THE EFFECTS OF CREATINE MONOHYDRATE SUPPLEMENTATION AND
RESISTANCE TRAINING IN STROKE SURVIVORS

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By
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Sara Marie Butchart, candidate for the degree of Master of Science in Kinesiology & Health Studies, has presented a thesis titled, *The Effects of Creatine Monohydrate Supplementation and Resistance Training in Stroke Survivors*, in an oral examination held on May 12, 2020. The following committee members have found the thesis acceptable in form and content, and that the candidate demonstrated satisfactory knowledge of the subject material.

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Abstract

The purpose was to investigate the effects of progressive resistance training and creatine supplementation in individuals’ post-stroke. Participants were randomized to one of two groups: creatine (n = 5; 51 ± 15 yrs, 173.04 ± 10.75 cm, 84.74 ± 19.24 kg) or placebo (n = 3; 73 ± 8 yrs, 171.26 ± 5.31 cm, 73.33 ± 5.83 kg) during 10 weeks of supervised, progressive resistance training. Prior to and following training and supplementation, assessments were made for body composition (lean tissue, fat mass, bone mineral; dual energy x-ray absorptiometry), muscle thickness (elbow and knee flexors and extensors; ultrasound), muscle strength (1-repetition maximum leg-press, chest-press), tasks of functionality (berg balance scale, six-minute walk test), cognition (Montreal Cognitive Assessment), and symptoms of anxiety (Generalized Anxiety Disorder Assessment) and depression (Center for Epidemiological Studies Depression Scale). The creatine group experienced a significant increase (p < 0.05) in leg press (pre 170 ± 62 kg, post 230 ± 82 kg) and chest press strength (pre 51 ± 34 kg, post 74 ± 45 kg), muscle thickness of the elbow flexors (left side: pre 3.31 ± 0.68 cm, post 3.65 ± 0.53 cm; right side: 3.08 ± 0.52 cm, post 3.56 ± 0.70 cm), 6-minute walking performance (pre 598.80 ± 168.92 sec, post 638.00 ± 160.15 sec) and a decrease in anxiety over time (pre 4.80 ± 3.83, post 1.40 ± 1.51). There were no changes in the placebo group for any variable. In conclusion, creatine monohydrate supplementation and progressive resistance training is an effective lifestyle intervention for improving strength, muscle thickness, walking performance and decreasing anxiety in a very small cohort of stroke survivors.

Key words: Medical, Strength, Functionality, Lean Tissue Mass, Stroke
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Abbreviations

1-RM – One Repetition Maximum

4E – BP1 - Eukaryotic translation initiation factor 4E-binding protein 1

ADP – Adenosine Diphosphate

AGAT - Arginine Glycine Amidinotransferase

AMP – Adenosine Monophosphate

ANOVA – Analysis of variance

ATP – Adenosine Triphosphate

BBB – Blood Brain Barrier

BBS – Berg Balance Scale

BMC- Bone Mineral Content

BMD – Bone Mineral Density

CES-D – Center for Epidemiological Studies Depression Scale

CK – Creatine Kinase

CR – Creatine

CNS – Central Nervous System

CRT - Creatine Transporter Protein

DXA – dual-energy X-Ray absorptiometry

ERK6 - Extracellular signal-regulated kinase 6

GAA – Guanidinoacetic Acid

GAD – The Generalized Anxiety Disorder Assessment

GNMT - guanidine N-methyltransferase
IGF-1 – Insulin Like Growth Factor 1
ISSN – The International Society of Sports Nutrition
MAPK - muscle kinases p38
MET – Metabolic Equivalent
MRF – 4 – Myogenic Regulatory Facotor-4
MTOR - Mammalian target of rapamycin
MOCA – The Montreal Cognitive Assessment
NA – Nicotinamide adenine
NAD+ - Nicotinamide adenine dinucleotide
PARP-1 - poly(ADP-ribose) polymerase-1
PASIPD – Physical Activity Scale for Persons with Physical Disabilities
PKB/Ak – Protein Kinase B
PCr – Phosphocreatine
Pi – Inorganic phosphate
RT – Resistance Training
SAMs-adenosylmethionine
SAH - s-adenosylhomocysteine
SC – Satellite Cells
TBI – Traumatic Brain Injury
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1 Introduction

Stroke is characterized by an abrupt disturbance in cerebral circulation causing a neurological deficit (Bath & Lees, 2000). Following a stroke, brain function deteriorates quickly leading to neuronal cell death (Arvidsson et al. 2002). This in turn results in a major cause of adult neurological disability in North America, often resulting in significant muscle loss, weakness and functional limitations (English et al., 2010). Disability associated with stroke limits independent living and social participation in at least half of all stroke survivors (Dobkin, 2005). A sedentary lifestyle after stroke can increase the risk for recurrent stroke, cardiovascular disease, and diabetes mellitus (Frizzell, 2005). All of these factors may adversely affect independence and quality of life (van Mierlo, et al. 2016).

The majority of stroke survivors have residual impairments such as hemiparesis, spasticity, cognitive dysfunction, and aphasia, with full recovery reached in a small portion of these individuals (Billinger, 2014). One of the major consequences of these impairments is physical inactivity which inevitably contributes to muscle loss, decreased muscle function (i.e. strength, endurance) and impaired functionality (Singh, 2002). Sarcopenia, the loss of fat-free mass with age, increases the risk for subsequent injury and disability (Reid et al., 2008). The progression and consequences of sarcopenia may be especially severe after stroke due to inactivity as well as reduced strength and fitness levels in stroke survivors (Ryan et al., 2011). One intervention which may help improve muscle mass, muscle function and functionality in stroke survivors is supervised resistance training. Resistance training does not lead to muscle spasticity in stroke survivors (Sharp & Brouwer, 1997) and has been shown to improve the ability to perform activities of daily
living (Ada, Vattanaslip, O’Dwyer, Crosbie, 1998; Bohannaon, Warren, Cogman, 1991; Hamrin et al., 1982). One of the main objectives post-stroke is to restore a patient’s ability to perform activities of daily living which may be done by improving muscle mass, strength and functionality.

Another intervention which may be beneficial for stroke survivors is creatine supplementation. Creatine has been shown to increase muscle mass, muscle function and tasks of functionality when combined with resistance training, possibly by influencing cellular hydration status, high-energy phosphate metabolism, muscle protein kinetics, satellite cells, anabolic growth factors, and inflammation (for reviews see Candow et al. 2019; Chilibeck et al. 2017; Kreider et al., 2017). Creatine may also exhibit cognitive (Dolan et al., 2018; Gualano et al., 2016), and antidepressant effects (Kious et al. 2019). Adenosine has several roles within the CNS that are crucial for proper brain function, including the regulation of behavior, mood and emotion (Cunha et al., 2008; Ruby et al., 2010; Asatryan et al., 2011). After stroke, ATP levels have been shown to be significantly decreased suggesting a decrease in ATP production, an increase in ATP utilization, or both (Li et al., 2017). Because cognitive tasks rely on creatine and phosphocreatine to maintain brain ATP levels, increasing brain creatine through creatine supplementation may improve cognitive processing. Creatine supplementation has shown a positive effect on both working memory and intelligence (Rae et al., 2003), mental fatigue (Watanabe et al., 2002), forward recall, spatial recall, long term memory (McMorris et al., 2007), memory scanning, number pair matching, and sustained attention (Ling et al., 2009).

Despite the potential beneficial effects of resistance training and creatine supplementation for stroke survivors, no study has examined the combined effects of
supervised resistance training and creatine supplementation in this clinical population. Therefore, the purpose of this thesis was to examine the effects of resistance training and creatine supplementation on body composition, muscle thickness, muscle strength, tasks of functionality, cognition and symptoms of anxiety and depression in stroke survivors.

2 Literature review

2.1 Stroke Pathophysiology

Stroke can be subdivided into 2 categories, ischemic and hemorrhagic. Ischemic stroke is the most common and occurs in approximately 87% of all cases (Rosamond et al., 2007). A hemorrhagic stroke occurs when bleeding takes place within the brain (intracerebral hemorrhage) or within the subarachnoid space (subarachnoid hemorrhage). An ischemic stroke occurs due to either a thrombosis, an embolism or systemic hypoperfusion, all of which result in a restriction of blood flow to the brain (Jefferson et al., 2007). Ischemia causes brain damage by activating the ischemic cascade, which progresses to local depletion of oxygen and or glucose, causing failure of production of high energy phosphate compounds like ATP (Deb, Sharma, Hassan, 2009). This, in turn, causes insufficient oxygen and glucose delivery to support cellular homeostasis which elicits multiple processes that lead to cell death (Kalogeris et al., 2014). The contributing factors of stroke include excitotoxicity, acidotoxicity and ionic imbalance, oxidative stress, nitrative stress, inflammation and apoptosis (Gonzalez et al., 2006). These pathological processes have distinct time frames, some occurring quickly while others occur within days, causing injury to the neurons, glia, and endothelial cells (Doyle, Simon, Stenzel-Poore, 2008).
Stroke of the left hemisphere may disturb language and comprehension, whereas stroke of the right hemisphere may affect intuitive thinking, reasoning, problem solving as well as perception, judgment and the visual spatial functions (Constans, Pin-barre, Temprado, Decherchi & Laurin, 2016).

2.2 Ischemic Stroke

Ischemic stroke occurs when cerebral blood flow is interrupted, usually due to either thrombosis or embolism. Compromised vascular supply to the brain is the primary cause of acute stroke (Deb, Sharma, Hassan, 2009). The interruption of cerebral blood flow causes cell necrosis and subsequent cerebral edema in the core area of ischemia, followed by destruction of the blood-brain barrier (BBB) (Danton & Dietrich, 2003). The release of necrotic cells induces apoptosis and inflammatory cytokines that cause the death of half of the cells in the vicinity of the infraction (Rock & Kono, 2008). The ultimate result of ischemic cascade initiated by acute stroke is neuronal death along with an irreversible loss of neuronal function (Deb, Sharma, Hassan, 2009). Ischemia causes brain damage by activating the ischemic cascade, which progresses to local depletion of oxygen or glucose, causing failure of production of high energy phosphate compounds, like adenine triphosphate (ATP) (Eltzschig & Eckle, 2011). This then adversely affects energy-dependent processes necessary for tissue cell survival as well as cell death (Deb, Sharma, Hassan, 2009).

An embolic stroke occurs when a blood clot or plaque fragment forms somewhere in the body, usually the heart, and travels to the brain. It results in cell hypoxia and depletion of cellular adenosine triphosphate (ATP) (Rink & Khanna, 2011). Without ATP, energy failure results in an inability to maintain ionic gradients across the cell membrane
and cell depolarization. Moreover, cell depolarization leads to the release of glutamate and free radicals, mitochondrial membrane disruption and eventually apoptotic cellular death (Dong, Wang & Qin, 2009). Ischemia also results in dysfunction of the cerebral vasculature with breakdown of the blood-brain barrier occurring within 4-6 hours (Keep et al., 2014).

2.3 Intracerebral Hemorrhage

During an intracerebral hemorrhage a rapid accumulation of blood within the brain parenchyma leads to a disruption and increases local pressure (Aronowski & Zhao, 2011). The primary damage occurs within minutes from the onset of bleeding which is the primary result of mechanical damage (Qureshi et al., 2003). The secondary damage is mostly due to the presence of intraparenchymal blood may be due to the initial hematoma volume, age, or ventricle volume (Qureshi et al., 2003). The secondary effect may occur through many pathological pathways such as cytotoxicity of blood (Wagner, Sharp, Ardizzone, Lu & Clark, 2003), hyper metabolism (Wagner, Sharp, Ardizzone, Lu & Clark, 2003), excitotoxicity (Qureshi et al., 2003), spreading depression (Mun-Bryce, Wilkerson, Papiushvili, Okada, 2001), and oxidative stress and inflammation (Keep & Holt, 2001). This pathogenesis leads to irreversible disruption of the components of the neurovascular unit which leads to BBB disruption and extreme brain edema with massive brain cell death (Aronowski & Zhao, 2011).

2.4 Subarachnoid Hemorrhage

A subarachnoid hemorrhage occurs when bleeding occurs in the subarachnoid space – the area between the arachnoid membrane and the pia matter surrounding the brain. This is a rare type of stroke and diagnosis can be challenging and missed or delayed diagnosis can be catastrophic (Carpenter et al., 2016). Subarachnoid hemorrhage may
occur as a result as a traumatic brain injury or as a ruptured blood vessel. The cause of a spontaneous subarachnoid hemorrhage can be classified into either an aneurysmal, nonaneurysmal, and perimesencephalic causes (van Gijn & Rinkel, 2001). Aneurysmal subarachnoid hemorrhage is associated with a 30-day mortality of approximately 45% and 30% of survivors have major disabilities (Hop et al., 1997). Of the individuals who survive hospital, less than a fifth have no remaining symptoms (Molyneux, Kerr, Yu LM, et al, 2005).

2.5 Risk Factors for Stroke

There are various risk factors that potentially affect why a stroke occurs in the first place and the chances of another stroke occurring in the future. Current protocols of primary stroke management and secondary prevention focuses on modifiable risk factors such as hypertension, smoking, carotid stenosis, atrial fibrillation, physical inactivity, diabetes mellitus, and dyslipidemia (Smajlović, 2015). It has been shown that three months of progressive resistance was associated with reduced fat mass which was related to improvements in walking capacity in older adults (Vahlberg et al., 2015). It has also been shown that progressive resistance training has a large effect on muscular strength and activities of daily living (Dorsch et al., 2018). For the purpose of this thesis, supervised resistance training was used as the physical activity intervention.

2.6 Resistance Training Post-Stroke

There is substantial evidence that stroke occurs at a higher rate in aging individuals, a population already susceptible to muscle and strength loss. The European Working Group on Sarcopenia in Older People has recently defined sarcopenia as a muscle disease (ICD-10-MC Diagnosis Code) characterized by low muscle strength, muscle mass and
functionality (Cruz-Jentoft et al., 2018). While sarcopenia occurs in the course of normal aging, specific disease-related sarcopenia should be considered in conditions where accelerated muscle atrophy occurs. The concept of ‘stroke-related sarcopenia’ has recently emerged. Skeletal muscle is the main effector organ accountable for disability in stroke. This is supported by changes in skeletal muscle post-stroke (Gariballa et al., 1998). Following stroke, skeletal muscle demonstrates similarities to aging muscle (Sions et al., 2012), such as a progressive decrease in muscle fibre size, but with a greater decrease on the more affected side (Scelsi et al., 1984). Stroke results in a reduction in muscle mass and muscle function predominantly on the paretic side with mild weakness of the ipsilateral, non-paretic side (Eng, 2004). Following a stroke, the number of type II fibres progressively decrease, resulting in a loss of skeletal muscle cross-sectional area (Torfolla et al., 2001; Scelsi et al., 1984). Andrews and Bohannon (2000) have shown that strength of eight paretic muscles were only 29 to 45% of age-matched subjects’ strength, tested using a hand-held dynamometry. Due to the decrease in the number of Type II fibres, force production and contractile speed is reduced, which in turn can result in difficulty with sit to stand transfers (Bohannon, 2007; Cheng et al., 2004) and balance (Marigold et al., 2004).

The age-related loss in muscle mass increases the risk for subsequent injury and disability (Reid et al., 2008). Resistance training has been considered one of the most efficient interventions to counteract the decline in muscle mass and function in older individuals (Ferri et al., 2003). Stroke results in a reduction in muscle mass and muscle function predominantly on the paretic side with mild weakness of the ipsilateral, non-paretic side (Eng, 2004). It has been shown that myostatin levels are higher in the paretic side than the non-paretic muscle (Ryan et al., 2011). Myostatin is a negative key regulator
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of muscle mass (works against human growth hormone) (McPherron, 1997), which has been shown to have an important regulatory role in atrophy after stroke (Ryan et al., 2011).

