 1987; Renzi, Zambolin, & Crisi, 1987; Von cramon, Hebel, & Schuri, 1988). Factors such as decreased working memory, decreased visuospatial attention and difficulty in attending to visual information following a non-frontal lesion (participants with impaired EF =53.9%) or posterior lesion (participants with impaired EF =61.5%) may have led to poor CTMT performance.

Although it is known that right-hemisphere lesions are associated with visuospatial and perceptual deficits whereas left hemisphere lesions are associated with speech and language disorders (Lezak et al., 2012; Spaccavento et al., 2019), no such associations were found in the present study. In support of these findings, a long-term post-stroke study by Barker-Collo and colleagues (2012) found that left and right hemisphere did not have a significantly different profiles of performance. Contrary to previous studies which have shown that subcortical stroke leads to impaired EF (Cumming et al., 2013; R. Vataja et al., 2003), no association was found in the present study. However, the literature also suggests that both cortical and subcortical lesions play an important role in impaired EF (Saczynski et al., 2009). Therefore, further research will be beneficial in understanding the relationship between stroke characteristic and long-term impaired EF.

Association between Vascular Risk Factors and Impaired EF

Hypertension and coronary artery disease were the vascular risk factors in the present study that were found to be associated with impaired EF at four years post-stroke. No association was found between other vascular risk factors such as cholesterol, diabetes, peripheral vascular disease, epilepsy or migraine, and impaired EF.

Results showed that 57.5% of the participants with hypertension experienced impaired EF in the long-term post-stroke. From the post-stroke literature, it is evident that hypertension leads to cognitive decline (Lo et al., 2017; Rowan et al., 2005). However, only very few long-term studies have investigated the relationship between hypertension and impaired EF in the long-term post-stroke. Contrary to the findings of the present study, a lone study which investigated the long-term relationship between impaired EF and hypertension in stroke survivors noted that participants who lacked hypertension had a faster decline of EF (measured by AFT) over the years post-stroke (Levine et al., 2018).

However, in support of the present study, several longitudinal studies on healthy participants have suggested that hypertension potentially causes impaired EF and attention deficits (Gottesman et al., 2017; Reitz, Tang, Manly, Mayeux, & Luchsinger, 2007; Waldstein, Giggey, Thayer, & Zonderman, 2005). Moreover, from the literature it is known that hypertension can trigger lesions in white matter as well as frontal lobe regions (Raz, Rodrigue, & Acker, 2003; Sizova et al., 2018; Suzuki et al., 2017) which may lead to impaired EF (Chuang et al., 2014; X. Li et al., 2015), specifically deficits in executive control and inhibition (measured by TMT, California Verbal Learning Test, Colour Trail Test, COWAT, and SCWT) (Witkowska et al., 2019). This neurobiological mechanism is explained in detail later in the chapter. To gain a conclusive understanding of the long-term consequence of hypertension for impaired EF post-stroke, more long-term follow-up studies need to be conducted.

Consistent with previous literature, coronary artery disease is strongly associated with impaired EF (Burkauskas et al., 2018; Mohammad et al., 2019). Impaired EF may be due to the white matter lesions, brain infarct and reductions in the hippocampal and cortical grey matter which are associated with coronary artery disease; however, this study did not examine this relationship (Zheng et al., 2012). Nevertheless, there is a lack

of long-term studies investigating the association between coronary artery disease and impaired EF. The present study found no association between other vascular risk factors such as cholesterol, diabetes, peripheral vascular disease, epilepsy and migraine, and impaired EF four years after a stroke. Although the relationship between cognition and cholesterol, diabetes mellitus, peripheral vascular disease, epilepsy and migraine has been previously studied (Alexandrova & Danovska, 2016; Cordonnier et al., 2007; Lu et al., 2016; Rist & Kurth, 2013; Sahathevan et al., 2012), not many studies have explored the relationship between these variables and impaired EF in the long term post-stroke.

Association between Outcome Measures and Impaired EF

The current study found that impaired baseline cognition and lower quality of life were associated with long-term impaired EF. Surprisingly, the baseline level of independence in activities of daily living, mood, fatigue and degree of disability were not found to be associated with impaired EF after four years post-stroke.

In the present study, 72% of the participants who were assessed for baseline cognition were found to have cognitive impairment (MoCA scores ≤26) and 48.5% of the participants had impaired EF post-stroke. The present findings are in accord with studies suggesting that baseline cognitive impairment (Informant Questionnaire on Cognitive Decline in the Elderly score ≥3.60, MMSE score <15) is associated with long-term impaired EF (TMT-B and DSST) after a stroke (Douven et al., 2018). Two long-term follow-up studies have suggested a persistent increase in cognitive decline from the baseline cognition and over the years; impaired EF is the most prominent domain that declines post-stroke (Barker-Collo, Feigin, Parag, et al., 2010; Levine et al., 2015). Given the prevalence of baseline cognitive impairment and subsequent impaired EF at four years post-stroke, more studies need to be conducted exploring the association between these variables.

Consistent with previous research, a significant association was found between lower quality of life post-stroke and impaired EF (Conti et al., 2015; Leśniak et al., 2008). Previous studies also suggested that a drop in EF was associated with poor emotional and functional well-being after a stroke (Theeke et al., 2014). Along the same lines, an association between impaired EF and reduced quality of life also negatively impacted stroke survivors' ability to work (Conti et al., 2015). Given the above, the finding from the present study is not surprising.

Contrary to expectations, this study did not find an association between outcome measures such as the baseline level of independence in activities of daily living, mood, fatigue or degree of disability, and long-term impaired EF. Previous studies have found that severe levels of dependency (BI <10; a score 5-9 indicates severe dependency), depression (DSM-IV diagnosis), severe fatigue (FSS=4.6; a score of 4 and above shows fatigue) disability (mRS >2; range from 0 to 6, with a higher score indicating significant disability) are strongly associated with impaired EF (Hubacher et al., 2012; Kim et al., 2011; Laakso et al., 2019; Leśniak et al., 2008; Mandzia et al., 2016). The discrepancy in findings could be attributed to the difference in sample characteristics in the present study. Our participants had a better level of functioning (BI mean score of 18.69; a score of 15-19 indicates mild dependency), no symptoms of depression or anxiety (HADS mean scores are 5.15 and 4.22 respectively indicating no depression or anxiety), mild-moderate fatigue (VAFS mean score of 47.26) and a minimal degree of disability (mRS mean score of 1.67; 0 being no disability to 6 being deceased). The degree of difference in the sample characteristics, between the participants of the present study and those of previous studies may have potentially led to no association being observed between these outcome measures and impaired EF.

Consistent with the present findings, several studies have found no association between impaired EF and fatigue or degree of disability (Ojagbemi & Owolabi, 2013;

Pihlaja et al., 2014; Schepers et al., 2006). However, the findings in the literature must be interpreted with caution as these results are not based on a population-based follow-up study. In addition to this, only very few studies have discussed the association between long-term anxiety and impaired EF. The present study is unique as that it is one of the very few studies focusing on the long-term relationship between impaired EF and baseline outcome measures of stroke in the long term post-stroke.

Predictors of Impaired EF

The highlight of the study is that it is one of the very few studies which analyse the predictors of impaired EF in long-term stroke survivors. Results from the multivariate logistic regression showed that older age, a history of hypertension and impaired cognitive function during the baseline testing are significant predictors of EF at four years post-stroke.

Sociodemographic Factors: Age

The results from this study show that older stroke survivors who are above the age of 75 (21.2% of the participants) were over four times more at risk of having long-term impaired EF compared with the younger stroke survivors. Although it is known that increasing age (>45 years) is predictive of cognitive decline (M=60 years, OR=1.44, CI 1.03-2.02) (Sarfo, Akassi, Adamu, Obese, & Ovbiagele, 2017), only a limited number of studies have investigated the predictive relationship between age and EF in long-term post-stroke survivors. Consistent with the current study, older age (61-80 years) was predictive of impaired EF as indexed by SCWT and Raven's Advanced Progressive Matrices in patients with frontal stroke and tumour (Cipolotti et al., 2015). However, the results do not indicate a long-term predictive relationship. A study by Nakling and colleagues (2017) found that patients who were over 65 years of age were more prone to having impaired EF compared with patients who were below the age of 65 years after a year post-stroke. However, limited evidence is presented in the study by

Nakling and colleagues (2017) to explain the long-term association between age and impaired EF after a stroke. Findings from our study are concordant with a longitudinal study which shows that impaired EF was more greater with an increase in age (65-75 years, $p<0.01$) post-stroke (Levine et al., 2018).

