Severe obesity is associated with elevated risk for poor neurocognitive outcomes. The mechanisms underlying this association have not yet been fully elucidated, but cerebrovascular pathology resulting from obesity and its associated vascular risk factors has been identified as a likely contributor. The CHA$_2$DS$_2$-VASc is a clinical composite score used to assess risk for vascular events and has been used to estimate severity of cerebrovascular pathology. Past research shows associations between higher scores on the CHA$_2$DS$_2$-VASc and poorer cognitive function in persons with atrial fibrillation and advanced heart failure. However, no study has examined the predictive validity of CHA$_2$DS$_2$-VASc in persons with severe obesity. The current study examined the relationship between the CHA$_2$DS$_2$-VASc and cognitive function before and after bariatric surgery in a sample of individuals with severe obesity. Data from 87 bariatric surgery patients were extracted from a larger parent project. Cognitive function was assessed at baseline and 12 months following bariatric surgery. Self-report questionnaires were completed at the baseline visit to gain medical and demographic information. It was hypothesized that CHA$_2$DS$_2$-VASc scores would predict cognitive function in individuals with severe obesity prior
to bariatric surgery, as well as improvements in cognitive function 12 months post-surgery. Additionally, the CHA$_2$DS$_2$-VASc was hypothesized to predict percent weight loss. Analyses revealed significant improvements in cognitive function from pre- to post-surgery in domains of memory, attention, and executive function. No significant associations were observed between the CHA$_2$DS$_2$-VASc and cognitive function at baseline and the stroke risk score did not predict the cognitive improvements seen in memory, executive function, or attention post-surgery. However, an association was found between CHA$_2$DS$_2$-VASc scores and percent weight loss 12 months post-surgery, such that higher CHA$_2$DS$_2$-VASc scores were negatively associated with percent weight loss. Future work is needed to clarify these findings and determine whether the CHA$_2$DS$_2$-VASc may have clinical utility in this population.
THE RELATIONSHIP BETWEEN CHA₂DS₂-VASc STROKE RISK SCORES AND
COGNITIVE FUNCTION PRE- AND POST-BARIATRIC SURGERY

A thesis submitted
to Kent State University in partial
fulfillment of the requirements for the
degree of Master of Arts

By

Amber Rochette

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Introduction

The number and proportion of adults with obesity, defined as a body mass index (BMI) ≥ 30 kg/m², have risen dramatically over the past several decades and continue to rise at an alarming rate (Ng et al., 2014). Globally, the number of individuals with obesity was estimated at 396 million (9.8% of the population) in 2005 and this number is estimated to increase to as high as 1.12 billion (20% of the population) by 2030 (Kelly, Yang, Chen, Reynolds, & He, 2008). The prevalence is even higher in the United States, as an estimated 29% of the population was obese in 2005 and this number is projected to increase to 50% by 2030 (Kelly et al., 2008; Finkelstein et al., 2012). Treatment for obesity consumes approximately 10% of the national health care budget and costs are expected to double over the next decade as prevalence rates of obesity continue to increase (Andreyeva, Sturm, & Ringel, 2004; Wang, Beydoun, Liang, Caballero, & Kumanyika, 2008).

Public Health Implications of Obesity

The growing prevalence of obesity has significant consequences at the individual and societal level. Together, obesity and its medical comorbidities significantly diminish quality of life and increase mortality (Vallis, 2016; Peeters et al., 2003). As individuals with obesity in midlife enter older adulthood, they develop limitations in activities of daily living 5 to 6 years earlier than their normal weight peers (Peeters, Bonneux, Nusselder, De Laet, & Barendregt, 2004). BMI has also been shown to predict declines in perceived health and mobility, even after controlling for presence and severity of comorbid conditions (Damush, Stump, & Clark, 2002). Research from the Framingham Heart Study found that midlife obesity reduces life duration by 6
to 7 years (Peeters et al., 2003). In 2000, excess weight was the second leading modifiable cause of death, accounting for approximately 17% of deaths in the United States, and researchers predict that excess weight will soon overtake tobacco as the leading modifiable cause of death if its increasing prevalence is not abated (Mokdad, Marks, Stroup, & Gerberding, 2004). Some research indicates that without successful intervention, obesity may lead to the first decline in human life expectancy in centuries (Olshansky et al., 2005).

Obesity is associated with a host of comorbid medical conditions. Obesity is an independent risk factor for cardiovascular disease (CVD) and is associated with many vascular risk factors, including hypertension, type 2 diabetes mellitus, and dyslipidemia (Poirer et al., 2006; Ogden, Yanovski, Carroll, & Flegal, 2007). Other conditions commonly associated with obesity include sleep apnea, osteoarthritis, gastroesophageal reflux disease, and certain cancers (Must et al., 1999; Jacobson et al., 2006; Deng, Lyon, Bergin, Caligiuri, & Hsueh, 2016).

In addition to these many medical conditions, research demonstrates that obesity is also an independent risk factor for poor neurological outcomes. Obesity is associated with an increased risk for stroke, as a meta-analysis of 25 prospective studies found that individuals with obesity have a 64% higher likelihood of stroke compared to their normal weight peers (Strazzullo et al., 2010). Similarly, longitudinal research by Whitmer and colleagues followed individuals for approximately 36 years and found that individuals with obesity in midlife were at a 3 times greater risk of developing Alzheimer’s disease and a 5 times greater risk of developing vascular dementia (Whitmer, Gunderson, Quesenberry, Zhou, & Yaffe, 2007).