Progressive resistance training has shown to stimulate significant muscle hypertrophy and intramuscular fat reduction in stroke survivors (Ryan et al., 2011) as well as increases in both strength, power and function (Morris, Dodd & Morris, 2004; Badics et al., 2002). Therefore, resistance training is an important rehabilitation intervention for stroke survivors (Eng, 2004; Hill et al., 2012). Resistance training has also been shown to produce substantial improvements in functional performance after stroke, including walking, stair climbing, sit to stand, balance, and upper extremity function (Jeon, Hwang, 2018). The magnitude of hypertrophy with resistance training in stroke survivors is consistent with muscle hypertrophy after resistance training in healthy older males (Ivey et al., 2000; Treuth et al., 1994). The American Stroke Association recommends physical activity and exercise for stroke survivors across all stages of recover (Billinger et al, 2014).

Additionally, a reduction in physical activity may lead to an increased loss of bone mineral. Mechanical loading (i.e. resistance training) downregulates sclerostin expression in bones which in turn increases osteoblastic bone formation and decreases bone reabsorption by inhibiting osteoclast activity (Galea, Lanyon & Price, 2017). With resistance training, the mechanical load applied to bones should exceed that which is encountered during daily physical activities in order to elicit an osteogenic effect (Frost, 1988).
3 Creatine Monohydrate

Creatine has become one of the most extensively studied and scientifically validated nutritional ergogenic aids (Buford et al., 2007). It is naturally synthesized in the kidneys and liver from the amino acids arginine, methionine, and glycine (Walker, 1979). The first step involves the synthesis of guanidinoacetic acid (GAA) from glycine and arginine in the kidney catalyzed by the reversible reaction involving arginine:glycine amidinotransferase (AGAT). In the second step, irreversible methylation of GAA by guanidine N-methyltransferase (GNMT) utilizes s-adenosylmethionine (SAM) as the methyl donor and results in the formation of creatine and s-adenosylhomocysteine (SAH) in the liver (Kalhan et al., 2016). Individuals who eat red meat and/or seafood obtain approximately 1 g/day of creatine from the diet and approximately 1 g/day synthesized endogenously (Balsom, Söderlund, Ekbolm, 1994). It has been recommended that due to health benefits of creatine, individuals should consume approximately 3 g/day of creatine in their diet, especially as one ages (Wallimann, Tokarska-Schlattner, Schlattner, 2011).

The majority of creatine is stored in skeletal muscle (95%), with two thirds being phosphocreatine (PCr) and one third being free creatine (Kreider et al., 2017). When it comes to endogenous creatine there appears to be a maximum capacity for which synthesis can occur (Harris, Soderlund, Hultman, 1992). The uptake of creatine involves the absorption of creatine into the blood and is followed by uptake from the target tissue (Jagar et al., 2011). Plasma creatine levels peak approximately 60 minutes after consumption (Hultman et al., 1996).
3.1 Phosphocreatine Energy System and Shuttle

The clinical relevance of creatine supplementation is based primarily on its role in adenosine triphosphate (ATP) generation. At rest, creatine is phosphorylated by creatine kinase (CK) to form PCr (Guerrero-Ontiveros & Wallimann, 1998). During muscle contraction, PCr donates its high-energy phosphate to adenosine diphosphate (ADP) to regenerate ATP. Creatine is subsequently recycled in the reaction or is converted to creatinine (Wyss & Kaddurah-Daouk, 2000).

Creatinine is formed as a metabolic by-product from the conversion of PCr to Cr, which is then excreted via the kidneys (Hoberman et al., 1948). Creatine can function to buffer the pH changes that occur due to the accumulation of lactic acid and hydrogen ions by using the hydrogen ions to buffer in the creatine kinase reaction (Wyss & Kaddurah-Daouk, 2000).

3.2 Muscle Protein Kinetics

Creatine is an osmotically active compound. Increases in total creatine content have been linked to concomitant increases in water retention. This partly explains the typical body mass increases of 1-2 kg after a creatine loading phase (20 g/day) for 5-7 days (Willoughby, 2008). Due to increased cell volume, which appears to act as an anabolic signal, creatine may stimulate properties and pathways involved in protein synthesis (Willoughby, 2008). It has been shown that cell hydration affects protein synthesis in liver cells, where cell swelling stimulates protein synthesis (Waldegger et al., 1997). Although cell hydration and cell function has been most extensively studied in liver cells, it appears that these regulatory mechanisms also occur in other cell types (Häussinger, 1996).
Creatine supplementation in combination with resistance training has been shown to increase lean body mass and muscle fiber cross-sectional area (Candow et al., 2012; Candow et al., 2011; Kreider et al., 1998; Volek, Duncan, Mazzetti, & Staron, 1999). The recognized hypertrophic action of creatine has been linked to variables associated with an increase in protein synthesis and/or reduction in protein breakdown (Persky & Brazeau, 2001). Myogenin and MRF-4 (myogenic regulatory factor-4) have been associated with an increase in muscle-specific gene expression, increased CK mRNA expression and MHC expression (Hespel et al., 2001; Willoughby, 2008; Willoughby & Rosene, 2001; Willoughby & Rosene, 2003).

It has been hypothesized that creatine supplementation improves muscle protein kinetics and anabolic hormone secretion (Candow et al., 2012). Short-term creatine supplementation for 10 days (20 g/day for 3 days; 5 g/day for 7 days) up-regulated the expression of genes and proteins involved in the synthesis of protein and glycogen, as well as satellite cell proliferation in young, healthy men (Safdar, Yardley, Snow, Melov, & Tarnopolsky, 2008). In particular, muscle kinases p38 MAPK, ERK6 (extracellular signal-regulated kinase 6) and PKB/Akt were shown to be significantly elevated. Moreover, 5 days of creatine supplementation (21 g/day) in young men increased IGF-1 mRNA expression at rest and the phosphorylation of anabolic signaling molecules (i.e. mTOR downstream target 4E-BP1) 24 hours after a bout of high-intensity resistance exercise (Delicque, et al., 2005). Greater increases in intramuscular IGF-1 content was shown in healthy men and women after 8 weeks of resistance training combined with creatine supplementation compared to placebo ingestion (Burke et al., 2008).
3.2.1 Satellite Cell Activity

The ratio between the number of myonuclei and fibre cross-sectional area has been defined as the myonuclear domain, where each nucleus regulates a specific volume of cytoplasm (Allen, Roy & Edgerton, 1999). Satellite cells (SC) are located between the sarcolemma and the basal lamina of the muscle fibre (Mauro, 1961). Satellite cells are normally in a non-proliferative quiescent state, but when stimulated during exercise, they proliferate and produce additional myonuclei, which in turn, increases the capacity of muscle protein synthesis and potentially muscle growth (Grounds, 1998, 1999; Viereck et al., 2000; Yan, 2000). The primary benefit of satellite cells when dealing with muscular hypertrophy appears to be their ability to donate nuclei to muscle fibers, facilitating the synthesis of contractile proteins by increasing myonuclear domain (Moss & Leblond, 1971; Schoenfeld, 2010). It has been shown that resistance training can increase SC and number of myonuclei in trained muscles. This suggests that training-induced activation of SC may be an important adaptive mechanism during hypertrophy (Kadi & Thornell, 2000; Roth et al., 2001; Kadi et al. 2004b). The activation of SC during resistance training indicates that the myonuclear domain remains constant despite an increase in fibre size due to myonuclei additions during cellular hypertrophy (Allen et al., 1999). Unfortunately, aging adults appear to exhibit reduced quantities of myogenic satellite cells which may likely contribute to the age-related loss of skeletal muscle mass (Kadi et al., 2004). Olsen et al. (2006) showed that 16 weeks of heavy resistance training combined with creatine supplementation increased the amount of satellite cells at 4 and 8 weeks. Additionally, they found a greater number of myonuclei, which was associated with the increase in muscle fiber cross-sectional area in the creatine group.
3.3 Creatine and Resistance Training in Aging Adults

Meta-analyses have shown that creatine should be combined with resistance training to produce significant muscle benefits in aging adults. In the most recent analysis, Chilibeck et al., (2017) examined the effects of creatine supplementation during resistance training to placebo during resistance training (7-52 weeks) in over 700 aging adults (57-70 years of age). Compared to placebo, creatine during resistance training resulted in greater improvements in lean tissue mass (~ 1.37 kg) and leg press and chest press strength over time. Previously, Devries & Phillips (2014) analyzed over 300 men and women (55-71 years of age) who consumed creatine (3-25 grams) during resistance training (7-26 weeks). Similar to the findings of Chilibeck et al. (2017), creatine resulted in greater gains in lean tissue mass (~1.33 kg), leg press and chest press strength. Results across meta-analyses indicates that creatine supplementation and resistance training is an effective lifestyle intervention for increasing muscle mass and strength.

3.4 Creatine and Bone Mineral

Prevention of bone fracture in aging adults is primarily dependent on two important factors: bone strength and falls prevention (Crockett et al., 2018). Stroke patients with hemiparesis are at an increased risk of developing osteoporosis on the paretic side (Yavuzer et al., 2002). Excessive bone loss starts immediately post-stroke and progressively deteriorates for up to 3-4 months after stroke (Hamdy et al., 1995; Takamoto et al., 1995). Bone loss then subsequently progresses at a reduced rate until the end of the first year following the stroke (Sato et al., 1998; Rammmemark et. al., 1999).

The requirement for PCr breakdown to buffer ATP levels in bone is most likely highest when osteoblasts are active during the bone remodeling cycle (Candow et al. 2019).
Creatine is capable of stimulating the activation and differentiation of osteoblast cells (Geber et al., 2005) which in turn causes the release of osteoprotegerin, a protein-like compound which inhibits the activation of osteoclasts (Yasuda et al., 1998). For example, aging males (55-77 years) who were supplemented with creatine (0.1g/kg/day) during 10 weeks of supervised resistance training (3 days/week) had a 27% reduction in bone resorption compared to a 13% increase in the placebo group (Candow et al., 2008). Another study conducted by Chilibeck et al., (2015) concluded that creatine supplementation (~8 g/day) during 12 months of supervised resistance training (3 day/week) in postmenopausal women attenuated the loss of bone mineral density at the femoral neck compared to placebo. An increase in osteoblast activity (cells involved in bone formation), coupled with a reduced in osteoclast activity (cells involved in bone resorption), could lead to net bone accretion over time.

3.5 Creatine and Brain Function

Although the brain represents 2% of the body’s total mass, it uses approximately 20% of oxygen and calories consumed (Clark & Sokoloff, 1999). The brain requires a significant amount of ATP in order to maintain its membrane potential and signaling capacity. As with skeletal muscle, during brain activity, PCr donates its phosphate group to ADP to maintain ATP (Sappey-Marinier et al. 1992; Rango et al. 1997). From plasma, creatine is transported via the creatine transporter protein (CRT). This transporter is critical for the distribution of creatine through the cell as well as passing the blood brain barrier (BBB), which gives creatine access to the central nervous system (CNS) (Christie, 2007; Lowe, Faull & Christie, 2015). CK is mostly expressed in regions of the brain that exhibit higher levels of activity, such as the hippocampus and cerebellum (Kaldis et al., 1996).
Increasing brain creatine levels with exogenous creatine supplementation improves energy availability which in turn may improve brain performance (Gualano et al., 2016). Dechent et al. (1999) demonstrated that creatine supplementation could increase brain creatine levels in humans. The ingestion of creatine monohydrate (20 g/day for 4 weeks) increased brain creatine levels by 4.7% in grey matter and by 11.5% in cerebral white matter (as measured by $^1$H magnetic resonance spectroscopy [MRS]). Furthermore, Lyoo et al. (2012) found that males supplementing with creatine (0.3 g/kg/day for one week followed by 0.03 g/kg/day for an additional week) increased brain [tCr]/[acetyl aspartate] ratios by 8.1% and brain [tCr]/[choline] by 9.3% as measured by $^1$H MRS.

While the effects of creatine supplementation on skeletal muscle metabolism are fairly well documented, research investigating the effects of creatine on properties of brain health and function is scarce. Thus far, the limited research indicates that creatine supplementation may be beneficial in the treatment of various neurological conditions, including age-related cognitive decline (e.g., Alzheimer’s disease) and neurocognitive diseases (e.g., Parkinson’s disease, Huntington’s disease, Amyotrophic lateral sclerosis), all of which are linked to dysfunctional energy metabolism (Andres et al., 2008; Gualano et al., 2010). Stroke survivors have more than twice the risk of developing dementia compared to individuals who have never suffered a stroke (Tatemichi et al., 1992; Patel et al., 2002). McMorris et al. (2007) examined the effects of creatine ingestion in older adults and found that forward and backward recall spatial short-term memory tests, a forward recall verbal short-term memory test, and a long-term memory test were all improved with creatine supplementation. Because cognitive tasks rely on creatine and PCr to maintain brain ATP levels, increasing brain creatine content through creatine supplementation may
improve cognitive processing. For example, a double-blind, placebo controlled, cross-over trial conducted by Rae et al. (2003) assessed whether creatine supplementation (5g/day for 6 weeks) could enhance intelligence test scores and working memory performance in young adults. Results showed that creatine supplementation had a positive effect \( p < 0.0001 \) on both working memory (backward digital span) and intelligence (Ravens Advanced Progressive Matrices) compared to placebo. In conditions where baseline bioenergetics may not be optimal, creatine supplementation has been shown to supportive cognitive enhancement (Rae & Bröer, 2015).

### 3.6 Creatine for Anxiety and Depression

The most commonly reported psychological consequence of suffering a stroke is depression. Following stroke, the incident of depression can range from 25-97%, with most studies showing a rate of approximately 30% (Kneebone, 2000). Adenosine has several roles within the CNS that are crucial for proper brain functioning, including the regulation of behavior, mood and emotion (Cunha et al., 2008; Ruby et al., 2010; Asatryan et al., 2011). Moreover, depressive patients show a significant decrease in ATP production rates in muscle and brain compared to control individuals (Gardner and Boles, 2011), while individuals with GAD have been shown to have decreased choline and creatine concentrations in centrum semiovale (Coplan, 2005). Following stroke, ATP levels have been shown to be significantly decreased in non-exercise patients for up to 3 days, suggesting a decrease in ATP production, an increase in ATP utilization, or both (Li et al., 2017). Potentially, the decrease in ATP production following stroke could be a main contributor to symptoms of anxiety and depression post-stroke. Creatine supplementation has shown promise in the treatment of depression and anxiety. A study conducted by Allen
et al. (2010) showed that female Sprague-Dawley rats who ingested a 4% creatine enriched chow for 5 weeks experienced a decrease in immobility during a forced swim test (an animal model selectively sensitive to antidepressants with clinical efficacy in humans) and less anxiety during an open field exploration compared to control rats. Hellem et al. (2015) studied the effects of 5g of creatine supplementation on depressive symptoms over 8 weeks. They found that Hamilton Depression Rating Scale and Beck Anxiety Inventory scores were significantly reduced. Moreover, Brain phosphocreatine concentrations were higher at the second phosphorus magnetic resonance spectroscopy scan compared to the baseline scan suggesting that creatine increased phosphocreatine levels. In addition, Lyoo et al. (2012) observed an improvement in the Hamilton Depression Rating Scale score in females with major depressive disorder after supplementing with creatine (5 g/day) for 8 weeks compared to placebo. Using the same population used in the Lyoo et al. (2012) study, Yoon et al. (2015) found an increase in N-acetylaspartate levels and rich club connections after creatine supplementation. Moreover, Kious et al. (2017) combined the treatment of creatine and 5-hydroxytrptophan resulting in reduced depressive symptoms scores by 60%. While it is difficult to compare results across studies, preliminary research indicates that creatine supplementation has the potential to decrease symptoms of depression and anxiety.

4. Creatine and Stroke

Animal research indicates that creatine supplementation may provide neuroprotection from injury (Sullivan et al., 2000; Smith, Agharkar & Gonzales, 2014). Mice who supplemented with creatine (1% and 2% of their overall diet) experienced a significant reduction in neuronal damage compared to control mice following middle
cerebral artery occlusion (Prass et al., 2007). Based on these limited, yet promising results, speculation exists that creatine could potentially be beneficial for individuals at risk or who have suffered a stroke (Perasso et al., 2013). However, no study has examined the effects of creatine supplementation in post-stroke survivors.