A five-year follow-up study found that increasing age contributed to a reduced attention level, memory and poor psychomotor speed after one year post-stroke (Barker-Collo et al., 2016). Similar to our results, older patients (>55 years) with TBI were more prone to long-term impaired EF (measured using TMT-B, DS, COWAT, Hayling and Brixton Test and Sustained Attention to Response Test) than younger patients (<35 years) (Senathi-Raja et al., 2010). These studies suggest that older patients with post-stroke or brain injury are more at risk of developing impaired EF.

Reduction in the structural and functional connectivity of the brain with increasing age potentially has an effect on impaired EF. Research shows that increasing age affects the prefrontal brain structures, which leads to impaired EF in both healthy older adults and patients with brain injury (Cipolotti et al., 2015; Fjell, Sneve, Grydeland, Storsve, & Walhovd, 2016). For example; Fjell et al. (2016) found a longitudinal relationship between increasing age (63- 86 years) and a decline in EF (measured by SCWT) in healthy adults; and 84% of the age-related decline in EF can be attributed to the structural and functional connectivity of the brain. Moreover, decreased activity of the frontal cortex and age-related brain abnormalities leading to a reduction of processing power exacerbate the EF impairment (measured by WCST and TMT) for older patients with brain injury (70-77 years) (Leskelä et al., 1999; Raz et al., 2003; Valenzuela, Breakspear, & Sachdev, 2007). Thus, structural and functional age-related changes cause impaired EF, and this further substantiates our findings.

Lack of social engagement in older adults could be another contributing factor for impaired EF. Previous research has suggested that elderly stroke survivors (>65

years) who are not working were three times more at risk of developing impaired EF (as measured by the Initiation/Perseveration subscale of the Dementia Rating Scale) compared to those who are employed (Kim et al., 2011). In addition, the inability to generate adequate compensatory strategies and inhibition in confronting cognitive challenges with increasing age affects impaired EF after stroke (D. C. Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014). These relationships suggest a need to focus on EF-specific rehabilitation strategies and social wellbeing in elderly stroke survivors to mitigate the effect of impaired EF, and thus improve their quality of life.

Vascular Risk Factor: Hypertension

In the current study, hypertension was a significant predictor of impaired EF well after stroke; the results indicate that the stroke survivors with hypertension (57.5% of the participants) were three times more at risk of having an impaired EF. It is well known that hypertension is one of the prominent vascular risk factors for impaired cognitive function post-stroke (Sahathevan et al., 2012; Walker et al., 2017). In addition, impaired EF is one of the commonly reported cognitive deficits in hypertensive patients following a brain infarct, white matter hyperintensities and haemorrhages (Gąsecki et al., 2013; He et al., 2017). Contrary to the present findings, an eight-year longitudinal study found that non-hypertensive participants aged 45 years and above were more at risk of developing an impaired EF (95% CI -1.12 - -0.04, p=0.03) post-stroke (Levine et al., 2018). Only a few studies have examined the relationship between hypertension and EF in long-term stroke populations, and future studies are needed to understand the predictive relationship between these variables post-stroke.

In the present study, hypertension was more prevalent in stroke survivors who are over the age of 65 (65.75%) compared to those who are below the age of 50 (5.4%). Moreover, impaired EF was found to be more prevalent in hypertensive participants

who were 65 years and older (76%) compared to those below 50 years of age (4.7%) post-stroke. In the light of our findings, it could be argued that increasing age and increased blood pressure contribute to impaired EF (e.g.Mahoney, Verghese, Goldin, Lipton, & Holtzer, 2010). However, a review showed that the impact of hypertension on impaired EF is prevalent regardless of age (Walker et al., 2017). Therefore, future studies need to examine the relationship between age and the presence of hypertension and impaired EF in long-term stroke survivors.

The plausible explanation of the strong association between impaired EF and hypertension post-stroke may be attributed to the underlying biological processes. For example, deficits in EF could be a consequence of disruption of blood flow and vascular damage triggered by hypertension (Iadecola et al., 2016; Obisesan, 2009; Tadic, Cuspidi, & Hering, 2016). Research has shown that having high blood pressure is associated with impaired EF (Oveisgharan & Hachinski, 2010) and white matter lesions (Longstreth et al., 1998). EF is predominantly a frontal lobe function, and this cerebral area is the most affected by hypertension (Vicario et al., 2005). Also, ischaemic damage triggered by hypertension affects the cortical-subcortical region, leading to targeted loss of EF (Kuo et al., 2004). This is because the disruption to brain autoregulation and increased cerebral blood pressure caused by hypertension increases the risk of psychomotor slowing and frontal lobe dysregulation leading to impaired EF (Bossers, van der Woude, Boersma, Scherder, & van Heuvelen, 2012; Muller, van der Graaf, Visseren, Mali, & Geerlings, 2012; Scuteri et al., 2014).

Increased blood pressure in the arterial wall due to blood vessel narrowing or plaque results in white matter lesions (McEvoy et al., 2015). It is evident from the literature that white matter lesions lead to impaired EF in elderly stroke patients (Black, Gao, & Bilbao, 2009; Ihle-Hansen et al., 2012). It must be noted that the current study did not examine the presence of white matter lesions which may potentially affect EF.

The majority of studies which have examined the relationship between impaired EF and hypertension have excluded participants with stroke (Iadecola & Gottesman, 2019). The exclusion was to mediate the effect of hypertension on cognition (Gottesman et al., 2017). Thus, a number of longitudinal studies have chosen stroke-free samples while investigating the relationship between hypertension and impaired EF to understand the independent effect of vascular risk factors on cognition (Cerhan et al., 1998; Elias, Elias, Sullivan, Wolf, & D'Agostino, 2003; Wadley et al., 2007). Similarly, 12-year, 20-year and 29-year longitudinal studies also identified the relationship between impaired EF and baseline hypertension in elderly patients (Power, Tchetgen, Sparrow, Schwartz, & Weisskopf, 2013; Singh-Manoux & Marmot, 2005; Wolf et al., 2007). Thus, there is a lack of data investigating the relationship between impaired EF and hypertension within long-term post-stroke populations. There is a complex interplay of a multitude of factors which can affect EF in hypertensive patients post-stroke, and further studies are recommended.

Outcome Measures: Baseline cognition

The results from the present study indicate that the participants with baseline cognitive impairment (MoCA scores ≤26) are over ten times more at risk of having an impaired EF at four years post-stroke. There are very limited post-stroke studies which investigated the predictive relationship between the baseline cognition and impaired EF long-term post-stroke. However, studies have investigated the trajectory of global cognitive impairment and impaired EF post-stroke.

The findings of this study are consistent with earlier studies, which have shown that impaired cognition in the acute phase of stroke is predictive of long-term cognitive impairment post-stroke (Nys et al., 2007; Nys et al., 2005). For example, a prospective cohort study (n=1369) found that baseline cognition was associated with a lower Mini-Mental State Exam score (MMSE <24) score after 3.8 years post-stroke (Rist et al.,

2013). Similarly, a 10-year post-stroke study found baseline cognitive impairment is predictive of long-term cognitive impairment (MoCA<23), and impaired EF was the most prevalent cognitive impairment ten years post-stroke (Delavaran et al., 2017). Additionally, a four-year follow-up study showed that cognitive impairment in the acute phase of stroke predicted persistent long-term cognitive impairment after stroke (Mahon, 2018).

Findings from the present study are consistent with a recent study exploring the relationship between baseline cognition, impaired EF and functional recovery in a stroke population (Kapoor et al., 2019). Baseline cognitive impairment (measured by the Depression, Obstructive sleep apnea, and Cognitive impairment screen [DOC screen], and MoCA) was a significant predictor of lower functional independence in activities of daily living (Frenchay Activities Index); and impaired EF (COWAT, TMT, DS) was strongly associated with lower functional independence long-term post-stroke (Kapoor et al., 2019). Interestingly, similarities exist in the sample size, mean age and the period of the study described by Kapoor et al.'s study (n=124, mean age= 66 and follow-up 2-3 years post-stroke) and the current study (n=132, mean age=64 and follow-up 3-4 years post-stroke).

A 10-year follow-up study noted that cognitive and EF were more significantly impaired at each year of follow-up post-stroke; also, compared to the baseline cognitive status the rate of decline in EF was faster over time (Levine et al., 2015; Levine et al., 2018). When extrapolating the findings from these studies, it is crucial to consider that these studies excluded participants with baseline cognitive impairment (Six-Item Screener, <5) to understand the true effect of stroke on cognitive and EF decline.

It is known that long-term cognitive impairment and impaired EF post-stroke can lead to severe functional impairment, depression and mortality (Dhamoon et al., 2009). Therefore, specific rehabilitation focusing on baseline cognition would reduce

the risk of long-term impaired EF. Cognitive rehabilitation would positively contribute to long-term EF and the long-term functional wellbeing of stroke survivors (Lipskaya-Velikovsky et al., 2018; Y. H. Park et al., 2015).

Integrative Findings

A promising finding in our research is that younger stroke survivors (below the age of 50) without MCA lesion, with no hypertension and with intact cognitive function at the time of stroke had better EF at four years post-stroke (94.05% chances of not having impaired EF) compared to older stroke survivors with MCA lesion, hypertension, and impaired baseline cognition. This could be attributed to higher cognitive reserves in patients with no hypertension/treated hypertension and higher resilience to neuropathophysiological changes (Giordano et al., 2012). For example, a population-based study noted that participants aged 53-94 years with hypertension had 6% lower cognitive reserve than normotensive patients; the presence of hypertension was associated with impaired memory and EF (Giordano et al., 2012). It is known that cognitive deficits could be aggravated by vascular diseases such as hypertension or with increasing age (Jiménez-Balado et al., 2019; Zaninotto, Batty, Allerhand, & Deary, 2018).

Limitations

There were several limitations of the present study which need to be acknowledged. These limitations include the lack of a diverse ethnic sample, lack of control group, missing data at the baseline assessment, lack of a supplementary assessment of impaired EF, lack of a qualitative analysis of CTMT data, and lack of premorbid cognitive functioning data.

Lack of Ethnic Diversity in the Sample

One of the limitations of the is study is that NZ Europeans were over-represented and Māori and Pasifika populations were underrepresented. This study

consisted of only 3.8% (n=5) Māori participants, 1.5% (n=2) Pasifika and 14% (n=19) Asian or other ethnicities, while 80.3 % (n= 106) of participants were NZ Europeans. Thus, the ethnicities had to be categorised as NZ Europeans and Non-Europeans. Although the consent rates in the present study were similar to the previous ARCOS study (Feigin et al., 2015), more Asian, Māori and Pasifika participants would have enabled separate demographic categories for analysis.

Lack of Control Group

Having a matched control group with no history of stroke would have strengthened the results of the study. A control group would have been beneficial to compare the trajectory of impaired EF (e.g.Levine et al., 2015). Moreover, a control group would have helped to differentiate whether the decline is due to stroke-related factors or non-stroke related factors.

Missing Data at Baseline Assessment

Another limitation was missing data at baseline assessment across all outcome measures such as MoCA, BI, HADS, VAFS, mRS and EQ-5D. Data collected on outcome measures were missing for 62-75 participants at the baseline assessment (nearly half of the participants). During the acute phase of hospitalisation, many patients were not approached for the assessment of outcome measures. Another cause of missing data is may be due to early discharge from the hospital or it may be that the participants were too unwell to assess. The potential for sample bias cannot be disregarded. Patients who are too unwell, experienced aphasias or are unable to speak the English language (mainly the Pasifika and Asian population) may not have approved participation consent, and were therefore not included in the study.

Influence of Fatigue

Fatigue is one of the most debilitating difficulties and a common symptom after a stroke. Nevertheless, many studies have noted the impact of PSF while assessing

impaired EF (Ponchel et al., 2015; Radman et al., 2012). Although the present research has shown no association between PSF and impaired EF, several reasons could have led to this finding. A large number of missing data during the baseline assessment may be one of the reasons for this non-significant relationship. Moreover, the association between fatigue and impaired EF is complicated by the effects of medication, older age and sleep disturbances. Future longitudinal studies will help decipher the complicated relationship between fatigue and impaired EF. This information will be beneficial in guiding the provision of adequate treatment and EF-specific rehabilitation.

Measures of Impaired EF

The current study did not measure CTMT at the baseline assessment post-stroke. A measurement of EF (measured using CTMT) at the baseline and the four-year follow-up could have given a holistic understanding of the prevalence of impaired EF over the span of four years. The study used only a single measure of EF, which is CTMT. Although CTMT gives a comprehensive evaluation of impaired EF post-brain injury, future studies may benefit from having additional tests of impaired EF (focusing on different components of EF). The present research focused on global impaired EF. Future studies can be conducted focusing on different components of impaired EF, such as decision making, judgement, inhibitory control and verbal fluency.

In addition, the study did not consider a qualitative analysis of the CTMT trails or the qualitative analysis of the error scores. A qualitative analysis of the individual CTMT trails of the participants would be informative in understanding the underlying brain damage through the observation of, for example, visual neglect, perseveration or repetition. Reynolds (2002) hypothesised that the presence of two or more errors are possible indications of frontal lobe damage. Therefore, future studies are encouraged to do more qualitative analysis of individual trails and error scores for each participant.

Lack of Premorbid Cognitive Function Data

One of the limitations of the study is the lack of data on premorbid cognitive functioning. Research has investigated the importance of a significant relationship between the premorbid cognition and impaired EF in acute stroke (Zinn, Bosworth, Hoenig, & Swartzwelder, 2007). Very few longitudinal studies have been conducted investigating the relationship between these variables for post-stroke participants. Research on post-stroke cognitive decline (especially impaired EF and attention) has pointed out the effect of premorbid cognitive function and the cognitive reserve on the post-stroke recovery (Umarova, 2017). Given the above, future studies focusing on premorbid cognitive status will give a more precise understanding of long-term impaired EF post-stroke. Also, it will assist in providing EF-targeted rehabilitation to those who are likely to have future decline.

Strengths

The present study is a sub-study of large population-based study ARCOS-IV. Population-based data is considered to be the gold standard method as the data collection occurs over a period of time. In this study, the data was meticulously collected at the baseline and four years post-stroke. To the best of my knowledge, this is one of the first few studies to have focused exclusively on the long-term predictors of impaired EF after a stroke.

This study provides an overview of long-term impaired EF across a spectrum of adult ages after a stroke. Furthermore, the present study has addressed the longitudinal predictive relationship between sociodemographic characteristics, stroke-related characteristics, vascular characteristics and outcome measures, and impaired EF in the long term after a stroke, which have not been frequently addressed in previous studies.

Another strength of the study is the adequate sample size (n=132), with an extensive range of covariate measures and long-term follow-up. This study is one of

very few studies which have revealed the variables that have a potential impact on long-term impaired EF.

Suggestions for Further Research and Practice

Social and emotional support are protective factors of cognitive functioning and have the potential to shield the negative consequences which follow a brain injury. Considering that the majority of participants who were impaired were elderly participants, they would benefit from the social interactions and companionship which can buffer the degree of disability and depression and improve the cognitive wellbeing.

Previous research has suggested that rehabilitation, exercise and recreation improve EF after a stroke. It would be beneficial to examine the effect of exercise and recreation on long-term EF in future studies. As exercise and recreation improve motor coordination skills, increase cerebral blood flow and improve team-based strategising skills, they could, in turn, improve EF. Future studies can examine aspects of the impact of exercise and rehabilitation on long-term post-stroke participants.