4.1 Safety

The International Society of Sports Nutrition (ISSN) published a recent position stand paper which concluded that creatine supplementation poses no greater adverse effects compared to placebo. The only consistently reported adverse effect from from creatine supplementation is weight gain (Buford et al., 2007; Kreider et al., 2003; Rawson, 2011; Rodriguez, 2009; Thomas, 2016). Additionally, clinical populations can be supplemented with high levels of creatine monohydrate without suffering clinically significant or serious adverse events (Kreider et al., 2017).

5 Research Proposal and Hypothesis

The purpose of this thesis was to compare the effects of creatine supplementation and supervised resistance training on body composition, muscle thickness and strength, tasks of functionality, cognition and symptoms of depression and anxiety in stroke survivors. It was hypothesized that creatine supplementation and resistance training would increase muscle and bone mass, strength, tasks of functionality and cognition and reduce symptoms of depression and anxiety compared to placebo and resistance training.

6 Methods

6.1 Participants

An a priori power analysis (G*Power v. 3.1.5.1) showed that 34 participants were required. This calculation was based on a moderate effect size (Cohen’s $d = 0.25$), an alpha level of
THE EFFECTS OF CREATINE MONOHYDRATE SUPPLEMENTATION AND RESISTANCE TRAINING IN STROKE SURVIVORS

.05, a β-value of 0.8 for a repeated measure: within-between interactions, ANOVA approach (Faul, Erdelder, Lang & Buchner, 2007). Males and females (≥ 30 years of age) who were diagnosed with a stroke by a medical doctor, who were not engaged in supervised resistance training for ≥ 6 weeks prior to the start of the study, and who were able to walk without an assistive device were eligible for the study. Eligible participants were excluded if they were taking medications that affected muscle biology (i.e. corticoids) or creatine monohydrate ≤ 12 weeks prior to the start of the study; if they had diseases that were known to affect muscle biology; if they suffered from severe osteoarthritis; if they had an additional neurological disorder (i.e. Dementia, Parkinson’s disease, Cerebral Palsy), if they had pre-existing kidney or liver abnormalities, if they were vegetarian; or if they were planning to travel during the study period for ≥ 1 week in duration. Vegetarians were excluded as they have been shown to have significantly lower intramuscular muscle creatine stores compared to individuals who consume meat and/or fish products (Delanghe, DeSlypere, DeBuyzere, Robbrecht, Wieme, Vermenlen, 1989; Shomrat, Weinstein, Katz, 2000) which may have influenced the results.

Non-resistance trained participants were included as they may respond better to creatine supplementation (Candow, Chilibeck, Burke, Mueller, Lewis, 2011). Participants were required to obtain medical clearance before starting the study, and were asked to disclose all current medications and past medical history before the start of the intervention. Participants ranged from 30 years of age to 82 years of age. All participants reported experiencing left sided weakness due to their stroke. Only one participant reported having a hemorrhagic stroke where the remaining 7 participants experienced an ischemic stroke. No participant required a walking aid.
Participants completed a Physical Activity Scale for Persons with Physical Disabilities (PASIPD) questionnaire at the start of the study (Appendix A). The PASIPD assessed leisure, household, and work-related physical activity over the last 7 days, specifically looking at frequency and duration. The average hours that a specific task was completed was multiplied by a metabolic equivalent (MET) value associated with the intensity of the activity. Scores ranged from 0 (no activity) to > 100 METS (Washburn et al., 2002).

Participants also completed a Stroke Impact Scale (SIS) (Appendix B). The SIS is a stroke-specific, self-report, health status measurement. It is designed to assess multidimensional stroke outcomes which covers eight dimensions and provides a composite disability score (Jenkinson et al., 2013).

The study was approved by the University Ethics Review Board for research in human subjects at the University of Regina and University of Saskatchewan. All participants were informed of the potential risks and the purpose of the study before their written consent (Appendix C) was obtained.

6.2 Research Design

This randomized control trial (ClinicalTrials.gov Identifier: NCT03941678; Appendix D) involved a double-blind, placebo-control, repeated measures design. In order to minimize group differences, participants were matched according to age, gender, type of stroke and body mass. After exclusion criteria was applied, participants were randomized on a 1:1 basis to one of two groups: Creatine (CR) or Placebo (PL; corn-starch maltodextrin). The primary dependent variables that were measured at baseline and after the intervention included: (1) body composition, (2) muscle thickness, (3) muscle strength,
(4) tasks of functionality, (5) cognition, and (6) symptoms of depression and anxiety. Participants also completed a 3-day food log during the 1st and last week of training and supplementation to determine whether total calories consumed as well as macronutrient intake changed over the duration of the study.

6.3 Supplementation

Creatine (Creapure® AlzChem Trostberg GmbH, Germany) and placebo (Globe Plus 10 DE Maltodextrin, Univar Canada) were in powder form. Both products were similar in taste, color, texture and appearance. Contents of Creapure® was verified by testing in an independent laboratory (The Cary Company, Addison, Ill., USA) and purity was established as > 99.9%. For days 1-7, participants ingested 0.3 g/kg of creatine monohydrate (0.075 g/kg x 4 times daily). This ingestion strategy has been shown to be effective for increasing intramuscular creatine stores (Hultman et al., 1996; Harris, Soderlund, Hultman, 1992). Thereafter, participants consumed 0.1 g/kg per day as this dosage has been shown to be effective for increasing muscle mass without resulting in adverse effects (Candow et al., 2008). On training days, participants consumed their supplementation immediately after each training session mixed with water, as post-exercise creatine supplementation has been shown to increase muscle mass and strength (Forbes and Candow, 2018). On non-training days, the supplement was consumed at the participant’s leisure. An individual not involved in any other aspect of the study was responsible for randomization as well as the preparation of participant study kits. Each kit contained the participants supplement for the duration of the study, detailed supplementation instructions, as well as measuring spoons. Adherence with creatine supplementation, placebo, and resistance training program was assessed by training and
supplementation compliance logs. Upon completion of the study, participants were asked whether they believed if they were randomized into the creatine group, placebo group or unsure of which group they were allocated to.

6.4 Bilateral Resistance Training Program

Prior to the start of supplementation, participants performed three supervised familiarization sessions with the resistance training equipment in the Aging Muscle and Bone Health Laboratory, University of Regina and William’s Building training facility, University of Saskatchewan. Participants were shown how to properly breathe while exercising, use the equipment, and perform repetitions to muscle fatigue with proper form. Machine-based resistance training equipment was chosen (Pulse Exercise Systems Inc., Winnipeg, Canada; Life Fitness; Franklin Park, IL) because they are considered safer and easier to learn, especially for untrained individuals (Boyer, 1990; Ratamass et al., 2009). All exercises were performed bilaterally. In a meta-analysis of bilateral movement training, outcomes were positive overall during sub-acute and chronic phases of recovery from stroke which may have been due to positive neural effects for both hemispheres, whereas unilateral training might result in reorganization of the ipsilesional hemisphere (Stewart et al., 2006).

During the first familiarization session, participants performed 1 set of 10 repetitions for each exercise; 2 sets of 10 repetitions for each exercise during the second familiarization session and 3 sets of 10 repetitions for each exercise during the final familiarization session. Exercises performed in the following order were leg press, knee extension, knee flexion, chest press, elbow extension and elbow flexion.
THE EFFECTS OF CREATINE MONOHYDRATE SUPPLEMENTATION AND RESISTANCE TRAINING IN STROKE SURVIVORS

During each supervised training session, participants completed a 5-10 minute warm up on a cycle ergometer, which was followed by light static stretching (if applicable). Participants then performed 3 sets of 10 repetitions at 70% baseline 1-RM (for the leg press, leg extension, leg curl, chest press, triceps extension, and biceps curl), 2 times per week, on non-consecutive days, for 10 weeks (Appendix E). Each set was separated by a two-minute rest period. The load was increased (i.e. 2.5-5 lbs) once an individual was able to complete the required number of repetitions (30 in total) for an exercise. The resistance training program design was based off the recommendations by the American College of Sports Medicine (ACSM, 2008) for individuals suffering from a cerebral vascular accident. Participants took 2 seconds to perform the concentric phase and 2 seconds to perform the eccentric phase of each muscle contraction, which was separated by a 1 second pause between the concentric and eccentric movements. This pause helped reduce the stretch-reflex of muscle shortening (Bosco, Tarkka, & Komi, 1982) and potential momentum. Training logs were used to determine total training volume (load x sets x repetitions).

7 Primary Dependent Variables

7.1 Body Composition Lean tissue, fat mass and bone mineral were assessed by dual-energy X-ray absorptiometry (DXA) in the Aging Muscle and Bone Health Laboratory at the University of Regina and William’s Building training facility at the University of Saskatchewan, using the Hologic Discovery DXA system. Participants were instructed not to participate in physical activity for 48 hours prior to their DXA scan because muscle protein turnover is upregulated 48 hours post-exercise (Phillips et al., 1997). Before the scan occurred, participants were required to take off all removable objects containing metal (i.e. glasses, jewelry, clothing with buttons/zippers). Participants
were instructed to lay in the supine position along the scanning table centerline longitudinal axis for the duration of the scan. Feet were taped together at the toes to immobilize the legs while the hands were placed in a pronated position within the scanning region. The same nuclear medicine technologist performed the pre- and post-testing scan at each site. The coefficients of variation from previous research were 1.0% for lean tissue mass, 0.9% for bone mineral density (Chilibeck et al. 2015), 2.9% for fat mass (Chrusch et al. 2001), and 0.6% for bone mineral content (Chilibeck et al. 2005).

7.2 Muscle Thickness Muscle thickness (right side and left side) of the elbow and knee flexor and extensor muscle groups was measured using B-Mode ultrasound (LOGIQe, GE Medical Systems). To properly measure elbow flexor and extensor muscle thickness, a non-permanent mark was placed on the lateral side of each arm to indicate approximately 65% of the distance down from the acromion process to the olecranon process (Farthing & Chilibeck, 2003). A tape measure was then wrapped around the arm at approximately the 65% mark and used as a reference and another non-permanent mark was placed on the bulk of the elbow flexors and extensors where the center of the ultrasound probe was placed. In order to measure elbow flexor thickness, the participant placed their arms flat on a table with the biceps facing upwards and the forearms supinated. In order to measure elbow extensor muscle thickness, participants were seated with their back facing the researcher and their arms relaxed and fully extended.

To measure knee flexor and extensor muscle thickness, a small mark was drawn on the lateral side of the leg to indicate approximately 70% of the distance down from the greater trochanter to the lateral epicondyle of the tibia (Abe et al., 2001). A tape measure was then wrapped around the leg at approximately the 70% mark.
For each muscle thickness measurement, precise markings on the skin were taken using overhead transparency film and permanent marker to ensure that identical sites were measured on each occasion (Farthing & Chilibeck, 2003). An 8-MHz scanning transducer head was placed on the measurement site, perpendicular to the muscle area. Water-soluble transmission gel was placed on the measurement site to provide acoustic contact with the surface of the muscle. When a clear image on the screen was produced, the image was frozen. With the image frozen, a cursor was enabled to quantify muscle thickness (cm) at three sites: proximal, mid and distal, as determined by divisions (1cm) on the monitor. Muscle thickness measurements were determined from the monitor screen by measuring the distance from the bottom of the subcutaneous adipose layer to the surface of the humerus for elbow flexor and extensor muscle thickness, and to the surface of the femur for knee flexor and extensor muscle thickness. Three muscle thickness measurements were taken at each of the three sites. The closest two values were then taken and averaged to achieve a final muscle thickness value for that site. The coefficients of variation from previous research were 2.6% for the elbow flexors, 2.1% for the elbow extensors, 2.3% for the knee flexors and 2.1% for the knee extensors (Chilibeck et al. 2015).

7.3 Muscle Strength Leg press and chest press strength was assessed using a 1-repetition maximum (1-RM) standard testing procedure in the Aging Muscle and Bone Health Laboratory, University of Regina and William’s Building training facility, University of Saskatchewan. To measure the 1-RM leg press, a bilateral leg press machine was used. Prior to the 1-RM assessment, participants completed 5-minutes of cycling on a stationary cycle ergometer at a self-selected intensity. Following a demonstration, participants were positioned in the leg press so that a 90° angle at the knee was achieved.
(if possible) and feet were placed shoulder width apart. Participants were then instructed
to push the weight away from their body to full extension without locking their knees
before returning to the starting position. Participants then performed two warm-up sets in
order: 1 set of 10 repetitions using a weight determined by each participant to be
comfortable and 1 set of 5 repetitions using increased weight. Two minutes following the
warm-up sets, weight was increased for each subsequent 1-RM attempt with a 5-minute
rest interval. For the 1-RM chest press, participants were positioned in a bilateral chest
press machine with both feet on the floor. Following a demonstration, participants were
instructed not to arch their back during the lift. Participants were positioned in the chest
press machine so that the adjacent bars lined up at mid-chest level. Participants then were
instructed to grasp the bars (overhand grip) at approximately shoulder width apart and push
the weight away from the body until full extension and then lower the weight back to the
starting position. Five to ten minutes of rest separated the determination of 1-RM leg press
and chest press strength. The coefficients of variation from previous research were 0.30% for the leg press and 0.46% for the chest press (Johannsmeyer et al. 2016).

7.4 Functionality The six-minute walk test and the Berg Balance Scale was used
to assess functional capacity and ability to complete activities of daily living. The six-
minute walk test was performed to measure the distance participants could quickly walk in
a period of 6 minutes on a 30-m course. Participants did not warm up before the test began,
but rather sat on a chair for 10 minutes prior to the start of the test. Participants were
instructed to walk as fast as they could (without running) along a 30-meter track. Once the
6 minutes was completed, the number of meters the participant completed was recorded
for a final score. The Berg Balance Scale (BBS) (Appendix F) was used to objectively
determine the participant’s ability or inability to maintain balance (Berg, 1995). The BBS is a 14-item list, with each item consisting of a five-point ordinal scale ranging from 0-4. With 0 indicating the lowest level of function and 4 the highest level of function. Sitting to standing, standing unsupported, sitting with back unsupported by feet supported, standing to sitting, transfers, standing unsupported with eyes closed, standing unsupported with feet together, reaching forward with outstretched arm while standing, picking up an object from the floor, turning to look behind over shoulder, turning 360 degrees, placing an alternate foot on step, standing unsupported one foot in front, and standing on one leg were evaluated. Participants received a total score out of maximum score of 56. A systematic review on the usefulness of the BBS in stroke rehabilitation patients found that internal consistency was excellent (Cronbach alpha = 0.92 - 0.98) as was interrater reliability (interclass correlation coefficients (ICC’s = 0.92 - 0.98) and test-retest reliability (ICC = 0.98 (Blum & Korner-Bitensky, 2008).

7.5 Cognition The Montreal Cognitive Assessment (MoCA; Appendix G) was used to indirectly assess cognition. The MoCA is a screening tool for mild cognitive dysfunction and contained thirty items: short-term memory (5 points); visuospatial abilities via clock drawing (3 points), and a cube copy task (1 point); executive functioning via an adaptation of Trail Making Test Part B (1 point), phonemic fluency (1 point), and verbal abstraction (2 points); attention, concentration, and working memory via target detection (1 point), serial subtraction (3 points), digits forward (1 point), and digits backward (1 point); language via confrontation naming with low-familiarity animals (3 points), and repetition of complex sentences (2 points); and orientation to time and place (6 points) (Nasreddine et al., 2005). The MoCA is scored by obtaining an item total out of 30. The
MoCA has higher internal reliability, less ceiling effect, and has a strong relationship to rehabilitation functional outcomes and improvements as the Mini-Mental State Examination does (Toglia et al., 2010).

7.6 Anxiety and Depression The Generalized Anxiety Disorder Assessment (GAD-7; Appendix H) was used to assess symptoms of anxiety. This self-reported questionnaire is a seven-item instrument which asked the participant to rate his or her symptoms over the past two weeks. Responses included: not at all, several days, more than half the days, and nearly every day. Research has indicated the GAD-7 shows excellence internal consistency, good test-retest reliability, and strong criterion validity for identifying possible cases of GAD (Spritzer et al., 2006).