Future research could focus on evaluating impaired EF at different time points post-stroke. Improvement in EF was noted at six months post-stroke; however, no improvement was observed between the six- and twelve-months post-stroke (Barker-Collo et al., 2016). The present study has investigated the prevalence of impaired EF at four years post-stroke. EF is the orchestrator of different cognitive functions and functional independence, and understanding the prevalence of impaired EF at different time points post-stroke could be beneficial to understanding the trajectory of the functional recovery of a stroke survivor. Understanding the functional recovery and degree of impaired EF will help clinicians in providing EF-specific rehabilitation. This may improve the quality of life and functional wellbeing of a stroke survivor. Moreover, this periodic evaluation of EF will enable future researchers to examine the trajectory of the long-term impact of impaired EF post-stroke.

Future studies have to be conducted to understand the impact of using mobile and computer applications as a protective factor or a risk factor for long-term impairment in EF. Studies have found that smartphone-assisted technology is helpful in the rehabilitation of specific cognitive domains after a brain injury (Cicerone et al., 2019; Cicerone et al., 2011). Considering the accessibility of digital technology, computers and mobile applications across all age groups, the effects of these technologies on long-term impaired EF post-stroke are worth exploring.

It is known that impaired EF is a reliable predictor for recovery from disability after a stroke (Y. H. Park et al., 2015). Therefore, identifying and treating the baseline predictors of long-term impaired EF (e.g., baseline cognition and hypertension) would help in reducing long-term impaired EF. This improved EF would help in recovery from disability post-stroke. Modifiable risk factors such as vascular hypertension should be targeted through the implication of primary treatment strategies which can reduce the risk of stroke as well reduce the impact on EF impairment (Stroke Foundation of New Zealand, 2019).

The influence of sociodemographic factors such as older age (>75 years) and unemployment/retirement on impaired EF need clinical attention. Lack of social engagement and social support have a potential impact on impaired EF in older stroke survivors who are not working (Ellwardt, Aartsen, Deeg, & Steverink, 2013). Improving social activities and support has been found to improve EF (R. C. Sims, Levy, Mwendwa, Callender, & Campbell, 2011).

Impaired EF is prevalent even after a long time post-stroke. This highlights the importance of having a holistic management plan involving EF-specific cognitive rehabilitation. Further neuropsychological re-evaluation to assess progress and increased long-term structured support may potentially improve the quality of life of a stroke survivor.

Conclusion

The main goal of the present study was to investigate the prevalence and predictors of impaired EF at four years post-stroke. Impaired EF following a stroke often has detrimental effects in various aspects of a survivor's life, resulting in functional dependency, disability and reduced quality of life. This study has identified that impaired EF is prevalent even after four years post-stroke and nearly half of the stroke survivors (48.5%) experienced post-stroke impaired EF (CTMT<43). Impaired EF was noted on domains such as sustained attention, divided attention and cognitive set-shifting (CTMT Trail 3 and Trail 5) as measured by the individual CTMT trails.

Factors associated with impaired EF included age, unemployment/retirement, POCI (OCSP stroke subtype), non-frontal lobe stroke (stroke location), stroke in MCA (vascular territory), a history of previous stroke, a history of hypertension, a history of coronary artery disease, impaired baseline cognition, and lower quality of life. Older age (>75 years), presence of hypertension and impaired baseline cognitive function (MoCA ≤26) were shown to be reliable predictors of long-term impaired EF.

The findings from this study indicate the need to identify people who are over 75 years of age, have a history of hypertension and poor cognition at the baseline; and the need to provide specific rehabilitation from the time of stroke to enhance the long-term EF. This, in turn, would lead to better coping and functional independence post-stroke. Behavioural interventions focusing on reducing the health-related risk factors, such as hypertension, and encouraging participants to engage in cognitively stimulating activities to improve their cognitive function post-stroke can improve long-term EF. Taken together, the evidence from this study emphasises the need for specific cognitive, behavioural and health programmes tailored to the needs of stroke survivors, which would lead to improvements in EF even after four years. Moreover, an early

rehabilitation programme would, in turn, reduce the stroke burden and disability, and improve the quality of life.

Though this is one of the few seminal studies done to investigate the predictors of impaired EF, it has some limitations. As the results of the study are significantly based on NZ Europeans, a further study could systematically conduct controlled trials with an adequate representation in the sample of Māori, Pasifika, Asian, and other ethnicities. The current study used a quantitative methodology to measure the domains of EF. Further research based on their activities of daily living is needed to understand impaired EF and the factors affecting impaired EF.

Notwithstanding these limitations, the findings from this study have numerous implications for future practice. This information is essential in developing targeted interventions post-stroke. Continued efforts are required to reduce the impairment of EF post-stroke.

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Glossary

ACA	Anterior Cerebral Artery
AFT	Animal Fluency Test
ARCOS-IV	Auckland Stroke Community Outcomes Study
BI	Barthel Index
CBF	Cerebral Blood Flow
CNS-VS	Computerized Neuropsychological Vital Signs Test
COWAT	Controlled Oral Word Association Test
CTMT	Comprehensive Trail Making Test
CVA	Cerebrovascular Accident
DES	Depression-Executive Dysfunction
DKEFS	Delis-Kaplan Executive Function System
DS	Digit Span test
DSST	Digit Symbol Substitution Test
EF	Executive Functioning
EQ-5D	European Quality of Life - 5 Dimensions
HADS	Hospital Anxiety and Depression Scale
HDEC	Health and Disability Ethics Committee
LACI	Lacunar Circulation Infarct
MCA	Middle Cerebral Artery
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NZ	New Zealand
OCSP	Oxfordshire Community Stroke Project
PACI	Partial Anterior Circulation Infarct
PCA	Posterior Cerebral Artery

PICA	Posterior Inferior Cerebral Artery
POCI	Posterior Circulation Infarct
PSF	Post-Stroke Fatigue
SCT	Star Cancellation Test
SCWT	Stroop Colour Word Test
TACI	Total Anterior Circulation Infarct
TBI	Traumatic Brain Injury
TMT	Trail Making Test
TOAST	Trial of Org 10172 in Acute Stroke Treatment
VAFS	Visual Analogue Fatigue Scale
VFT	Verbal Fluency Test
WAIS	Wechsler Adult Intelligence Scale
WCST	Wisconsin Card Sorting Test

Appendices

Appendix A: Letter of Ethical Approval Health and Disability Ethics Committee (HDEC)

Health and Disability Ethics Committees

Health and Disability Ethics Committees
Ministry of Health
C/- MEDSAFE, Level 6, Deloitte House
10 Brandon Street
PO Box 5013
Wellington
6011

0800 4 ETHICS
hdecs@moh.govt.nz

24 April 2014

Professor Valery L. Feigin
National Institute for Stroke and Applied Neurosciences
90 Akoranga Drive
AUT University
Northcote 0627
Auckland 0627

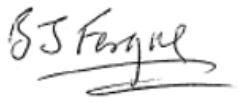
Dear Professor Feigin

Re:	**Ethics ref:**	**NTX/10/09/090/AM07**
	Study title:	Auckland Regional Community Stroke Study: Measuring and reducing stroke in New Zealand

I am pleased to advise that this amendment has been *approved* by the Northern A Health and Disability Ethics Committee. This decision was made through the HDEC Expedited Review pathway.

Please don't hesitate to contact the HDEC secretariat for further information. We wish you all the best for your study.

Yours sincerely,



Dr Brian Fergus
Chairperson
Northern A Health and Disability Ethics Committee

Encl: appendix A: documents submitted
appendix B: statement of compliance and list of members

Appendix A
Documents submitted

Document	Version	Date
PIS/CF: Patient Information Sheet and Consent Form for ARCOS IV 3 year follow-up study.	1	30 March 2014
Protocol: Protocol Version 1 for ARCOS IV 3 year follow-up study	1	20 March 2014
Survey/questionnaire: Participant Questionnaire for ARCOS IV 3 year follow-up	1	15 April 2014
Survey/questionnaire: Stroke Proxy questionnaire ARCOS IV 3 year follow up	1	15 April 2014
Survey/questionnaire: TIA participant questionnaire	1	15 April 2014
Post Approval Form	1	15 April 2014

Appendix B
Statement of compliance and list of members

Statement of compliance

The Northern A Health and Disability Ethics Committee:

- is constituted in accordance with its Terms of Reference
- operates in accordance with the *Standard Operating Procedures for Health and Disability Ethics Committees*, and with the principles of international good clinical practice (GCP)
- is approved by the Health Research Council of New Zealand's Ethics Committee for the purposes of section 25(1)(c) of the Health Research Council Act 1990
- is registered (number 00008714) with the US Department of Health and Human Services' Office for Human Research Protection (OHRP).

List of members

Name	*Category*	*Appointed*	*Term Expires*
Dr Brian Fergus	Lay (consumer/community perspectives)	01/07/2012	01/07/2015
Dr Karen Bartholomew	Non-lay (intervention studies)	01/07/2013	01/07/2016
Ms Susan Buckland	Lay (consumer/community perspectives)	01/07/2012	01/07/2015
Ms Shamim Chagani	Non-lay (health/disability service provision)	01/07/2012	01/07/2014
Dr Christine Crooks	Non-lay (intervention studies)	01/07/2013	01/07/2015
Mr Kerry Hiini	Lay (consumer/community perspectives)	01/07/2012	01/07/2014
Dr Etuate Saafi	Non-lay (intervention studies)	01/07/2012	01/07/2014
Ms Michele Stanton	Lay (the law)	01/07/2012	01/07/2014

http://www.ethics.health.govt.nz

Appendix B: Letter of Ethical Approval AUT University Ethics Committee (AUTEC)

AUTEC SECRETARIAT

13 May 2014

Valery Feigin
Faculty of Health and Environmental Sciences

Dear Valery

Re: Ethics Application: **11/297 Auckland Regional Community Stroke Study (ARCOS IV). Measuring and reducing the stroke burden in New Zealand. Part 1: ARCOS IV incidence and outcomes study (2010-2013)**

Thank you for your request for approval of an amendment to your ethics application.

I have approved a minor amendment to your ethics application allowing a 3 year follow up with participants who had previously agreed to be approached.

I remind you that as part of the ethics approval process, you are required to submit the following to the Auckland University of Technology Ethics Committee (AUTEC):

- A brief annual progress report using form EA2, which is available online through http://www.aut.ac.nz/researchethics. When necessary this form may also be used to request an extension of the approval at least one month prior to its expiry on 31 October 2014;
- A brief report on the status of the project using form EA3, which is available online through http://www.aut.ac.nz/researchethics. This report is to be submitted either when the approval expires on 31 October 2014 or on completion of the project.

It is a condition of approval that AUTEC is notified of any adverse events or if the research does not commence. AUTEC approval needs to be sought for any alteration to the research, including any alteration of or addition to any documents that are provided to participants. You are responsible for ensuring that research undertaken under this approval occurs within the parameters outlined in the approved application.

AUTEC grants ethical approval only. If you require management approval from an institution or organisation for your research, then you will need to obtain this. If your research is undertaken within a jurisdiction outside New Zealand, you will need to make the arrangements necessary to meet the legal and ethical requirements that apply there.

To enable us to provide you with efficient service, please use the application number and study title in all correspondence with us. If you have any enquiries about this application, or anything else, please do contact us at ethics@aut.ac.nz.

All the very best with your research,

Kate O'Connor
Executive Secretary
Auckland University of Technology Ethics Committee

Cc: Rita Krishnamurthi; Kathryn McPherson; Max Abbot; Sue Mahon

Auckland University of Technology Ethics Committee
WA505F Level 5 WA Building City Campus
Private Bag 92006 Auckland 1142 Ph: +64-9-921-9999 ext 8316 email ethics@aut.ac.nz

Appendix C: Participant Questionnaire

IKURA RORO AKO O T E ROHE O T AMAKI MAKAURAU WHANUI

ARCOS IV

Auckland Regional Community Outcome Stroke

ARCOS-IV 4 Year Follow-up: Stroke

(For ALL Participants)

Information to be obtained from interview

Registration Number

Participant Initials

Date Of Birth

Day Month Year

Date of first stroke during ARCOS-IV period

Day Month Year

Data entered

Signed

Day Month Year

ARCOS IV

Auckland Regional Community Outcome Stroke

ARCOS - IV 4 Year Follow - Up: Stroke

Registration Number	Participant Initials	Date Of Birth
		Day Month Year

Answer all questions. DO NOT LEAVE BLANK SPACES. Tick circles, write numbers in boxes.

If the data are unavailable put an asterisk '*' and clearly note reason and date on form.

If the data are not applicable put a dash '-' and clearly note reason and date on form.

Yes/No Responses: for each question, please mark 'Yes' or 'No

1.0 Patient Details

1.1 [ ][ ][ ] Date of birth
Day Month Year

1.2 Gender: ○ Male ○ Female

2.0 Assessment Details

2.1 [ ][ ][ ] Date of assessment
Day Month Year

2.2 Date of first stroke during ARCOS-IV period (2011-2012): [ ][ ][ ]
Day Month Year

2.3 Signed informed consent to study participation obtained for ARCOS-IV 3 year follow up.

Yes ○ No ○ If No, note reason for decline and stop here. [ ]

2.4 If Yes, who signed consent form?

○ Patient

Note: For proxy assessments (stroke only) use Proxy form.

3.0 Baseline Demographic Information

3.1 What is your current marital status? (tick one only)

○ Married, civil union or defacto relationship

○ Never married

○ Separated, divorced, or widowed

3.2 Has this changed since your stroke?

○ Yes ○ No

3.3 What is your current living status? (tick one only)

○ Living with partner / family

○ Living with others

○ Living alone

ARCOS IV

Auckland Regional Community Outcome Stroke

ARCOS - IV 4 Year Follow - Up: Stroke

Registration Number	Participant Initials	Date Of Birth
		Day Month Year

3.4 What is your current dwelling place?

- ○ Own home
- ○ Rented accommodation
- ○ Living with family or friends
- ○ Retirement village
- ○ Rest home or private hospital
- ○ Other

3.5 What is your current employment status?

- ○ Employed
- ○ Unemployed
- ○ Retired

3.5.1 If employed, what is your current occupation?

3.5.2 In what industry or organisation?

4.0 Medical History since February 2012

Note: if more than one event of any type since February 2012, enter date of earliest event first.

4.1 Have you had a new stroke since February 2012?

Yes No If No, go to 4.2

4.1.1 If Yes, date: Day Month Year

4.1.2 Did your diagnosis take place at:

○ Hospital GP ○ If other, specify:

4.1.3 If hospital, which:

4.1.4 Supporting evidence attached (e.g. discharge summary) Yes No N/A

4.1.4 Dates of any other stroke events:

4.2 Have you had a TIA since February 2012?

Yes No If No, go to 4.3

4.2.1 If Yes, date: Day Month Year

4.2.2 Did you seek medical advice from:

○ Hospital ○ GP only ○ None ○ Other, specify:

4.2.3 If hospital, which:

4.1.4 Supporting evidence attached (e.g. discharge summary) Yes No N/A

4.2.4 Dates of any other TIA events:

ARCOS IV
Auckland Regional Community Outcome Stroke

ARCOS - IV 4 Year Follow - Up: Stroke

Registration Number | Participant Initials | Date Of Birth (Day Month Year)

4.3 Have you had a heart attack/myocardial infarction since February 2012?

○ Yes ○ No 4.3.1 If Yes, date: [ ][ ][ ] (Day Month Year) If No, go to 4.4

4.3.2 Did your diagnosis take place at:

○ Hospital ○ GP ○ If other, specify: [ ]

4.3.3 If hospital, which: [ ]

4.1.4 Supporting evidence attached (e.g. discharge summary) ○ Yes ○ No ○ N/A

4.3.4 Dates of any other MI events: [ ]

Have you had any of the following procedures conducted since February 2012?