The Center for Epidemiological Studies Depression Scale (CES-D; Appendix I) was used to measure depressive symptoms. The CES-D is a 20-item measure that asked the participant to rate how often over the past week they experienced symptoms of depression. Response options range from 0 to 3 for each item (0= rarely or none of the time, 1= some or little of the time, 2 = moderately or much of the time, and 3= most or almost most of the time). Scores range from 0 to 60, with high scores indicating greater symptoms of depression. The suggested cutoff for depression is a score of 16 or more. CSE-D is a valid reliable screening tool for depression (Baron, Davies & Lund, 2016).

7.7 Dietary Records. Dietary intake was recorded during the first and final week of training and supplementation to assess differences in total energy (kcal) and macronutrient composition between groups. Participants used a 3-day food record to record their intake for two weekdays and one weekend day. Participants were instructed to record all food and drink items, along with details relating to portion sizes for the three designated
days. MyFitnessPal (http://www.myfitnesspal.com) was used to analyze average kcal, carbohydrate, fat and protein consumption. MyFitnessPal shows good validity compared to standard paper-based food records (Teixeira et al. 2018).

7.8 Adverse Event Assessment. In the case of an adverse event, participants were required to complete an adverse event form (Appendix J) in order to describe details on the type and of severity of the event (i.e. mild, moderate, severe, or life threatening), the frequency, and the relationship to the study (i.e. not related, unlikely, possible, probable, or definite).

7.9 Statistical Analyses. Due to the very small sample size and the likelihood that the data would not be normally distributed, the Wilcoxon Signed-Rank Test was used to analyze differences in all dependent variables over time. The Mann-Whitney U test was used to assess baseline data and training volume. Significance was set a priori at an alpha level of $p < 0.05$. Cohen’s $d$ effect size (ES) was calculated as post-training mean minus pre-training mean / pooled pre-training standard deviation mean (Cohen, 1992). An ES of 0.00-0.19 was considered trivial, 0.20-0.49 was considered small, 0.50-0.79 was considered moderate, and $\geq 0.80$ was considered large (6). Statistical analyses were performed using IBM® SPSS® Statistics, v. 26 (Chicago, IL).

8 Results

8.1 Participants

Nine participants were randomized into the study (see Figure 1 for a summary of recruitment, allocation and analysis). One participant withdrew due to time constraints unrelated to the study, prior to their first training session. No adverse events were reported
during the study. Eight participants (CR = 5, PLA = 3) completed the study. Six participants (CR = 5, PLA = 1) were able to provide 3-day food records.

Following the intervention, participants were asked whether they believed they were randomized into the creatine group or placebo group. Three of the five participants in the CR group correctly guessed they were receiving creatine and two participants incorrectly guessed. In the PLA group, two participants correctly guessed they were receiving placebo while one participant incorrectly guessed. Training compliance was similar between groups over time (CR: 188/192 sessions completed or 98%; PLA: 182/192 or 95%). Supplementation compliance, based on participants entries in their logs, was similar between groups over time (CR: 69/70 days or 99%; PLA: 68/70 days or 98%).

There was no change over time in the CR group for total energy (pre: 1911.73 ± 411.46 kcal, post: 1896.80 ± 470.03 kcal, p = 0.893), carbohydrate (pre: 226.33 ± 59.87 g, post: 222.33 ± 63.85 g, p = 0.893), fat (pre: 73.46 ± 23.67 g, post: 64.73 ± 11.00 g, p = 0.500) or protein (pre: 86.80 ± 16.17 g, post: 89.73 ± 22.21 g, p = 0.684).
Figure 1. Summary of recruitment, allocation and analyses.
Table 1

Baseline data is presented in Table 1. There were no significant differences between groups for any baseline measurement.
### Table 1. Baseline data.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Creatine (n = 5)</th>
<th>Placebo (n = 3)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass (kg)</td>
<td>84.74 (19.24)</td>
<td>73.33 (5.83)</td>
<td>0.456</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>25.99 (7.55)</td>
<td>17.33 (2.99)</td>
<td>0.447</td>
</tr>
<tr>
<td><strong>Lean tissue mass (kg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole-body</td>
<td>49.76 (14.19)</td>
<td>48.43 (10.18)</td>
<td>0.881</td>
</tr>
<tr>
<td>Left arm</td>
<td>2.78 (1.41)</td>
<td>2.86 (1.15)</td>
<td>0.881</td>
</tr>
<tr>
<td>Right arm</td>
<td>3.02 (1.26)</td>
<td>2.99 (1.14)</td>
<td>0.881</td>
</tr>
<tr>
<td>Upper body</td>
<td>5.81 (2.68)</td>
<td>5.85 (2.26)</td>
<td>0.655</td>
</tr>
<tr>
<td>Left leg</td>
<td>8.43 (2.68)</td>
<td>8.00 (2.13)</td>
<td>0.881</td>
</tr>
<tr>
<td>Right leg</td>
<td>8.76 (2.32)</td>
<td>7.60 (1.50)</td>
<td>0.297</td>
</tr>
<tr>
<td>Lower body</td>
<td>17.20 (4.98)</td>
<td>15.61 (2.88)</td>
<td>0.456</td>
</tr>
<tr>
<td><strong>Muscle thickness(cm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left elbow flexor</td>
<td>3.31 (0.68)</td>
<td>3.88 (1.48)</td>
<td>0.655</td>
</tr>
<tr>
<td>Right elbow flexor</td>
<td>3.08 (0.52)</td>
<td>3.02 (0.54)</td>
<td>0.764</td>
</tr>
<tr>
<td>Left elbow extensor</td>
<td>3.07 (0.81)</td>
<td>3.74 (1.51)</td>
<td>0.655</td>
</tr>
<tr>
<td>Right elbow extensor</td>
<td>3.49 (0.64)</td>
<td>3.47 (1.28)</td>
<td>0.881</td>
</tr>
<tr>
<td>Upper body</td>
<td>12.96 (1.31)</td>
<td>14.12 (4.67)</td>
<td>0.655</td>
</tr>
<tr>
<td>Left knee flexor</td>
<td>3.86 (0.31)</td>
<td>3.83 (1.40)</td>
<td>0.456</td>
</tr>
<tr>
<td>Right knee flexor</td>
<td>3.72 (0.58)</td>
<td>4.22 (1.28)</td>
<td>0.655</td>
</tr>
<tr>
<td>Left knee extensor</td>
<td>3.67 (0.64)</td>
<td>3.50 (0.54)</td>
<td>0.480</td>
</tr>
<tr>
<td>Right knee extensor</td>
<td>3.59 (0.56)</td>
<td>3.29 (0.45)</td>
<td>1.000</td>
</tr>
<tr>
<td>Lower Body</td>
<td>14.96 (1.94)</td>
<td>8.06 (2.68)</td>
<td>0.724</td>
</tr>
<tr>
<td>Left Side</td>
<td>14.53 (1.36)</td>
<td>14.96 (4.69)</td>
<td>0.724</td>
</tr>
<tr>
<td>Right Side</td>
<td>13.83 (1.96)</td>
<td>14.02 (2.86)</td>
<td>1.000</td>
</tr>
<tr>
<td>Appendicular</td>
<td>24.92 (8.08)</td>
<td>22.18 (7.35)</td>
<td>0.881</td>
</tr>
<tr>
<td><strong>Bone Mineral Content (g)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole-Body</td>
<td>1947.88 (432.44)</td>
<td>2189.41 (301.12)</td>
<td>0.655</td>
</tr>
<tr>
<td>Left Arm</td>
<td>169.77 (45.02)</td>
<td>189.30 (39.30)</td>
<td>0.655</td>
</tr>
<tr>
<td>Right Arm</td>
<td>169.77 (45.02)</td>
<td>189.30 (39.30)</td>
<td>0.655</td>
</tr>
<tr>
<td>Upper Body</td>
<td>345.82 (90.67)</td>
<td>378.82 (82.19)</td>
<td>0.456</td>
</tr>
<tr>
<td>Left leg</td>
<td>475.30 (133.80)</td>
<td>492.31 (20.7)</td>
<td>0.655</td>
</tr>
<tr>
<td>Right leg</td>
<td>500.57 (123.25)</td>
<td>642.82 (314.15)</td>
<td>0.655</td>
</tr>
<tr>
<td>Lower Body</td>
<td>975.88 (255.59)</td>
<td>1135.14 (293.77)</td>
<td>0.655</td>
</tr>
<tr>
<td><strong>Bone Mineral Density (g/cm^2)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole-body</td>
<td>0.98 (0.10)</td>
<td>1.13 (0.19)</td>
<td>0.297</td>
</tr>
<tr>
<td>Left arm</td>
<td>0.77 (0.10)</td>
<td>0.79 (0.13)</td>
<td>0.881</td>
</tr>
<tr>
<td>Right arm</td>
<td>0.78 (0.10)</td>
<td>0.78 (0.13)</td>
<td>0.655</td>
</tr>
<tr>
<td>Upper body</td>
<td>1.56 (0.20)</td>
<td>1.58 (0.25)</td>
<td>0.881</td>
</tr>
<tr>
<td>Left leg</td>
<td>1.40 (0.48)</td>
<td>1.24 (0.07)</td>
<td>0.297</td>
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<tr>
<td>Right leg</td>
<td>1.20 (0.14)</td>
<td>1.73 (0.76)</td>
<td>0.655</td>
</tr>
<tr>
<td>Lower body</td>
<td>2.62 (0.55)</td>
<td>2.97 (0.69)</td>
<td>0.456</td>
</tr>
</tbody>
</table>
THE EFFECTS OF CREATINE MONOHYDRATE SUPPLEMENTATION AND RESISTANCE TRAINING IN STROKE SURVIVORS

<table>
<thead>
<tr>
<th>Muscle Strength (kg)</th>
<th>Before Baseline</th>
<th>After Baseline</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leg press</td>
<td>170.08 (62.83)</td>
<td>128.66 (46.66)</td>
<td>0.456</td>
</tr>
<tr>
<td>Chest press</td>
<td>51.08 (34.10)</td>
<td>40.46 (21.34)</td>
<td>0.881</td>
</tr>
<tr>
<td>Total body</td>
<td>221.16 (95.17)</td>
<td>169.13 (66.98)</td>
<td>0.456</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tasks of Functionality</th>
<th>Before Baseline</th>
<th>After Baseline</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-Minute walk (m)</td>
<td>598.80 (168.92)</td>
<td>427.00 (7.54)</td>
<td>0.025*</td>
</tr>
<tr>
<td>Berg Balance</td>
<td>53.60 (1.51)</td>
<td>52.66 (1.15)</td>
<td>0.353</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cognition</th>
<th>Before Baseline</th>
<th>After Baseline</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOCA</td>
<td>24.2 (2.58)</td>
<td>25.00 (3.60)</td>
<td>0.651</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anxiety and Depression</th>
<th>Before Baseline</th>
<th>After Baseline</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAD</td>
<td>4.80 (3.83)</td>
<td>2.66 (3.05)</td>
<td>0.356</td>
</tr>
<tr>
<td>CES</td>
<td>18.80 (6.76)</td>
<td>19.00 (1.00)</td>
<td>0.451</td>
</tr>
</tbody>
</table>

Values are means (standard deviation). * Significant difference at baseline
Body Composition

There were no changes over time for body mass, fat mass, lean tissue mass (Table 2) or bone mineral (Table 3).
Table 2. Body mass, fat mass and lean tissue mass (kg) measurements before and after 10 weeks of supplementation and resistance training.

<table>
<thead>
<tr>
<th>kg</th>
<th>Pre</th>
<th>Post</th>
<th>p-value</th>
<th>Pre</th>
<th>Post</th>
<th>p-value</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass</td>
<td>84.74 (19.24)</td>
<td>84.82 (16.64)</td>
<td>0.893</td>
<td>73.33 (5.83)</td>
<td>73.40 (7.97)</td>
<td>1.000</td>
<td>0.001</td>
</tr>
<tr>
<td>Fat mass</td>
<td>25.99 (7.55)</td>
<td>25.75 (8.44)</td>
<td>0.893</td>
<td>17.33 (2.99)</td>
<td>16.66 (3.60)</td>
<td>0.109</td>
<td>0.069</td>
</tr>
<tr>
<td>Lean tissue mass</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole-body</td>
<td>49.76 (14.19)</td>
<td>50.95 (14.65)</td>
<td>0.138</td>
<td>48.43 (10.18)</td>
<td>48.22 (8.36)</td>
<td>1.000</td>
<td>0.106</td>
</tr>
<tr>
<td>Left arm</td>
<td>2.78 (1.41)</td>
<td>2.91 (1.41)</td>
<td>0.080</td>
<td>2.86 (1.15)</td>
<td>2.90 (0.82)</td>
<td>1.000</td>
<td>0.061</td>
</tr>
<tr>
<td>Right arm</td>
<td>3.02 (1.26)</td>
<td>3.03 (1.21)</td>
<td>0.893</td>
<td>2.99 (1.14)</td>
<td>3.25 (1.01)</td>
<td>0.109</td>
<td>0.205</td>
</tr>
<tr>
<td>Upper body</td>
<td>5.81 (2.68)</td>
<td>5.95 (2.61)</td>
<td>0.225</td>
<td>5.85 (2.26)</td>
<td>6.15 (1.79)</td>
<td>0.109</td>
<td>0.063</td>
</tr>
<tr>
<td>Left leg</td>
<td>8.43 (2.68)</td>
<td>8.74 (2.71)</td>
<td>0.345</td>
<td>8.00 (2.13)</td>
<td>7.72 (1.66)</td>
<td>0.285</td>
<td>0.231</td>
</tr>
<tr>
<td>Right leg</td>
<td>8.76 (2.32)</td>
<td>9.04 (2.29)</td>
<td>0.225</td>
<td>7.60 (1.50)</td>
<td>7.53 (1.35)</td>
<td>1.000</td>
<td>0.183</td>
</tr>
<tr>
<td>Lower body</td>
<td>17.20 (4.98)</td>
<td>17.78 (4.99)</td>
<td>0.500</td>
<td>15.61 (3.63)</td>
<td>15.25 (2.88)</td>
<td>0.593</td>
<td>0.203</td>
</tr>
</tbody>
</table>

Values are means (standard deviation).
Table 3. Bone mineral measurements before and after 10 weeks of supplementation and resistance training.