4.4 Carotid endartectomy ○ Yes ○ No If No, go to 4.5

4.4.1 If Yes, date: [ ][ ][ ] (Day Month Year)

4.4.2 Where was procedure performed? [ ]

4.4.3 Supporting evidence attached (e.g. discharge summary) ○ Yes ○ No

4.5 Carotid artery stenting ○ Yes ○ No If No, go to 4.6

4.4.1 If Yes, date: [ ][ ][ ] (Day Month Year)

4.4.2 Where was procedure performed? [ ]

4.4.3 Supporting evidence attached (e.g. discharge summary) ○ Yes ○ No

4.6 Coronary artery bypass graft ○ Yes ○ No If No, go to 4.7

4.4.1 If Yes, date: [ ][ ][ ] (Day Month Year)

4.4.2 Where was procedure performed? [ ]

4.4.3 Supporting evidence attached (e.g. discharge summary) ○ Yes ○ No

4.7 Coronary artery stenting ○ Yes ○ No If No, go to 4.8

4.4.1 If Yes, date: [ ][ ][ ] (Day Month Year)

4.4.2 Where was procedure performed? [ ]

4.4.3 Supporting evidence attached (e.g. discharge summary) ○ Yes ○ No

4.8 Peripheral vascular revascularisation procedure ○ Yes ○ No If No, go to 4.9

4.4.1 If Yes, date: [ ][ ][ ] (Day Month Year)

4.4.2 Where was procedure performed? [ ]

4.4.3 Supporting evidence attached (e.g. discharge summary) ○ Yes ○ No

ARCOS IV

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ARCOS - IV 4 Year Follow - Up: Stroke

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Since February 2012, have you had a **new** diagnosis of any of the following:

	Yes	No		Hospital only: if Yes, daignosis confirmed?
4.9	○	○	Elevated blood lipids (cholesterol)	○
4.10	○	○	Hypertension, elevated blood pressure	○
4.11	○	○	Diabetes	○
4.12	○	○	Coronary artery disease, angina	○
4.13	○	○	Irregular pulse (arrhythmia), atrial fibrillation, valvular heart disease	○
4.14	○	○	Heart disease	○
4.15	○	○	Peripheral vascular disease (pain in legs when walking)	○
4.16	○	○	Epilepsy/seizures	○
4.17	○	○	Any other diagnosis?	○

4.17.1 If yes, specify: _____

5.0 Lifestyle

5.1 What is your current smoking status?

- ○ Never smoked (If never smoked, go to 5.2)
- ○ Ex-smoker
- ○ Current smoker (smoked within past month)

5.1.1 If ex-smoker or current smoker, has your smoking changed since your first stroke event during the ARCOS period (2011-2012)?

○ Yes ○ No

5.1.2 If yes, what changes have you made?

- ○ Stopped smoking successfully
- ○ Reduced smoking
- ○ Smoking more often

5.2 Do you regularly drink any type of alcohol?

○ Yes ○ No (If No, go to 5.2.2)

5.2.1 If Yes, which of the following best describes how often have you drank in the past three months?

- ○ All day
- ○ Four or more times a day
- ○ Two or three times a day
- ○ Once a day
- ○ Every 2 days
- ○ Every 3 or 4 days
- ○ Every 5 or 6 days
- ○ Once a week
- ○ Every 10 days
- ○ Once a fortnight
- ○ Once a month

Registration Number | Participant Initials | Date Of Birth (Day / Month / Year)

5.2.2 Have you made any changes to your drinking since your first stroke event during the ARCOS period (2011-2012)?
○ Yes ○ No

5.2.3 If yes, what change have you made?
○ Stopped drinking
○ Reduced amount of drinking
○ Increased amount of drinking

5.3 How would you rate your current diet or eating habits?
Very healthy Mostly healthy
A mixture of healthy and unhealthy Mostly unhealthy

5.4 On average how many servings of vegetables and fruit do you eat per day?
○ None ○ Less than one ○ One
○ Two ○ Three ○ Four or more

5.5 How often do you add salt to your food?
○ Never ○ Rarely ○ Sometimes
○ Regularly ○ Always ○ Don't know

5.6 How often do you remove fat from your food or choose low fat options?
○ Never ○ Rarely ○ Sometimes
○ Regularly ○ Always ○ Don't know

5.7 Have you made any changes to your diet since your first stroke event during the ARCOS period (2011-2012)?
Yes No

5.7.1 If yes, what changes have you made?
○ Smaller amounts of food ○ More fruit and/or vegetables
○ Reduced fat ○ Less healthy diet
○ Reduced salt ○ Other:

5.8 During the past month, on how many days per week did you engage in at least 30 minutes of moderate exercise or activity that made you breathe harder than normal?
○ None ○ 1 day ○ 2 days ○ 3 days
○ 4 days ○ 5 days ○ 6 days ○ 7 days

5.7 Are there any lifestyle areas you would like to change to reduce your risk of recurrent stroke?
○ Yes ○ No

5.7.1 If Yes, what changes would you like to make?

Appendix D: Montreal Cognitive Assessment

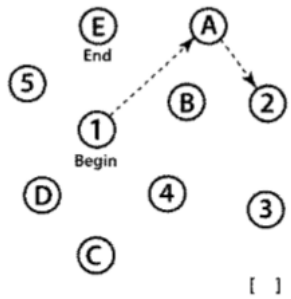
ARCOS IV — ARCOS - IV 3 Year Follow - Up:Stroke

Registration Number | Participant Initials | Date Of Birth (Day / Month / Year)

MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

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

VISUOSPATIAL / EXECUTIVE — POINTS



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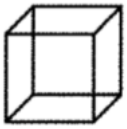


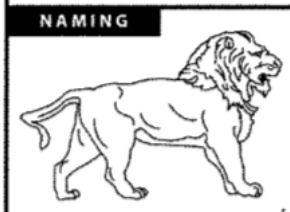
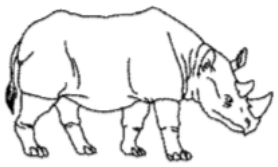
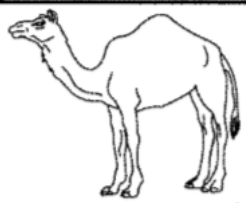
[ ] [ ]

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING

[ ] [ ] [ ]

__/3

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

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

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

__/1

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

__/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

© Z.Nasreddine MD www.mocatest.org Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

MOCA Test Scores

(Instructions for RA: please use the information and sub-scores above to complete the following section)

18.1 MOCA (tick one only)

(Instruction: If Not Done, go to section 10)

- ○ Full test
- ○ Short test, reason: ____
- ○ Not done, reason: ____

18.2 ☐☐ : ☐☐ Start Time
hh mm

18.3 ☐☐ : ☐☐ Finish Time
hh mm

18.4 ☐ Visuospatial/executive

18.5 ☐ Naming

18.6 ☐ Attention

18.7 ☐ Language

18.8 ☐ Abstraction

18.9 ☐ Delayed recall

18.10 ☐ Orientation

18.11 ☐ Total MOCA Score

Please record the following additional information from the MoCA during testing:

18.12 ☐☐ **Verbal fluency**

Number of words beginning with f generated in the first 15 seconds

18.13 ☐☐ **Delayed recall (category cue)**

Number of words recalled with category cue (if patient does not spontaneously recall all the words)

18.14 ☐☐ **Delayed recall (multichoice cue)**

Number of words recalled with a multichoice cue (if patient fails to recall the words with a category cue)

Appendix E: Barthel Index

7.0 Rehabilitation

7.1 Did you receive inpatient rehabilitation following your stroke?

○ Yes ○ No

7.1.1 If yes, specify length of stay

7.2 Did you receive community rehabilitation following your stroke?

○ Yes ○ No

7.2.1 If yes, which service?

7.2.2 How often did you receive community rehabilitation?

○ Once per week ○ Once per fortnight ○ Once per month ○ Once per 6 months Other:

8.0 Barthel Index

Guidelines for Completion

a. *The index should be used as a record of what a participant does, not as a record of what a participant, could do.*

b. *The main aim is to establish the degree of independence from any help, physical or verbal, however minor or for whatever reason.*

c. *The need for supervision renders the participant not independent.*

d. *A participant's performance should be established using the best available evidence. Asking the participant, friends/relatives and nurses are the usual sources, but direct observation and common sense are also important. However, direct testing is not needed.*

e. *Usually the participant's performance over the proceeding 24-48 hours is important, but occasionally longer periods will be relevant.*

f. *Middle categories imply that the patient supplies over 50 percent of the effort.*

g. *Use of aids to be independent is allowed.*

Choose the scoring point for the statement that most closely corresponds to the patient's current level of ability for each of the following 10 items. Record actual, not potential, functioning. Information can be obtained from the patient's self-report, from a separate party who is familiar with the patient's abilities (such as a relative), or from observation.
Refer to the Guidelines section for detailed information on scoring and interpretation.