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
<th>p-value</th>
<th>Pre</th>
<th>Post</th>
<th>p-value</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Content (g)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole-body</td>
<td>1947.88 (432.44)</td>
<td>1921.91 (411.00)</td>
<td>0.893</td>
<td>2189.41 (301.12)</td>
<td>2176.58 (254.72)</td>
<td>0.593</td>
<td>0.033</td>
</tr>
<tr>
<td>Left arm</td>
<td>169.77 (45.02)</td>
<td>168.77 (44.38)</td>
<td>0.500</td>
<td>189.30 (39.3)</td>
<td>190.64 (33.49)</td>
<td>1.000</td>
<td>0.060</td>
</tr>
<tr>
<td>Right arm</td>
<td>176.05 (46.20)</td>
<td>179.38 (48.54)</td>
<td>0.686</td>
<td>189.52 (44.06)</td>
<td>204.32 (43.98)</td>
<td>0.285</td>
<td>0.252</td>
</tr>
<tr>
<td>Upper body</td>
<td>345.82 (90.67)</td>
<td>347.91 (92.54)</td>
<td>0.500</td>
<td>378.82 (82.19)</td>
<td>394.96 (76.01)</td>
<td>0.285</td>
<td>0.160</td>
</tr>
<tr>
<td>Left leg</td>
<td>475.30 (133.80)</td>
<td>480.59 (118.93)</td>
<td>0.686</td>
<td>492.31 (20.7)</td>
<td>475.38 (9.55)</td>
<td>0.109</td>
<td>0.202</td>
</tr>
<tr>
<td>Right leg</td>
<td>500.57 (123.25)</td>
<td>492.21 (110.30)</td>
<td>0.500</td>
<td>642.82 (314.15)</td>
<td>627.69 (253.75)</td>
<td>0.593</td>
<td>0.033</td>
</tr>
<tr>
<td>Lower body</td>
<td>975.88 (255.59)</td>
<td>972.81 (229.02)</td>
<td>0.893</td>
<td>1135.14 (293.77)</td>
<td>1103.08 (244.19)</td>
<td>0.593</td>
<td>0.108</td>
</tr>
<tr>
<td>Left side</td>
<td>645.08 (176.29)</td>
<td>649.12 (161.82)</td>
<td>0.893</td>
<td>681.61 (58.39)</td>
<td>666.03 (40.63)</td>
<td>0.285</td>
<td>0.133</td>
</tr>
<tr>
<td>Right side</td>
<td>676.62 (169.20)</td>
<td>671.59 (158.60)</td>
<td>0.686</td>
<td>832.34 (280.79)</td>
<td>832.01 (241.13)</td>
<td>1.000</td>
<td>0.008</td>
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<tr>
<td><strong>Density (g/cm²)</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole-body</td>
<td>0.98 (0.10)</td>
<td>1.18 (0.47)</td>
<td>0.786</td>
<td>1.13 (0.19)</td>
<td>1.13 (0.19)</td>
<td>0.593</td>
<td>1.353</td>
</tr>
<tr>
<td>Left arm</td>
<td>0.77 (0.10)</td>
<td>0.87 (0.25)</td>
<td>0.144</td>
<td>0.79 (0.13)</td>
<td>0.78 (0.12)</td>
<td>0.593</td>
<td>0.960</td>
</tr>
<tr>
<td>Right arm</td>
<td>0.78 (0.10)</td>
<td>0.78 (0.09)</td>
<td>0.686</td>
<td>0.78 (0.13)</td>
<td>0.79 (0.10)</td>
<td>1.000</td>
<td>0.063</td>
</tr>
<tr>
<td>Upper body</td>
<td>1.56 (0.20)</td>
<td>1.66 (0.32)</td>
<td>0.138</td>
<td>1.58 (0.25)</td>
<td>1.58 (0.22)</td>
<td>1.000</td>
<td>0.440</td>
</tr>
<tr>
<td>Left leg</td>
<td>1.40 (0.48)</td>
<td>1.20 (0.14)</td>
<td>0.345</td>
<td>1.24 (0.07)</td>
<td>1.52 (0.41)</td>
<td>0.285</td>
<td>1.218</td>
</tr>
<tr>
<td>Right leg</td>
<td>1.20 (0.14)</td>
<td>1.20 (0.15)</td>
<td>0.500</td>
<td>1.73 (0.76)</td>
<td>1.80 (0.89)</td>
<td>0.285</td>
<td>0.183</td>
</tr>
<tr>
<td>Lower body</td>
<td>2.62 (0.55)</td>
<td>2.41 (0.29)</td>
<td>0.345</td>
<td>2.97 (0.69)</td>
<td>3.33 (1.30)</td>
<td>0.285</td>
<td>0.916</td>
</tr>
<tr>
<td>Left side</td>
<td>2.18 (0.51)</td>
<td>2.08 (0.39)</td>
<td>0.893</td>
<td>2.03 (0.18)</td>
<td>2.59 (0.82)</td>
<td>0.285</td>
<td>1.514</td>
</tr>
<tr>
<td>Right side</td>
<td>1.99 (0.25)</td>
<td>1.99 (0.25)</td>
<td>0.893</td>
<td>2.51 (0.68)</td>
<td>2.60 (0.84)</td>
<td>0.593</td>
<td>0.185</td>
</tr>
</tbody>
</table>

Values are means (standard deviation).
Muscle Thickness

The creatine group experienced a significant increase in muscle thickness for the left and right elbow flexors and a decrease for the right elbow extensors. There were no other differences (Table 4).
Table 4. Muscle thickness measurements (cm) before and after 10 weeks of supplementation and resistance training.

<table>
<thead>
<tr>
<th>cm</th>
<th>Creatine</th>
<th>Placebo</th>
<th>p-value</th>
<th>Creatine</th>
<th>Placebo</th>
<th>p-value</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left elbow flexor</td>
<td>3.31 (0.68)</td>
<td>3.65 (0.53)*</td>
<td>0.043</td>
<td>3.88 (1.48)</td>
<td>4.35 (1.09)</td>
<td>0.109</td>
<td>0.167</td>
</tr>
<tr>
<td>Right elbow flexor</td>
<td>3.08 (0.52)</td>
<td>3.56 (0.70)*</td>
<td>0.043</td>
<td>3.02 (0.54)</td>
<td>3.62 (0.77)</td>
<td>0.109</td>
<td>0.209</td>
</tr>
<tr>
<td>Left elbow extensor</td>
<td>3.07 (0.81)</td>
<td>3.09 (0.75)</td>
<td>0.500</td>
<td>3.74 (1.51)</td>
<td>3.67 (1.16)</td>
<td>0.593</td>
<td>0.082</td>
</tr>
<tr>
<td>Right elbow extensor</td>
<td>3.49 (0.64)</td>
<td>3.06 (0.26)*</td>
<td>0.043</td>
<td>3.47 (1.28)</td>
<td>3.36 (0.44)</td>
<td>1.000</td>
<td>0.343</td>
</tr>
<tr>
<td>Upper body</td>
<td>12.96 (1.31)</td>
<td>13.38 (1.49)</td>
<td>0.080</td>
<td>14.12 (4.67)</td>
<td>15.01 (3.34)</td>
<td>0.285</td>
<td>0.165</td>
</tr>
<tr>
<td>Left knee flexor</td>
<td>3.86 (0.31)</td>
<td>3.76 (0.66)</td>
<td>0.465</td>
<td>3.83 (1.40)</td>
<td>4.17 (1.01)</td>
<td>0.109</td>
<td>1.363</td>
</tr>
<tr>
<td>Right knee flexor</td>
<td>3.72 (0.58)</td>
<td>3.79 (0.65)</td>
<td>0.465</td>
<td>4.22 (1.28)</td>
<td>4.24 (0.67)</td>
<td>1.000</td>
<td>0.065</td>
</tr>
<tr>
<td>Left knee extensor</td>
<td>3.67 (0.64)</td>
<td>3.69 (0.78)</td>
<td>0.686</td>
<td>3.50 (0.54)</td>
<td>3.49 (0.41)</td>
<td>1.000</td>
<td>0.030</td>
</tr>
<tr>
<td>Right knee extensor</td>
<td>3.59 (0.56)</td>
<td>4.03 (0.67)</td>
<td>0.225</td>
<td>3.29 (0.45)</td>
<td>3.42 (0.27)</td>
<td>0.593</td>
<td>0.601</td>
</tr>
<tr>
<td>Lower body</td>
<td>14.96 (1.94)</td>
<td>15.69 (2.37)</td>
<td>0.144</td>
<td>8.06 (2.68)</td>
<td>9.22 (1.61)</td>
<td>0.285</td>
<td>0.237</td>
</tr>
<tr>
<td>Left side</td>
<td>14.53 (1.36)</td>
<td>14.80 (1.88)</td>
<td>1.000</td>
<td>14.96 (4.69)</td>
<td>16.49 (3.45)</td>
<td>0.109</td>
<td>0.400</td>
</tr>
<tr>
<td>Right side</td>
<td>13.83 (1.96)</td>
<td>14.83 (1.60)</td>
<td>0.144</td>
<td>14.02 (2.86)</td>
<td>15.38 (2.40)</td>
<td>0.109</td>
<td>0.152</td>
</tr>
<tr>
<td>Appendicular</td>
<td>24.93 (8.08)</td>
<td>25.93 (9.78)</td>
<td>0.225</td>
<td>22.18 (7.35)</td>
<td>24.23 (4.81)</td>
<td>0.285</td>
<td>0.149</td>
</tr>
</tbody>
</table>

Values are means (standard deviation). * Significant difference from baseline
Appendicular = all muscle groups combined.
Muscle Strength, Tasks of Functionality, Cognition, Anxiety and Depression

The creatine group experienced a significant increase in leg press strength, chest press strength, total body strength (leg press and chest press combined), 6-minute walking performance and a reduction in anxiety. There were no changes for the placebo group.
Table 5. Muscle strength (kg), 6-minute walk (sec), Berg scale, cognition, anxiety and depression measurements before and after 10 weeks of supplementation and resistance training.

<table>
<thead>
<tr>
<th></th>
<th>Creatine</th>
<th></th>
<th>Placebo</th>
<th>p-value</th>
<th>p-value</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leg press</td>
<td>Pre</td>
<td>170.08 (62.83)</td>
<td>Post</td>
<td>230.92 (82.37)*</td>
<td>0.043</td>
<td>181.76 (70.60)</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>230.92 (82.37)*</td>
<td>p-value</td>
<td>0.043</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest press</td>
<td>Pre</td>
<td>51.08 (34.10)</td>
<td>Post</td>
<td>74.82 (45.82)*</td>
<td>0.043</td>
<td>58.83 (33.29)</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>74.82 (45.82)*</td>
<td>p-value</td>
<td>0.043</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total strength</td>
<td>Pre</td>
<td>221.16 (95.17)</td>
<td>Post</td>
<td>305.74 (125.06)*</td>
<td>0.043</td>
<td>240.60 (101.73)</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>305.74 (125.06)*</td>
<td>p-value</td>
<td>0.043</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-min walk</td>
<td>Pre</td>
<td>598.80 (168.92)</td>
<td>Post</td>
<td>638.00 (160.15)*</td>
<td>0.043</td>
<td>443.00 (12.52)</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>638.00 (160.15)*</td>
<td>p-value</td>
<td>0.043</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berg scale</td>
<td>Pre</td>
<td>53.60 (1.51)</td>
<td>Post</td>
<td>56.00 (0.01)</td>
<td>0.066</td>
<td>55.66 (0.57)</td>
</tr>
<tr>
<td>Moca</td>
<td>Pre</td>
<td>24.2 (2.58)</td>
<td>Post</td>
<td>26.6 (3.91)</td>
<td>0.066</td>
<td>26.33 (1.52)</td>
</tr>
<tr>
<td>GAD</td>
<td>Pre</td>
<td>4.80 (3.83)</td>
<td>Post</td>
<td>1.40 (1.51)*</td>
<td>0.039</td>
<td>0.66 (1.15)</td>
</tr>
<tr>
<td>CES</td>
<td>Pre</td>
<td>18.80 (6.76)</td>
<td>Post</td>
<td>11.80 (4.08)</td>
<td>0.066</td>
<td>15.00 (1.00)</td>
</tr>
</tbody>
</table>

Values are means (standard deviation). * Significant difference from baseline
Moca: Montreal Cognitive Assessment
GAD: Generalized Anxiety Disorder
CES: Centre for Epidemiologic Studies-Depression Scale
Training Volume

There were no differences between groups for the volume of training performed per exercise or for all exercises combined (Table 6).
Table 6. Training volume (load x sets x repetitions; kg) after 10 weeks of supplementation and resistance training.

<table>
<thead>
<tr>
<th>Exercise</th>
<th>Creatine</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leg press</td>
<td>81245.45 (23154.45)</td>
<td>131256.66 (34613.18)</td>
<td>0.053</td>
</tr>
<tr>
<td>Leg extension</td>
<td>36140.90 (7100.25)</td>
<td>45641.66 (23937.7)</td>
<td>0.881</td>
</tr>
<tr>
<td>Leg curl</td>
<td>33022.72 (6599.03)</td>
<td>23121.21 (8902.63)</td>
<td>0.180</td>
</tr>
<tr>
<td>Chest press</td>
<td>23789.54 (986.12)</td>
<td>22306.81 (6809.54)</td>
<td>0.881</td>
</tr>
<tr>
<td>Biceps curl</td>
<td>13267.72 (2815.10)</td>
<td>10719.69 (5248.63)</td>
<td>0.651</td>
</tr>
<tr>
<td>Triceps extension</td>
<td>15213.63 (3087.63)</td>
<td>16121.21 (3391.34)</td>
<td>0.881</td>
</tr>
<tr>
<td>Total volume</td>
<td>202680.00 (40447.30)</td>
<td>152677.27 (48364.63)</td>
<td>0.101</td>
</tr>
</tbody>
</table>

Values are means (standard deviation).
Discussion

This was the first study to examine the effects of creatine supplementation and resistance training in stroke survivors. The main findings were that creatine supplementation and resistance training significantly increased leg press and chest press strength, elbow flexor muscle thickness, 6-minute walking performance and decreased symptoms of anxiety over time. Furthermore, no participant reported any adverse events. These results suggest that creatine supplementation and resistance training is a safe and effective lifestyle intervention for stroke survivors.

The significant increase in muscle strength from creatine supplementation and resistance training is in agreement with the results of two recent meta-analysis reviews. In examining the effects of creatine supplementation during resistance training compared to placebo during resistance training in over 700 adults (57-70 years of age), Chilibeck et al., (2017) found a greater improvement in both leg press and chest press strength from creatine. These results expanded on the previous findings of Devries & Phillips (2014) who also found greater improvements in leg press and chest press strength from creatine supplementation vs. placebo during resistance training in a smaller cohort of aging adults (~ 300; 55-71 years of age). While the mechanisms explaining the greater increase in muscle strength from creatine remain to be determined, it is possible that creatine supplementation increased intramuscular PCr stores leading to accelerated PCr resynthesis during and following resistance training sessions which could have increased strength over time (Chilibeck et al, 2017). Unfortunately, no measure or assessment of intramuscular creatine was made in this study. In addition to high-energy phosphate metabolism, creatine may augment calcium uptake into the sarcoplasmic reticulum during muscle contraction which would result in faster detachment of the actin-myosin cross-bridge which may increase strength.
(Bazzucchi et al. 2009). The significant increase in leg press strength from creatine may have contributed to the significant improvement in the 6-minute walk test. It is important to note that an improvement of 50 meters corresponds to a meaningful clinical change (Perera, 2006). This is based on analyses from a sample of 692 community living older adults and individuals have survived a stroke (Perera, 2006). Unfortunately, neither group collectively showed a meaningful clinical change, although some participants did show a greater than 50m increase from baseline.

Creatine had a minimal effect on regional muscle thickness, with only the elbow flexors increasing over time. Mechanistically, the increase in elbow flexor muscle thickness may be related to the possible effects of creatine on muscle protein kinetics and inflammation. Creatine has been shown to increase actin and myosin protein synthesis, protein expression of type I, IIa and IIx muscle fibers, insulin-like growth factor-1 (IGF-1), myogenic regulatory factors, and satellite cell activation, proliferation and differentiation, and decrease indices of muscle protein breakdown, inflammation and oxidative stress (for reviews see Candow et al. 2019; Chilibeck et al. 2017). However, creatine had no effect on elbow extensor or knee flexor or extensor muscle thickness or whole-body lean tissue mass. These inconsistent results may be related to the very low sample size which decreased the ability to detect small differences in all muscle groups over time. Furthermore, ultrasound does not allow for the differentiation of contractile and non-contractile tissue and lean tissue measurements from dual energy x-ray absorptiometry may be influenced by hydration status (Formica et al., 1993; Going et al., 1993; Horber et al., 1992), size of the individual (Kendler et al., 2013), time of day the scan occurred (Lewiecki & Lane, 2008), and the duration of the study (Shetty et al., 2016). These instrument limitations may have decreased our ability to detect small gains in muscle accretion over time. In addition, according to their
submitted food records, participants in the creatine group were only consuming 1.04 ± 0.21 grams of protein/kg at the beginning of the study and 1.06 ± 0.18 grams of protein/kg at the end. It is now well established and recommended that adults should consume ≥ 1.2 grams of protein/kg to maintain or increase muscle mass (Morton et al. 2018; Philips et al. 2016). Potentially, the suboptimal ingestion of dietary protein may have blunted an anabolic response from creatine over time. The short duration of resistance training may have also jeopardized the muscle response to creatine over time. In the Chilibeck et al. (2017) meta-analysis, all studies showing a greater increase in muscle accretion from creatine vs. placebo occurred with the training program was ≥ 10 weeks in duration. Therefore, perhaps a longer training program was needed to produce detectable increases in regional and whole-body muscle mass over time. Additionally, all participants reported having left sided weakness post stroke and all exercises were performed bilaterally. In a meta-analysis of bilateral movement training, outcomes were positive overall during sub-acute and chronic phases of recovery which may have been due to positive neural effects for both hemispheres, whereas unilateral training might result in reorganization of the ipsilesional hemisphere (Stewart et al., 2006). This in turn may have had an effect on increasing muscle mass of the unaffected side. Finally, the dosage of creatine may have been too low to produce significant gains in all muscle groups and regions assessed.