8.1 Feeding (tick one only)

2 ○ Independent: Able to use any necessary device; feeds in a reasonable time; able to cut up food, use condiments, spread butter etc. on his/her own. Food may be placed within reach.

1 ○ Needs help: e.g. with cutting or spreading butter.

0 ○ Dependent: Needs to be fed.

8.2 Bathing (tick one only)

1 ○ Independent: Able to wash self all over; may be by using shower, a full bath or standing and sponging all over. Includes getting into and out of bath, or shower room.

0 ○ Dependent: Needs some help.

8.3 Grooming (tick one only)

1 ○ Independent: Doing all personal activities, e.g. washing hands and face, combing hair. Includes shaving and teeth. Not to need any help, except.

0 ○ Dependent: Needs some help.

8.4 Dressing (tick one only)

2 ○ Independent: Able to dress, includes (buttons, zip, laces) getting clothes out of closet/drawers. No needed at all, may use rail for stabilising.

1 ○ Needs help: Needs minor help verbal or physical managing clothes and balancing.

0 ○ Dependent: Unable to dress without major assistance.

8.5 Bowels (tick one only)

2 ○ Continent: If needs enema, suppository, must manage him/herself.

1 ○ Occasional accident: Rare (under once a week); needs help with enema.

0 ○ Incontinent

8.6 Bladder (tick one only)

2 ○ Continent: Able to use any device (e.g. catheter) if necessary.

1 ○ Occasional accident: Maximum once per 24 hours; needs help with device.

0 ○ Incontinent or catheterized and unable to manage.

8.7 Toilet (tick one only)

2 ○ Independent: Able to handle clothes, wipe self, flush toilet, empty commode completely unaided. Able to get on and off alone.

1 ○ Needs help: Able to manage with minor help balancing, handling clothes or toilet paper. However, still able to use toilet.

0 ○ Dependent: Unable to manage without major assistance.

8.8 Chair/Bed Transfers (tick one only)

3 ○ Independent: No help; includes locking wheelchair if necessary.

2 ○ Minimal help: Includes verbal supervision and minor physical help such as might be given by a not very strong spouse.

1 ○ Major help: Able to sit unaided, but needs much help (two people).

0 ○ Dependent: Unable to manage without major assistance.

Continued...

ARCOS IV
Auckland Regional Community Outcome Stroke

ARCOS - IV 4 Year Follow - Up: Stroke

Registration Number | Participant Initials | Date Of Birth (Day / Month / Year)

8.9 Mobility (tick one only)

3 ○ Independent: May use any aid; speed is not important. Able to mobilise about house.

2 ○ Needs help: Verbal or physical supervision, including help up into walking frame or other help standing.

1 ○ Independent in wheelchair: Must be able to negotiate corners alone.

0 Immobile: Including being wheeled by another.

8.10 Stairs (tick one only)

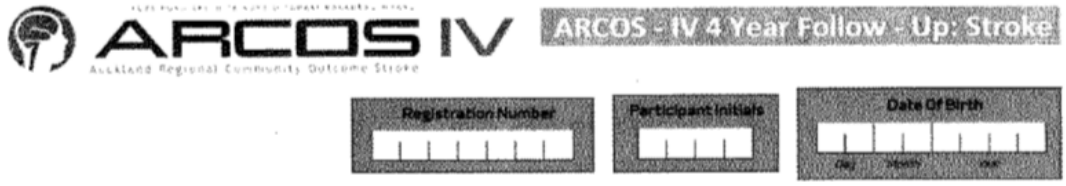
2 ○ Independent: Must carry walking aid if used.

1 Needs help: Physical or verbal supervision, carrying aid etc.

0 Unable: Needs lift (elevator), or cannot negotiate stairs.

8.11 Total Barthel Score

Appendix F: Hospital Anxiety and Depression Scale



Complete remaining sections in Part A at ALL assessments (ALL Participants)

Hospital Anxiety and Depression Scale (HADS)

Please indicate which of the following options best describes how you have been feeling during the last week.

I feel tense or wound up

- ○ 3 - Most of the time
- ○ 2 - A lot of the time
- ○ 1 - From time to time, occasionally
- ○ 0 - Not at all

I still enjoy the things I used to enjoy

- ○ 0 - Definitely as much
- ○ 1 - Not quite as much
- ○ 2 - Only a little
- ○ 3 - Hardly at all

I get a sort of frightened feeling as if something awful is about to happen

- ○ 3 - Very definitely and quite badly
- ○ 2 - Yes, but not too badly
- ○ 1 - A little, but it doesn't worry me
- ○ 0 - Not at all

I can laugh and see the funny side of things

- ○ 0 - As much as I always could
- ○ 1 - Not quite so much now
- ○ 2 - Definitely not as much now
- ○ 3 - Not at all

Worrying thoughts go through my mind

- ○ 3 - A great deal of the time
- ○ 2 - A lot of the time
- ○ 1 - From time to time, but not too often
- ○ 0 - Only occasionally

15.6 I feel cheerful (tick one only)

- ○ 3 - Not at all
- ○ 2 - Not often
- ○ 1 - Sometimes
- ○ 0 - Most of the time

15.7 I can sit at ease and feel relaxed (tick one only)

- ○ 0 - Definitely
- ○ 1 - Usually
- ○ 2 - Not often
- ○ 3 - Not at all

15.8 I feel as if I am slowed down (tick one only)

- ○ 3 - Nearly all the time
- ○ 2 - Very often
- ○ 1 - Sometimes
- ○ 0 - Not at all

15.9 I get a sort of frightened feeling like 'butterflies' in the stomach (tick one only)

- ○ 0 - Not at all
- ○ 1 - Occasionally
- ○ 2 - Quite often
- ○ 3 - Very Often

15.10 I have lost interest in my appearance (tick one only)

- ○ 3 - Definitely
- ○ 2 - I don't take as much care as I should
- ○ 1 - I may not take quite as much care
- ○ 0 - I take just as much care as ever

15.11 I feel restless as if I have to be on the move (tick one only)

- ○ 3 - Very much indeed
- ○ 2 - Quite a lot
- ○ 1 - Not very much
- ○ 0 - Not at all

15.12 I look forward with enjoyment to things (tick one only)

- ○ 0 - As much as I ever did
- ○ 1 - Rather less than I used to
- ○ 2 - Definitely less than I used to
- ○ 3 - Hardly at all

15.13 I get sudden feelings of panic (tick one only)

- ○ 3 - Very often indeed
- ○ 2 - Quite often
- ○ 1 - Not very often
- ○ 0 - Not at all

15.14 I can enjoy a good book or TV programme (tick one only)

- ○ 0 - Often
- ○ 1 - Sometimes
- ○ 2 - Not often
- ○ 3 - Very seldom

Anxiety Subscore	
Depression Subscore	
15.15 **Total HADS Score**	

Appendix G: Fatigue Visual Analogue Scale

ARCOS IV

Auckland Regional Community Outcome Stroke

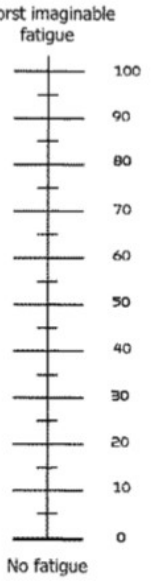
ARCOS - IV 4 Year Follow - Up: Stroke

Registration Number | Participant Initials | Date Of Birth (Day / Month / Year)

11.0 Fatigue Visual Analogue Scale

On a scale of 0 to 100, with 100 representing maximum fatigue and 0 representing no fatigue, how much fatigue have you experienced since your stroke?

Please put a line on the scale that represents how much fatigue you have experienced.



(Office Use only)

11.1 Fatigue score

[ ] If zero, go to 13.0

12.0 Fatigue Severity Scale

Please circle the number between 1 and 7 which you feel best fits the following statements. This refers to your usual way of life within the last week. 1 indicates "strongly disagree" and 7 indicates "strongly agree."

Read and circle a number.	Strongly disagree						Strongly agree
1. My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
2. Exercise brings on my fatigue.	1	2	3	4	5	6	7
3. I am easily fatigued.	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning.	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
8. Fatigue is among my most disabling symptoms.	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7

12.1 Total fatigue score: [ ]

Appendix H Modified Rankin Scale

9.0 Modified Rankin Scale

How would you describe your current symptoms or disability?

	SCORE	DESCRIPTION
○	0	No symptoms at all
○	1	No significant disability despite symptoms; able to carry out all usual duties and activities
○	2	Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance
	3	Moderate disability; requiring some help, but able to walk without assistance
○	4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
	5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
○	6	Dead

9.1 MRS Score

Appendix I: EuroQol Quality of Life Scale

ARCOS IV
Auckland Regional Community Outcome Stroke

ARCOS - IV 4 Year Follow - Up: Stroke

Registration Number | Participant Initials | Date Of Birth (Day / Month / Year)

10.0 Health related Quality of life

Instructions: *By placing one tick only in each question, please indicate which statements best describe your health today.*

10.1 Mobility (tick one only)

- ○ I have no problems walking about
- ○ I have some problems walking about
- ○ I am confined to bed

10.2 Self-Care (tick one only)

- ○ I have no problems with self-care
- ○ I have some problems washing or dressing myself
- ○ I am unable to wash or dress myself

10.3 Usual Activities (e.g. work, study, housework, family or leisure activities) (tick one only)

- ○ I have no problems with performing my usual activities
- ○ I have some problems with performing my usual activities
- ○ I am unable to perform my usual activities

10.4 Pain/Discomfort (tick one only)

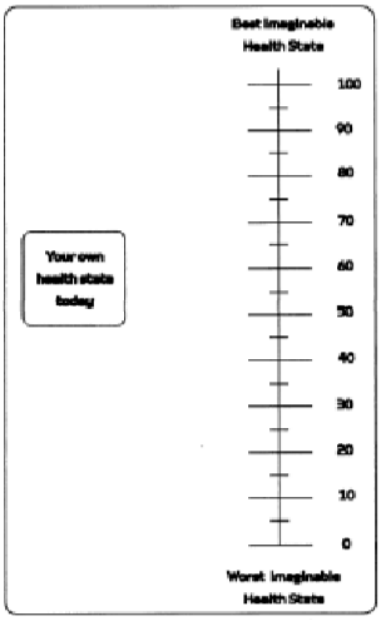
- ○ I have no pain or discomfort
- ○ I have moderate pain or discomfort
- ○ I have extreme pain or discomfort

10.5 Anxiety/Depression (tick one only)

- ○ I am not anxious or depressed
- ○ I am moderately anxious or depressed
- ○ I am extremely anxious or depressed

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.



10.6 Health state score: ☐

Appendix J Multicollinearity between outcome measures

	BI	HADS Anxiety	HADS Depression	mRS	VAFS	MoCA	EQ-5D Utility Scores	EQ-5D Mobility	EQ-5D Self-care	EQ-5D Usual Activities	EQ-5D Pain and Discomfort	EQ-5D Anxiety and Depression
BI	1	0.188	0.056	-.589**	-.307*	.287*	.327*	-.397**	-.673**	-0.25	-0.071	0
p-value		0.157	0.683	0	0.032	0.026	0.022	0.004	0	0.08	0.623	1
n	68	58	56	68	49	60	49	50	50	50	50	49
HADS Anxiety	0.188	1	.575**	0.048	.429**	0.031	-0.244	0.071	-0.024	0.203	0.249	.484**
p-value	0.157		0	0.718	0.003	0.821	0.102	0.636	0.874	0.171	0.092	0.001
n	58	62	60	59	46	55	46	47	47	47	47	46
HADS Depression	0.056	.575**	1	-0.003	0.266	-0.062	-.350*	0.266	0.052	.328*	0.227	0.233
p-value	0.683	0		0.981	0.081	0.657	0.02	0.078	0.737	0.028	0.134	0.128
n	56	60	60	57	44	53	44	45	45	45	45	44
mRS	-.589**	0.048	-0.003	1**	.365**	-0.23	-0.105	0.234	.304*	0.229	-0.018	-0.149
p-value	0	0.718	0.981	0	0.009	0.075	0.47	0.098	0.03	0.107	0.901	0.301
n	68	59	57	70	50	61	50	51	51	51	51	50

VAFS	-.307*	.429**	0.266	.365**	1	-0.181	-.267*	0.066	0.041	0.167	0.176	.297*
p-value	0.032	0.003	0.081	0.009		0.218	0.047	0.628	0.76	0.214	0.19	0.026
n	49	46	44	50	57	48	56	57	57	57	57	56
MoCA	.287*	0.031	-0.062	-0.23	-0.181	1	0.154	-0.278	-0.136	-0.216	0.078	0.014
p-value	0.026	0.821	0.657	0.075	0.218		0.296	0.053	0.353	0.135	0.596	0.924
n	60	55	53	61	48	61	48	49	49	49	49	48
EQ-5D Utility Scores	.327*	-0.244	-.350*	-0.105	-.267*	0.154	1	-.543**	-.535**	-.708**	-.624**	-.466**
p-value	0.022	0.102	0.02	0.47	0.047	0.296		0	0	0	0	0
n	49	46	44	50	56	48	57	57	57	57	57	57
EQ-5D Mobility	-.397**	0.071	0.266	0.234	0.066	-0.278	-.543**	1	.500**	.431**	0.016	-0.003
p-value	0.004	0.636	0.078	0.098	0.628	0.053	0		0	0.001	0.906	0.985
n	50	47	45	51	57	49	57	58	58	58	58	57
EQ-5D Self-care	-.673**	-0.024	0.052	.304*	0.041	-0.136	-.535**	.500**	1	.361**	.295*	0.046
p-value	0	0.874	0.737	0.03	0.76	0.353	0	0		0.005	0.024	0.735
n	50	47	45	51	57	49	57	58	58	58	58	57

EQ-5D Usual Activities	-0.25	0.203	.328*	0.229	0.167	-0.216	-.708**	.431**	.361**	1	0.225	0.031
p-value	0.08	0.171	0.028	0.107	0.214	0.135	0	0.001	0.005		0.09	0.818
n	50	47	45	51	57	49	57	58	58	58	58	57
EQ-5D Pain and Discomfort	-0.071	0.249	0.227	-0.018	0.176	0.078	-.624**	0.016	.295*	0.225	1	.352**
p-value	0.623	0.092	0.134	0.901	0.19	0.596	0	0.906	0.024	0.09		0.007
n	50	47	45	51	57	49	57	58	58	58	58	57
EQ-5D Anxiety and Depression	0.47	.484**	0.02	0.102	.297*	0.022	-.466**	0.154	-0.105	-0.244	.352**	1
p-value	1	0.001	0.128	0.301	0.026	0.924	0	0.985	0.735	0.818	0.007	
n	49	46	44	50	56	48	57	57	57	57	57	57

Note: ** A value of p<0.01 represent statistical significance. *A value of p<0.05 represent statistical significance
Note: MoCA=Montreal Cognitive Assessment, BI=Barthel Index, HADS=Hospital Anxiety and Depression Scale, VAFS= Visual Analogue Fatigue Scale, mRS= Modified Rankin Scale, EQ-5D=EuroQol Quality of Life Scale