Creatine had no effect on any measure of bone mineral. The limited research which exists is mixed regarding the effects of creatine supplementation during resistance training. According to the meta-analysis of Forbes et al. (2018), only two studies have reported significant bone benefits from creatine. In post-menopausal women, 12 months of creatine supplementation (~ 10 grams/day) during supervised whole-body resistance training attenuated the loss of bone mineral
density in the hip region compared to placebo (Chilibeck et al. 2015). In aging males, creatine supplementation (~ 10 grams/day) during supervised whole-body resistance training (12 weeks) increased bone mineral content in the upper limbs compared to placebo. However, Tarnopolsky et al. (2007) found no effect from creatine supplementation (5gram/day) during 6 months of whole-body resistance training on bone mineral density in aging adults and Candow et al. (2019) also found no effect from 8 months of creatine supplementation (0.1g/kg) and supervised whole-body resistance training on whole-body bone mineral. The lack of effect from creatine in the present study is likely related to the very small sample size, high variability in bone mineral turnover in stroke survivors, and short duration of training and supplementation.

Participants supplementing with creatine had a reduction in anxiety over time. Anxiety after stroke tends to be phobic and is associated with poorer patient outcomes (Campbell et al., 2013). In the case of general anxiety disorder, investigators have detected reduced levels of total creatine in cerebral white mater of patients (Coplan et al, 2006). It has also been shown that patients that actively experiencing panic attacks exhibited reduced levels of total creatine in the right amygdalohippocampal region (Massana et al., 2002). Additionally, patients diagnosed with post-traumatic stress disorder have shown reductions in total creatine in right and left hippocampal regions when compared to control subjects (Schuff et al., 2001; Villareal et al., 2002). Moreover, creatine metabolism and the creatine kinase/phosphocreatine system are important for brain function, and may be compromised in diseases of the central nervous system (Andres et al., 2008). Therefore, it is possible that the individuals who were supplemented with creatine monohydrate improved creatine metabolism resulting in reduced symptoms of anxiety.
Unfortunately, creatine supplementation had no significant effect on depression. As stated above, the CES-D is a 20-item scale with possible scores ranging from zero to 60 with the suggested cutoff for depression is a score of 16 or more. Although there was no significant difference both groups, both groups did reduce their CES-D score below 16. Altered purines levels in depressed women, but not men, have been associated with treatment response, suggesting that creatine may be more beneficial for treating depressed females (Renshaw et al., 2001). Additionally, the majority of studies showing a significant change in symptoms of depression with creatine monohydrate were in combination with another supplement or antidepressant (Roitman et al., 2007; Kious et al., 2017; Lyoo et al., 2012; Kondo et al., 2016). A meta-analysis and meta-regression of the efficacy of resistance training with depressive symptoms concluded resistance training was associated with a significant reduction in depressive symptoms (Gordon, McDowell & Hallgren, 2018). Alves et al. (2013) also concluded that creatine supplementation (4 x 5 g/day followed by 5g/day) in combination with strength training (24 weeks) in older women had no significant change in cognitive function and symptoms of depression. Moreover, some of the studies that did show a decrease in depressive symptoms supplemented participants with a high dosage creatine (20g/day) (McMorris et al., 2007; Alves et al., 2013; Bender et al., 2006). The lack of effect from creatine on symptoms of depression in the present study is likely related to the very small sample size, variability in depressive symptoms, and supplementation protocol/dosage.

There were several limitations to this study not previously mentioned. First, 34 participants were required to achieve 80% statistical power. Unfortunately, 8 participants completed the study. Secondly, it was assumed that all participants would respond to creatine supplementation. However, individual responsiveness to creatine may depend on initial PCr levels, type II muscle
fiber morphology, habitual dietary creatine intake, age and sex (for review see Candow et al. 2019). Benefits with creatine supplementation have been reported in men and women, although majority of studies have suggested that women may not see as great of an increase in strength and/or muscle mass during training in response to creatine supplementation (Candow et al., 2019; Benton & Donohoe, 2011; Vanderberghe et al., 1985; Grindstaff et al., 1997; Tarnopolsky & MacLennan, 2000; Ziegnfuss et al., 2002; Ayoma, Hiruma, Saski, 2003; Johannsmeyer et al., 2016; Ramirez-Campillo et al., 2016). Females may have higher initial intramuscular creatine stores (free creatine and PCr) than males which make them less responsive to supplementation (Forsberg et al., 1991; Johannsmeyer et al., 2016; Tarnopolsky, 2000). When replicating this experiment, it would be beneficial to measure initial muscle creatine concentration. This could be assessed using muscle biopsies or magnetic resonance spectroscopy to determine individual variation in muscle creatine content and accumulation in stroke survivors. Finally, no measure of muscle fiber type composition, muscle cross-sectional area, myogenic transcription factors, muscle protein kinetics, or inflammatory properties were measured. Future research should assess the mechanistic actions of creatine and resistance training post stroke to better understand its effect on muscle biology.
References


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THE EFFECTS OF CREATINE MONOHYDRATE SUPPLEMENTATION AND RESISTANCE TRAINING IN STROKE SURVIVORS


The Effects of Creatine Monohydrate Supplementation and Resistance Training in Stroke Survivors


THE EFFECTS OF CREATINE MONOHYDRATE SUPPLEMENTATION AND RESISTANCE TRAINING IN STROKE SURVIVORS


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Appendix A: Physical Activity Scale for Persons with Physical Disabilities

PHYSICAL ACTIVITY SCALE FOR PERSONS WITH PHYSICAL DISABILITIES

Instructions: This questionnaire is about your current level of physical activity and exercise. Please remember there are no right or wrong answers. We simply need to assess your current level of activity.

Leisure Time Activity

1. During the past 7 days how often did you engage in stationary activities such as reading, watching TV, computer games, or doing handcrafts?

1. Never (Go to question #2)
2. Seldom (1–2d)
3. Sometimes (3–4d)
4. Often (5–7d) What were these activities?

On average, how many hours per day did you spend in these stationary activities?

1. Less than 1hr
2. 1 but less than 2hr
3. 2–4hr
4. More than 4hr

2. During the past 7 days, how often did you walk, wheel, push outside your home other than specifically for exercise. For example, getting to work or class, walking the dog shopping, or other errands?

1. Never (Go to question #3)
2. Seldom (1–2d)
3. Sometimes (3–4d)
4. Often (5–7d)
On average, how many hours per day did you spend wheeling or pushing outside your home?

1. Less than 1hr
2. 1 but less than 2hr
3. 2–4hr
4. More than 4hr

3. During the past 7 days, how often did you engage in light sport or recreational activities such as bowling, golf with a cart, hunting or fishing, darts, billiards or pool, therapeutic exercise (physical or occupational therapy, stretching, use of a standing frame) or other similar activities?

1. Never (Go to question #4)
2. Seldom (1–2d)
3. Sometimes (3–4d)
4. Often (5–7d) What were these activities?

On average, how many hour per day did you spend in these light sport or recreational activities?

1. Less than 1hr
2. 1 but less than 2hr
3. 2–4hr
4. More than 4hr

4. During the past 7 days, how often did you engage in moderate sport and recreational activities such as doubles tennis, softball, golf without a cart, ballroom dancing, wheeling or pushing for pleasure or other similar activities?

1. Never (Go to question #5)
2. Seldom (1–2d)

3. Sometimes (3–4d)

4. Often (5–7d)  What were these activities?

**On average, how many hours per day did you spend in these moderate sport and recreational activities?**

1. Less than 1hr

2. 1 but less than 2hr

3. 2–4hr

4. More than 4hr

5. During the past 7 days, how often did you engage in strenuous sport and recreational activities such as jogging, wheelchair racing (training), off-road pushing, swimming, aerobic dance, arm cranking, cycling (hand or leg), singles tennis, rugby, basketball, walking with crutches and braces, or other similar activities

1. Never (Go to question #6)

2. Seldom (1–2d)

3. Sometimes (3–4d)

4. Often (5–7d)  What were these activities?

**On average, how many hours per day did you spend in these strenuous sport or recreational activities?**

1. Less than 1hr

2. 1 but less than 2hr

3. 2–4hr

4. More than 4hr
6. During the past 7 days, how often did you do any exercise specifically to increase muscle strength and endurance such as lifting weights, push-ups, pull-ups, dips, or wheel-chair push-ups, etc?

1. Never (Go to question #7)

2. Seldom (1–2d)

3. Sometimes (3–4d)

4. Often (5–7d)  What were these activities?

On average, how many hours per day did you spend in these exercises to increase muscle strength and endurance?

1. Less than 1hr

2. 1 but less than 2hr

3. 2–4hr

4. More than 4hr

Household Activity

7. During the past 7 days, how often have you done any light housework, such as dusting, sweeping floors or washing dishes?

1. Never (Go to question #8)

2. Seldom (1–2d)

3. Sometimes (3–4d)

4. Often (5–7d)

On average, how many hours per day did you spend doing light housework?

1. Less than 1hr

2. 1 but less than 2hr

3. 2–4hr

4. More than 4hr
8. During the past 7 days, how often have you done any heavy housework or chores such as vacuuming, scrubbing floors, washing windows, or walls, etc?

1. Never (Go to question #9)
2. Seldom (1–2d)
3. Sometimes (3–4d)
4. Often (5–7d)

On average, how many hours per day did you spend doing heavy housework or chores?

1. Less than 1hr
2. 1 but less than 2hr
3. 2–4hr
4. More than 4hr

9. During the past 7 days, how often you done home repairs like carpentry, painting, furniture refinishing, electrical work, etc?

1. Never (Go to question #10)
2. Seldom (1–2d)
3. Sometimes (3–4d)
4. Often (5–7d)

On average, how many hours per day did you spend doing home repairs?

1. Less than 1hr
2. 1 but less than 2hr
3. 2–4hr
4. More than 4hr
10. During the past 7 days how often have you done lawn work or yard care including mowing, leaf or snow removal, tree or bush trimming, or wood chopping, etc?

1. Never (Go to question #11)
2. Seldom (1–2d)
3. Sometimes (3–4d)
4. Often (5–7d)

On average, how many hours per day did you spend doing lawn work?

1. Less than 1hr
2. 1 but less than 2hr
3. 2–4hr
4. More than 4hr

11. During the past 7 days, how often have you done outdoor gardening?

1. Never (Go to question #12)
2. Seldom (1–2d)
3. Sometimes (3–4d)
4. Often (5–7d)

On average, how many hours per day did you spend doing outdoor gardening?

1. Less than 1hr
2. 1 but less than 2 hr
3. 2–4hr
4. More than 4hr

12. During the past 7 days, how often did you care for another person, such as children, a dependent spouse, or another adult?
THE EFFECTS OF CREATINE MONOHYDRATE SUPPLEMENTATION AND
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1. Never (Go to question #13)

2. Seldom (1–2d)

3. Sometimes (3–4d)

4. Often (5–7d)

On average, how many hours per day did you spend caring for another person?

1. Less than 1hr

2. 1 but less than 2hr

3. 2–4hr

4. More than 4hr

Work-Related Activity

13. During the past 7 days, how often did you work for pay or as a volunteer?
(Exclude work that mainly involved sitting with slight arm movement such as light office work, computer work, light assembly line work, driving bus or van, etc.)

1. Never (Go to END) 2. Seldom (1–2d) 3. Sometimes (3–4d) 4. Often (5–7d)

On average, how many hours per day did you spend working for pay or as a volunteer?

1. Less than 1hr

2. 1 but less than 4hr

3. 5 but less than 8hr

4. 8hr or more
THE EFFECTS OF CREATINE MONOHYDRATE SUPPLEMENTATION AND RESISTANCE TRAINING IN STROKE SURVIVORS

Scoring: PASIPD

Item multipliers

1. Not scored
2. 2.5
3. 3.0
4. 4.0
5. 8.0
6. 5.5
7. 1.5
8. 4.0
9. 4.0
10. 4.0
11. 4.0
12. 1.5
13. 2.5

Average Hours Per Day Calculation for Items 2–12

<table>
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<th>Category</th>
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<th>Average (hr/d)</th>
</tr>
</thead>
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<tr>
<td>Seldom (1–2d)</td>
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<td>.11</td>
</tr>
<tr>
<td></td>
<td>1–2</td>
<td>.32</td>
</tr>
<tr>
<td></td>
<td>2–4</td>
<td>.64</td>
</tr>
<tr>
<td></td>
<td>&gt;4</td>
<td>1.07</td>
</tr>
<tr>
<td>Sometimes (3–4d)</td>
<td>&lt;1</td>
<td>.25</td>
</tr>
<tr>
<td></td>
<td>1–2</td>
<td>.75</td>
</tr>
<tr>
<td></td>
<td>2–4</td>
<td>1.50</td>
</tr>
<tr>
<td></td>
<td>&gt;4</td>
<td>2.50</td>
</tr>
<tr>
<td>Often (5–7d)</td>
<td>&lt;1</td>
<td>.43</td>
</tr>
<tr>
<td></td>
<td>1–2</td>
<td>1.29</td>
</tr>
<tr>
<td></td>
<td>2–4</td>
<td>2.57</td>
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<td></td>
<td>&gt;4</td>
<td>4.29</td>
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Average Hours Per Day Calculation for Item 13

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<th>Average (hr/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seldom (1–2d)</td>
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<td>.12</td>
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<tr>
<td></td>
<td>1–4</td>
<td>.64</td>
</tr>
<tr>
<td></td>
<td>5–8</td>
<td>1.39</td>
</tr>
<tr>
<td></td>
<td>&gt;8</td>
<td>1.93</td>
</tr>
<tr>
<td>Sometimes (3–4d)</td>
<td>&lt;1</td>
<td>.28</td>
</tr>
<tr>
<td></td>
<td>1–4</td>
<td>1.5</td>
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<tr>
<td></td>
<td>5–8</td>
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<td></td>
<td>&gt;8</td>
<td>4.5</td>
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<tr>
<td>Often (5–7d)</td>
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<td>.49</td>
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<td></td>
<td>1–4</td>
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<td>5.57</td>
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<tr>
<td></td>
<td>&gt;8</td>
<td>7.71</td>
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</tbody>
</table>

NOTE. PASIPD score = sum of item multiplier × average hours per day over items 2–13.

Appendix B: Stroke Impact Scale – Version 3.0
Stroke Impact Scale
VERSION 3.0

The purpose of this questionnaire is to evaluate how stroke has impacted your health and life. We want to know from YOUR POINT OF VIEW how stroke has affected you. We will ask you questions about impairments and disabilities caused by your stroke, as well as how stroke has affected your quality of life. Finally, we will ask you to rate how much you think you have recovered from your stroke.
### Stroke Impact Scale

These questions are about the physical problems which may have occurred as a result of your stroke.

<table>
<thead>
<tr>
<th>1. In the past week, how would you rate the strength of your...</th>
<th>A lot of strength</th>
<th>Quite a bit of strength</th>
<th>Some strength</th>
<th>A little strength</th>
<th>No strength at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Arm that was most affected by your stroke?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>b. Grip of your hand that was most affected by your stroke?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>c. Leg that was most affected by your stroke?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>d. Foot/ankle that was most affected by your stroke?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

These questions are about your memory and thinking.

<table>
<thead>
<tr>
<th>2. In the past week, how difficult was it for you to...</th>
<th>Not difficult at all</th>
<th>A little difficult</th>
<th>Somewhat difficult</th>
<th>Very difficult</th>
<th>Extremely difficult</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Remember things that people just told you?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>b. Remember things that happened the day before?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>c. Remember to do things (e.g. keep scheduled appointments or take medication)?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>d. Remember the day of the week?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>e. Concentrate?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>f. Think quickly?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>g. Solve everyday problems?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
These questions are about how you feel, about changes in your mood and about your ability to control your emotions since your stroke.

<table>
<thead>
<tr>
<th>3. In the past week, how often did you...</th>
<th>None of the time</th>
<th>A little of the time</th>
<th>Some of the time</th>
<th>Most of the time</th>
<th>All of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Feel sad?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>b. Feel that there is nobody you are close to?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>c. Feel that you are a burden to others?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>d. Feel that you have nothing to look forward to?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>e. Blame yourself for mistakes that you made?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>f. Enjoy things as much as ever?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>g. Feel quite nervous?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>h. Feel that life is worth living?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>i. Smile and laugh at least once a day?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
The following questions are about your ability to communicate with other people, as well as your ability to understand what you read and what you hear in a conversation.

<table>
<thead>
<tr>
<th>4. In the past week, how difficult was it to...</th>
<th>Not difficult at all</th>
<th>A little difficult</th>
<th>Somewhat difficult</th>
<th>Very difficult</th>
<th>Extremely difficult</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Say the name of someone who was in front of you?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>b. Understand what was being said to you in a conversation?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>c. Reply to questions?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>d. Correctly name objects?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>e. Participate in a conversation with a group of people?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>f. Have a conversation on the telephone?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>g. Call another person on the telephone, including selecting the correct phone number and dialing?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
The following questions ask about activities you might do during a typical day.

<table>
<thead>
<tr>
<th>5. In the past 2 weeks, how difficult was it to...</th>
<th>Not difficult at all</th>
<th>A little difficult</th>
<th>Somewhat difficult</th>
<th>Very difficult</th>
<th>Could not do at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Cut your food with a knife and fork?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>b. Dress the top part of your body?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>c. Bathe yourself?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>d. Clip your toenails?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>e. Get to the toilet on time?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>f. Control your bladder (not have an accident)?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>g. Control your bowels (not have an accident)?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>h. Do light household tasks/chores (e.g. dust, make a bed, take out garbage, do the dishes)?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>i. Go shopping?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>j. Do heavy household chores (e.g. vacuum, laundry or yard work)?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
The following questions are about your ability to be mobile, at home and in the community.

6. In the past 2 weeks, how difficult was it to...

<table>
<thead>
<tr>
<th>Activity</th>
<th>Not difficult at all</th>
<th>A little difficult</th>
<th>Somewhat difficult</th>
<th>Very difficult</th>
<th>Could not do at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Stay sitting without losing your balance?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>b. Stay standing without losing your balance?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>c. Walk without losing your balance?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>d. Move from a bed to a chair?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>e. Walk one block?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>f. Walk fast?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>g. Climb one flight of stairs?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>h. Climb several flights of stairs?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>i. Get in and out of a car?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

The following questions are about your ability to use your hand that was MOST AFFECTED by your stroke.

7. In the past 2 weeks, how difficult was it to use your hand that was most affected by your stroke to...

<table>
<thead>
<tr>
<th>Activity</th>
<th>Not difficult at all</th>
<th>A little difficult</th>
<th>Somewhat difficult</th>
<th>Very difficult</th>
<th>Could not do at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Carry heavy objects (e.g. bag of groceries)?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>b. Turn a doorknob?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>c. Open a can or jar?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>d. Tie a shoe lace?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>e. Pick up a dime?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
The following questions are about how stroke has affected your ability to participate in the activities that you usually do, things that are meaningful to you and help you to find purpose in life.

<table>
<thead>
<tr>
<th></th>
<th>During the past 4 weeks, how much of the time have you been limited in...</th>
<th>None of the time</th>
<th>A little of the time</th>
<th>Some of the time</th>
<th>Most of the time</th>
<th>All of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Your work (paid, voluntary or other)</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>b</td>
<td>Your social activities?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>c</td>
<td>Quiet recreation (crafts, reading)?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>d</td>
<td>Active recreation (sports, outings, travel)?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>e</td>
<td>Your role as a family member and/or friend?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>f</td>
<td>Your participation in spiritual or religious activities?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>g</td>
<td>Your ability to control your life as you wish?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>h</td>
<td>Your ability to help others?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
9. Stroke Recovery

On a scale of 0 to 100, with 100 representing full recovery and 0 representing no recovery, how much have you recovered from your stroke?

|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 100 |   |   | Full Recovery |
THE EFFECTS OF CREATINE MONOHYDRATE SUPPLEMENTATION AND RESISTANCE TRAINING IN STROKE SURVIVORS

Item Clarifications

1. If patient says “I don’t have an affected side”, then instruct them to score using their perceived weaker side. If they still insist there is no affected, or weaker, side instruct them to score using their dominant side.

4. If patient says s/he does not do any or all of the items listed, code item(s) as Extremely Difficult.
   (Item f) If patient does not call but is handed the phone this is OK.
   (Item g) If patient cannot hold a phone book, if they can read it this is OK. This item addresses whether the patient is able to initiate a phone call, look up the number, and dial this number correctly.

5. If patient says s/he does not do any or all of the items listed, code item(s) as Cannot do at all.
   (Item a) If person is on pureed food, even if they feel they could cut the food, code as Cannot do at All (1/5/98)
   (Item c) Bathing oneself does not include getting into the tub.
   (Item e) This question is associated with movement. Does the person have the physical ability to get to the bathroom quickly enough?
   (Item f) Losing a little urine/dribbling is considered an accident.
     If person has intermittent catheter and is having no leaking problems code them as per report. (1/5/98)
     If person has an in-dwelling Foley catheter, code as Cannot do at all. (1/5/98)
   (Item g) Constipation is not counted here, person has to have an accident.
   (Item i) “Shopping” means any type of shopping and does not include driving.

6. If patient hasn’t done any of the items in the past two weeks code as Cannot do at all.
   (Item h) If patient hasn’t “climbed several flights of stairs” in two weeks, they may be prompted by saying “have you gone up and down one flight of stairs a couple of times in a row.” If they still say they have not done it then they must be coded as Cannot do at all.
   (Item i) If the patient wants to know what kind of car say “your car” or “the car you ride in most.”

7. If patient says “I don’t have an affected side”, then instruct them to score using their perceived weaker side. If they still insist there is no affected, or weaker, side instruct them to score using their dominant side.
   (Item a) If the patient says s/he has not been to the grocery store say “have you carried anything heavy with that hand.”
   (Item d) This item is to tie a shoelace/bow using both hands.

8. If patient does not do any of the specific items (and has never done), code interference as None of the time.
Appendix C: Research Participant Information and Consent Form

Title of the study: The effects of creatine supplementation and resistance training in stroke survivors.

Researchers: Darren G. Candow, Ph.D. (Principal Investigator), Faculty of Kinesiology and Health Studies, University of Regina, phone: 306-585-4906, email: Darren.Candow@uregina.ca; Sara Butchart, MSc student researcher, email: smb965@uregina.ca.

24-hour emergency telephone contact: 306-209-0280

Introduction:
You are being invited to participate in this research study because we are interested in determining the effects of supervised resistance training and creatine supplementation on muscle mass, muscle strength, tasks of functionality, cognition, and symptoms of depression and anxiety.

Before you decide to participate, it is important that you understand what the research involves. This consent form will tell you about the study, why the research is being performed, what will happen to you during the study, and the possible benefits, risks, and discomforts.

If you wish to participate, you will be asked to sign this form. Your participation is completely voluntary, so it is up to you to decide whether or not to participate in this study. If you decide to take part in this study, you are free to withdraw at any time without giving any reasons for your decision and your choice not to participate will not affect your relationship with any of the researchers or institutions conducting the research. Please take time to read the following information carefully and feel free to discuss it with your family, friends, and doctor or health professional before you decide.

Why is this study being done?
The purpose of the study is to compare the effects of supervised resistance training and creatine supplementation to supervised resistance training and placebo on muscle mass, muscle strength, tasks of functionality, cognition, and symptoms of depression and anxiety in stroke survivors. Creatine is a nitrogen-containing compound naturally produced in the body and found in red meat and seafood, and when given in higher amounts than usually consumed in the diet, may increase muscle mass and muscle strength and have beneficial effects on functionality, cognition, and symptoms of depression and anxiety.
Who can participate in this study?
You can participate if you have not engaged in supervised resistance training for ≥ 6 weeks prior to the start of the study. In addition, you cannot have pre-existing kidney or liver problems; taken medications that affect muscle biology or creatine monohydrate ≤ 12 weeks prior to the start of the study; have a history of fragility fractures; diseases that are known to affect muscle biology; suffer from severe osteoarthritis; are vegetarian or plan to travel during the study period for greater than two weeks duration at a time.

What does the study involve?
If you agree to participate in this study, the following will occur:

You will be required to get medical clearance before being enrolled into the study.

You will be given a physical activity questionnaire at the start of the study and upon completion. This will gather information about leisure, household and work-related physical activity over the past 7 days. The frequency (number of days a week) and duration (daily hours) specific activities are performed will be recorded.

Prior to the start of the study, you will be randomized into one of two groups. Group 1 will receive creatine and Group 2 will receive placebo (corn-starch maltodextrin) during 10 weeks of resistance training. During the first 7 days, you will ingest 0.3g/kg of creatine or placebo (0.075 g/kg, 4 times daily). For the next 63 days, you will consume 0.1 g/kg per day of creatine or placebo. Creatine and placebo will be in powder form and you will be asked to consume the supplement (mixed in water) within 5 minutes after your exercise session ends. On the days that you do not exercise, you can consume the supplement at your leisure. Resistance training will occur 2 days per week, on non-consecutive days. Neither you nor the researchers will know which group you are in until the end of the study, but we can find out what group you are in if there is an emergency (i.e. an adverse reaction to the creatine or placebo).

Both groups will participate in 10 weeks of supervised resistance training. Resistance exercises (leg press, leg curl, leg extension, chest press, biceps curl, and triceps extension) will be performed in the Aging Muscle and Bone Health Lab at the University of Regina. Two weeks prior to the start of supplementation, you will be shown how to use the resistance training equipment with proper form and technique and you will participate in three sessions of training to get accustomed to the exercises. Supplementation with creatine or placebo will begin on the first day of the study (after the three familiarization sessions to the resistance training equipment) and occur daily for the remainder of the study. During these sessions you will perform the 6 resistance training exercises. A warm-up (e.g., stretching and 5 minutes of stationary cycling exercise) will be part of the training session.

Although 100% compliance to the resistance training program is the expectation, it is unlikely that all participants will meet this goal. Our hope is that you will be able to attend approximately 90% of the sessions (i.e. 18/20 sessions). You are not expected to attend the training sessions on holidays.
The following measurements will be performed prior to the intervention (i.e. baseline) and after 10 weeks of supplementation and resistance training:

- Your whole-body muscle mass will be assessed by dual-energy X-ray absorptiometry (DXA) in the Aging Muscle and Bone Health Laboratory at the University of Regina. This procedure will take approximately 15 minutes.

- Your arm and leg muscle thickness will be determined using an ultrasound machine on the right side of your body. This procedure will take approximately 20 minutes.

- Your muscular strength will be determined for the leg press and chest press. This procedure will take approximately 20 minutes.

- Tasks of functionality will be determined by the berg balance scale and six minute walk test. The berg balance scale consists of 14 items assessing balance. The six minute walk test will be performed to measure the distance the participants can quickly walk in a period of 6 minutes on a 30-m course.

- Cognition will be determined by the Montreal Cognitive Assessment (MoCa). Various categories such as orientation, short term memory, executive function, visuospatial ability, language ability, abstraction, animal naming, attention, and drawing test will be assessed. This 30-question test will take approximately 15 minutes.

- Anxiety will be assessed via the Generalized Anxiety Disorder Assessment (GAD-7). This is a 7-item self-administered questionnaire. GAD-7 will measure severity of various signs of generalized anxiety disorder according to reported responses with assigned points. This 7-item self-administered questionnaire will take approximately 5 minutes.

- Depression will be assessed using the CES-D scale which is designed to measure depressive symptoms in the general population. This self-administered measure includes twenty items comprising of six scales reflecting on major facets of depression. This questionnaire will take approximately 5 minutes to complete.

What are the benefits of participating in this study?
You might increase your muscle mass, strength, functionality and cognitive ability by participating in this study. These benefits are not guaranteed.
What are the possible risks and discomforts?
The resistance training and strength testing may result in minor muscle pulls and strains. You will be given proper warm-up prior to exercising and be supervised by an exercise professional and this will minimize the risk. Adequate rest will be given between training and testing sessions to ensure that your muscles are recovered by the next training session.

There is a small amount of radiation exposure from the dual energy x-ray scans. The amount of radiation is less than 1% from what you would receive from a routine full-mouth dental X-ray.

What are alternatives to the study?
You do not have to participate in this study to have your muscle mass assessed. You could have your muscle mass determined through an appointment with the Dr. Paul Schwann Center, Faculty of Kinesiology and Health Studies at the University of Regina and this can be performed by a number of different techniques (i.e. skin folds, bio-electrical impedance analysis). You do not have to participate in this study to increase muscle performance. You can perform alternative exercises (i.e. free-body exercises such as push-ups and wall squats instead of the resistance exercises in this study). You could also increase your creatine consumption from your diet by consuming more red meat and seafood products instead of receiving creatine supplementation in this study.

What happens if I decide to withdraw?
Your participation in this research is voluntary. You may withdraw from this study at any time. You do not have to provide a reason. Your relationships with the researchers or the university will not be affected. If you choose to enter the study and then decide to withdraw before the study is finished, all data collected about you during your enrolment will be retained for analysis until all dissemination of results have occurred.

What happens if something goes wrong?
In the case of a medical emergency related to the study, you should seek immediate care and, as soon as possible, notify the principal investigator. Inform the medical staff you are participating in a clinical study. Necessary medical treatment will be made available at no cost to you. By signing this document, you do not waive any of your legal rights against the sponsor, investigators or anyone else.

What happens after completion of the study?
We will inform you of the overall study results after we have analyzed all data.

What will the study cost me?
You will not be charged for the creatine, placebo, or any research-related procedures. You will not be paid for participating in this study. Reimbursement for study-related expenses (e.g. travel, parking, meals) is not available.
Will my participation be kept confidential?
In Saskatchewan, the Health Information Protection Act (HIPA) defines how the privacy of your personal health information must be maintained so that your privacy will be respected. Your name will not be attached to any information, nor mentioned in any study report, nor be made available to anyone except the research team. It is the intention of the research team to publish results of this research in scientific journals and to present the findings at related conferences and workshops, but your identity will not be revealed.

Who do I contact if I have questions about the study?
If you have questions concerning the study you can contact Dr. Darren Candow at 306-585-4906 or 306-209-0280 (24 hour cell).

This study has received approval from the Research Ethics Board. If you have any questions about your rights as a research subject or concerns about this study, you may contact the Chair of the University of Regina Research Ethics Board at (306) 585-4775 or email research.ethics@uregina.ca. Out of town participants may call collect.

Consent statement

- I have read (or someone has read to me) the information in this consent form.
- I understand the purpose and procedures and the possible risks and benefits of the study.
- I have been informed of the alternatives to the study.
- I was given sufficient time to think about it.
- I had the opportunity to ask questions and have received satisfactory answers.
- I am free to withdraw from this study at any time for any reason and the decision to stop taking part will not affect my future relationships at the university.
- I agree to follow the principal investigator’s instructions and will tell the principal investigator at once if I feel I have had any unexpected or unusual symptoms.
- I have been informed there is no guarantee that this study will provide any benefits to me.
- I give permission for the use and disclosure of my de-identified personal health information collected for the research purposes described in this form.
- I understand that by signing this document I do not waive any of my legal rights.
- I will be given a signed and dated copy of this consent form.
- I give permission for my family physician to be informed about my participation in this study if need be:
  - Yes
  - No
  - I do not have a family physician

☐ I agree to participate in this study:

Printed name of participant: ____________________________

Signature ____________________________ Date ____________________________
THE EFFECTS OF CREATINE MONOHYDRATE SUPPLEMENTATION AND RESISTANCE TRAINING IN STROKE SURVIVORS

Printed name of person obtaining consent: ________________________________

Signature __________________ Date________________________
Creatine Supplementation During Resistance Training for People Recovering From Stroke

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

Sponsor:
University of Saskatchewan

Collaborator:
University of Regina

Information provided by (Responsible Party):
Phil Chilibeck, University of Saskatchewan

Brief Summary:
Creatine monohydrate is important for sustaining phosphocreatine stores in tissues such as muscle and brain. Phosphocreatine is an important source of energy in these tissues. Supplementation with creatine monohydrate is effective in healthy and clinical populations for improving muscle and brain function. The purpose of our study is to determine whether creatine supplementation is effective during resistance training for improving muscle and brain function in people recovering from stroke.
## Appendix E: Resistance Training Log

<table>
<thead>
<tr>
<th>Date:</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Participant Name:</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Session:</th>
<th>Machine Settings</th>
<th>Set</th>
<th>Weight</th>
<th>Reps</th>
<th>Rest</th>
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<tbody>
<tr>
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<th>PRE:</th>
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<td>HR:</td>
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<tr>
<td>BP:</td>
<td>BP:</td>
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</tbody>
</table>
Appendix F: Berg Balance Scale

BERG BALANCE TESTS AND RATING SCALE

Patient Name ____________________________________________________________
Date __________________________________________________________________
Location __________________________________________________________________
Rater ____________________________________________________________________

ITEM DESCRIPTION SCORE (0-4) Sitting to standing _____ Standing unsupported _____ Sitting
unsupported _____ Standing to sitting _____ Transfers _____ Standing with eyes closed _____
Standing with feet together _____ Reaching forward with outstretched arm _____ Retrieving object
from floor _____ Turning to look behind _____ Turning 360 degrees _____ Placing alternate foot
on stool _____ Standing with one foot in front _____ Standing on one foot _____ TOTAL ______

GENERAL INSTRUCTIONS
Please demonstrate each task and/or give instructions as written. When scoring, please record the
lowest response category that applies for each item.

In most items, the subject is asked to maintain a given position for a specific time. Progressively
more points are deducted if the time or distance requirements are not met, if the subject’s
performance warrants supervision, or if the subject touches an external support or receives
assistance from the examiner. Subjects should understand that they must maintain their balance
while attempting the tasks. The choices of which leg to stand on or how far to reach are left to the
subject. Poor judgment will adversely influence the performance and the scoring.

Equipment required for testing are a stopwatch or watch with a second hand, and a ruler or other
indicator of 2, 5 and 10 inches (5, 12 and 25 cm). Chairs used during testing should be of
reasonable height. Either a step or a stool (of average step height) may be used for item #12.

1. SITTING TO STANDING
INSTRUCTIONS: Please stand up. Try not to use your hands for support.
( ) 4 able to stand without using hands and stabilize independently
( ) 3 able to stand independently using hands
( ) 2 able to stand using hands after several tries
( ) 1 needs minimal aid to stand or to stabilize
( ) 0 needs moderate or maximal assist to stand

2. STANDING UNSUPPORTED
INSTRUCTIONS: Please stand for two minutes without holding.
( ) 4 able to stand safely 2 minutes
( ) 3 able to stand 2 minutes with supervision
( ) 2 able to stand 30 seconds unsupported
( ) 1 needs several tries to stand 30 seconds unsupported
( ) 0 unable to stand 30 seconds unassisted
If a subject is able to stand 2 minutes unsupported, score full points for sitting unsupported. Proceed to item #4.

3. SITTING WITH BACK UNSUPPORTED BUT FEET SUPPORTED ON FLOOR OR ON A STOOL
INSTRUCTIONS: Please sit with arms folded for 2 minutes.
( ) 4 able to sit safely and securely 2 minutes
( ) 3 able to sit 2 minutes under supervision
( ) 2 able to sit 30 seconds
( ) 1 able to sit 10 seconds
( ) 0 unable to sit without support 10 seconds

4. STANDING TO SITTING
INSTRUCTIONS: Please sit down.
( ) 4 sits safely with minimal use of hands
( ) 3 controls descent by using hands
( ) 2 uses back of legs against chair to control descent
( ) 1 sits independently but has uncontrolled descent
( ) 0 needs assistance to sit

5. TRANSFERS
INSTRUCTIONS: Arrange chairs(s) for a pivot transfer. Ask subject to transfer one way toward a seat with armrests and one way toward a seat without armrests. You may use two chairs (one with and one without armrests) or a bed and a chair.
( ) 4 able to transfer safely with minor use of hands
( ) 3 able to transfer safely definite need of hands
( ) 2 able to transfer with verbal cueing and/or supervision
( ) 1 needs one person to assist
( ) 0 needs two people to assist or supervise to be safe

6. STANDING UNSUPPORTED WITH EYES CLOSED
INSTRUCTIONS: Please close your eyes and stand still for 10 seconds.
( ) 4 able to stand 10 seconds safely
( ) 3 able to stand 10 seconds with supervision
( ) 2 able to stand 3 seconds
( ) 1 unable to keep eyes closed 3 seconds but stays steady
( ) 0 needs help to keep from falling

7. STANDING UNSUPPORTED WITH FEET TOGETHER
INSTRUCTIONS: Place your feet together and stand without holding.
( ) 4 able to place feet together independently and stand 1 minute safely
( ) 3 able to place feet together independently and stand for 1 minute with supervision
( ) 2 able to place feet together independently but unable to hold for 30 seconds
( ) 1 needs help to attain position but able to stand 15 seconds with feet together
( ) 0 needs help to attain position and unable to hold for 15 seconds
8. REACHING FORWARD WITH OUTSTRETCHED ARM WHILE STANDING
INSTRUCTIONS: Lift arm to 90 degrees. Stretch out your fingers and reach forward as far as you can. (Examiner places a ruler at end of fingertips when arm is at 90 degrees. Fingers should not touch the ruler while reaching forward. The recorded measure is the distance forward that the finger reaches while the subject is in the most forward lean position. When possible, ask subject to use both arms when reaching to avoid rotation of the trunk.)
( ) 4 can reach forward confidently >25 cm (10 inches)
( ) 3 can reach forward >12 cm safely (5 inches)
( ) 2 can reach forward >5 cm safely (2 inches)
( ) 1 reaches forward but needs supervision
( ) 0 loses balance while trying/requires external support

9. PICK UP OBJECT FROM THE FLOOR FROM A STANDING POSITION
INSTRUCTIONS: Pick up the shoe/slipper which is placed in front of your feet.
( ) 4 able to pick up slipper safely and easily
( ) 3 able to pick up slipper but needs supervision
( ) 2 unable to pick up but reaches 2-5cm (1-2 inches) from slipper and keeps balance independently
( ) 1 unable to pick up and needs supervision while trying
( ) 0 unable to try/needs assist to keep from losing balance or falling

10. TURNING TO LOOK BEHIND OVER LEFT AND RIGHT SHOULDERS WHILE STANDING
INSTRUCTIONS: Turn to look directly behind you over toward left shoulder. Repeat to the right. Examiner may pick an object to look at directly behind the subject to encourage a better twist turn.
( ) 4 looks behind from both sides and weight shifts well
( ) 3 looks behind one side only other side shows less weight shift
( ) 2 turns sideways only but maintains balance
( ) 1 needs supervision when turning
( ) 0 needs assist to keep from losing balance or falling

11. TURN 360 DEGREES
INSTRUCTIONS: Turn completely around in a full circle. Pause. Then turn a full circle in the other direction.
( ) 4 able to turn 360 degrees safely in 4 seconds or less
( ) 3 able to turn 360 degrees safely one side only in 4 seconds or less
( ) 2 able to turn 360 degrees safely but slowly
( ) 1 needs close supervision or verbal cueing
( ) 0 needs assistance while turning

12. PLACING ALTERNATE FOOT ON STEP OR STOOL WHILE STANDING UNSUPPORTED
INSTRUCTIONS: Place each foot alternately on the step/stool. Continue until each foot has touched the step/stool four times.
( ) 4 able to stand independently and safely and complete 8 steps in 20 seconds
( ) 3 able to stand independently and complete 8 steps in >20 seconds
( ) 2 able to complete 4 steps without aid with supervision
( ) 1 able to complete >2 steps needs minimal assist
( ) 0 needs assistance to keep from falling/unable to try
13. STANDING UNSUPPORTED ONE FOOT IN FRONT
INSTRUCTIONS: (DEMONSTRATE TO SUBJECT) Place one foot directly in front of the other. If you feel that you cannot place your foot directly in front, try to step far enough ahead that the heel of your forward foot is ahead of the toes of the other foot. (To score 3 points, the length of the step should exceed the length of the other foot and the width of the stance should approximate the subject's normal stride width)
( ) 4 able to place foot tandem independently and hold 30 seconds
( ) 3 able to place foot ahead of other independently and hold 30 seconds
( ) 2 able to take small step independently and hold 30 seconds
( ) 1 needs help to step but can hold 15 seconds
( ) 0 loses balance while stepping or standing

14. STANDING ON ONE LEG
INSTRUCTIONS: Stand on one leg as long as you can without holding.
( ) 4 able to lift leg independently and hold >10 seconds
( ) 3 able to lift leg independently and hold 5-10 seconds
( ) 2 able to lift leg independently and hold = or >3 seconds
( ) 1 tries to lift leg unable to hold 3 seconds but remains standing independently
( ) 0 unable to try or needs assist to prevent fall

TOTAL SCORE (Maximum = 56: __________

*References


**THE EFFECTS OF CREATINE MONOHYDRATE SUPPLEMENTATION AND RESISTANCE TRAINING IN STROKE SURVIVORS**

**Appendix G: Montreal Cognitive Assessment (MOCA)**

**MONTREAL COGNITIVE ASSESSMENT (MOCA™)**
Version 8.1 English

**VISUOSPATIAL/EXECUTIVE**
- Copy cube
  - Draw CLOCK (Ten past eleven) (3 points)
  - Points: __/5

**NAMING**
- [ ] Rhinoceros
- [ ] Camel
- Points: __/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.
  - 1st trial: [ ] 2 1 8 5 4
  - 2nd trial: [ ] 7 4 2
  - Points: __/2

**ATTENTION**
- Read list of digits (1 digit/sec.). Subject has to repeat them in the forward order.
  - [ ] 9 3
  - Points: __/1

- Read list of letters. The subject must tap with his hand at each letter A. No points if ≠ 2 errors
  - Points: __/1

- Serial 7 subtraction starting at 100.
  - [ ] 93
  - Points: __/5

**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.
  - Points: __/2

**ABSTRACTION**
- Similarity between e.g. banana - orange = fruit
  - train - bicycle = watch - ruler
  - Points for UNCLED recall only
  - Points: __/2

**DELAYED RECALL**
- Memory Index Score (MIS)
  - X3
  - X2
  - X1
  - MIS = __/15

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

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© www.mocatest.org

Training and Certification are required to ensure accuracy
THE EFFECTS OF CREATINE MONOHYDRATE SUPPLEMENTATION AND RESISTANCE TRAINING IN STROKE SURVIVORS

Appendix H: GAD

Generalized Anxiety Disorder 7-item (GAD-7) scale

<table>
<thead>
<tr>
<th>Over the last 2 weeks, how often have you been bothered by the following problems?</th>
<th>Not at all sure</th>
<th>Several days</th>
<th>Over half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Feeling nervous, anxious, or on edge</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Not being able to stop or control worrying</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. Worrying too much about different things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. Trouble relaxing</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. Being so restless that it’s hard to sit still</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. Becoming easily annoyed or irritable</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. Feeling afraid as if something awful might happen</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

\[
\text{Add the score for each column} = + + +
\]

\[
\text{Total Score (add your column scores)} =
\]

If you checked off any problems, how difficult have these made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all __________
Somewhat difficult __________
Very difficult __________
Extremely difficult __________

THE EFFECTS OF CREATINE MONOHYDRATE SUPPLEMENTATION AND RESISTANCE TRAINING IN STROKE SURVIVORS

Appendix I: CES-D

<table>
<thead>
<tr>
<th></th>
<th>Rarely or none of the time (less than 1 day)</th>
<th>Some or a little of the time (1 – 2 days)</th>
<th>Occasionally or a moderate amount of the time (3 – 4 days)</th>
<th>Most or all of the time (5 – 7 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>I was bothered by things that usually don’t bother me.</td>
<td></td>
<td></td>
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<tr>
<td>2.</td>
<td>I did not feel like eating; my appetite was poor.</td>
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<tr>
<td>3.</td>
<td>I felt that I could not shake off the blues, even with the help from family or friends.</td>
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<tr>
<td>4.</td>
<td>I felt that I was just as good as other people.</td>
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<tr>
<td>5.</td>
<td>I had trouble keeping my mind on what I was doing.</td>
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<tr>
<td>6.</td>
<td>I felt depressed.</td>
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<tr>
<td>7.</td>
<td>I felt that everything I did was an effort.</td>
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<tr>
<td>8.</td>
<td>I felt hopeful about the future.</td>
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<tr>
<td>9.</td>
<td>I thought my life had been a failure.</td>
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<tr>
<td>10.</td>
<td>I felt fearful.</td>
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</tbody>
</table>
THE EFFECTS OF CREATINE MONOHYDRATE SUPPLEMENTATION AND
RESISTANCE TRAINING IN STROKE SURVIVORS

<table>
<thead>
<tr>
<th></th>
<th>Rarely or none of the time (less than 1 day)</th>
<th>Some or a little of the time (1 – 2 days)</th>
<th>Occasionally or a moderate amount of the time (3 – 4 days)</th>
<th>Most or all of the time (5 – 7 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.</td>
<td>My sleep was restless.</td>
<td></td>
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<tr>
<td>12.</td>
<td>I was happy.</td>
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<tr>
<td>13.</td>
<td>I talked less than usual.</td>
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<td>15.</td>
<td>People were unfriendly.</td>
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<tr>
<td>16.</td>
<td>I enjoyed life.</td>
<td></td>
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<tr>
<td>17.</td>
<td>I had crying spells.</td>
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<td>18.</td>
<td>I felt sad.</td>
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<td>19.</td>
<td>I felt that people dislike me.</td>
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<tr>
<td>20.</td>
<td>I could not get “going”.</td>
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</tbody>
</table>

Total: ______/60 (CESDT)

Validation of VCI Neuropsychological Protocols
### Adverse Event Form

**STUDY NAME**

Site Name: ____________________________
Pt_ID: ____________________________

This form is cumulative and captures adverse events of a single participant throughout the study.

<table>
<thead>
<tr>
<th>Severity</th>
<th>Study Intervention Relationship</th>
<th>Action Taken Regarding Study Intervention</th>
<th>Outcome of AE</th>
<th>Expected</th>
<th>Serious Adverse Event (SAE)</th>
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</thead>
<tbody>
<tr>
<td>1 = Mild 2 = Moderate 3 = Severe 4 = Life-Threatening</td>
<td>0 = Not related 1 = Unlikely related 2 = Possibly related 3 = Probably related 4 = Definitely related</td>
<td>0 = None 1 = Dose modification 2 = Medical Intervention 3 = Hospitalization 4 = Intervention discontinued 5 = Other</td>
<td>1 = Resolved 2 = Recovered with minor sequelae 3 = Recovered with major sequelae 4 = Ongoing/Continuing treatment 5 = Condition worsening 6 = Death 7 = Unknown</td>
<td>1 = Yes 2 = No (if yes, complete SAE form)</td>
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**At end of study only: Check this box if participant had no adverse events** ☐ None

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<th>Adverse Event</th>
<th>Start Date</th>
<th>Stop Date</th>
<th>Severity</th>
<th>Relationship</th>
<th>Action Taken</th>
<th>Outcome of AE</th>
<th>Expected?</th>
<th>SAE?</th>
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**Page ____ of ____**

Adverse Event Form

Version 2.0