There is also a growing body of research demonstrating cognitive dysfunction in persons with obesity across the adult lifespan prior to the onset of these neurological conditions. A systematic review of the literature by Prickett and colleagues revealed consistent findings of
frontal systems dysfunction in adults with obesity, as evidenced by decreased performance on tasks of executive function and processing speed (Prickett, Brennan, & Stolwyk, 2015). Further, deficits in learning and memory are found in this population relative to controls, independent of age and other comorbidities (Cheke, Simons, & Clayton, 2016; Gunstad, Paul, Cohen, Tate, & Gordon, 2006).

Findings of adverse neurocognitive outcomes in persons with obesity are further supported by imaging studies. Inverse associations are noted between BMI and total brain volume, as well as gray matter volume in frontal and temporal brain regions (Taki et al., 2008; Gustafson, Lissner, Bengtsson, Bjorkelund, & Skoog, 2004; Gunstad et al., 2008; Pannacciulli et al., 2006). These findings exist independent of age and associated comorbidities, suggesting an independent influence of obesity on brain structure (Gunstad et al., 2008). Longitudinal work also links obesity with greater hippocampal atrophy (Driscoll et al., 2012; Debette et al., 2011). Structural alterations further extend to white matter, with compromises in white matter integrity found globally in the brains of individuals with higher BMIs (Verstynen et al., 2012). Functional brain alterations are also noted in this population, as individuals with higher BMI demonstrate reduced metabolic activity in the prefrontal cortex and cingulate gyrus and decreased regional blood flow in the prefrontal cortex (Volkow et al., 2009; Willeumier, Taylor, & Amen, 2011).

**Public Health Implications of Severe Obesity**

While it is informative to look at the health consequences of obesity, it obscures important variations across level of obesity severity. Risk for poor health outcomes increases exponentially with increasing BMI (Hensrud & Klein, 2006). A BMI of 30 to 34.9 is categorized as Class I Obesity and confers high relative risk of developing comorbidities, such as diabetes, hypertension, and cardiovascular disease. A BMI of 35 to 39.9 is labeled Class II
Obesity and brings very high relative risk, while a BMI greater than 40 is labeled Class III obesity and confers extremely high relative risk (NHLBI, 1998). For example, individuals with class I, II, and III obesity are 2.6, 3.7, and 4.8 times more likely to develop hypertension relative to their normal weight peers, respectively (Nguyen, Magno, Lane, Hinojosa, & Lane, 2008). A BMI of 35 or higher is considered severe obesity due to the higher risk profile compared to individuals with a lower BMI. For example, individuals with class I obesity are approximately 10 times more likely to develop diabetes than their normal weight peers, however, individuals with severe obesity are at a 17 times higher risk (Field et al., 2001). Additionally, individuals with severe obesity are more likely to have multiple comorbid conditions (Agborsangaya, Majumdar, Sharma, Gregg, & Padwal, 2014; Field et al., 2001).

The increased health risks in this population have significant public health implications. The rate of severe obesity is rising at a rate much higher than class I obesity and these individuals account for a disproportionate amount of medical conditions, health care utilization and costs (Sturm & Hattori, 2013; Field et al., 2001; Andreyeva, Sturm, & Ringel, 2004). For example, prevalence of class I obesity is expected to rise 30% by 2020, while the rate of class III obesity is expected to increase by 80% in the same time frame (Ruhm, 2007). Similarly, individuals with class I obesity have approximately 25% higher health care costs than normal weight individuals, while individuals with class III have 100% higher costs (Andreyeva, Sturm, & Ringel, 2004).

Less is known about the impact of severe obesity on the brain, but existing research indicates that individuals in this BMI range are at a higher risk for poor neurocognitive outcomes. For example, research in a sample of bariatric surgery candidates revealed deficits in executive functions in 18% of individuals and learning and recognition memory deficits in
approximately 23% of individuals (Gunstad et al., 2007). Recent work found that over half of persons in a sample with severe obesity met diagnostic criteria for mild cognitive impairment (defined as cognitive performance below expectations for age and education, but functionally independent), irrespective of age (Rochette et al., 2016). Individuals with severe obesity also demonstrate higher amounts of tau and amyloid-beta (Aβ) precursor protein in the hippocampus compared to normal weight controls upon autopsy, providing direct support for a link between obesity and the development of Alzheimer’s disease pathology (Mrak, 2009). Research also shows that stroke risk increases with obesity severity. For example, a study by Kurth and colleagues found that for every 1 unit increase in BMI, stroke risk increased by 4 to 6% in a sample of men (Kurth et al., 2002). While more work is needed to elucidate this relationship, initial findings suggest individuals with severe obesity are at an increased risk for poor neurocognitive outcomes.

**Potential Mechanisms Linking Severe Obesity and Cognitive Function**

The exact mechanisms underlying the relationship between obesity and adverse neurological outcomes are not yet fully understood, likely reflecting the involvement of complex and multifactorial pathways. Both weight gain and obesity are associated with increased release of pro-inflammatory cytokines and these biomarkers are associated with accelerated cognitive decline (Maachi et al., 2004; Park, Park, & Yu, 2005; Ahima & Flier, 2000; Trollor et al., 2012; Yaffe et al., 2004). Presence of comorbid medical conditions, such as hypertension and cardiovascular disease, are also common in individuals with obesity and confer impairments in cognitive function (Galioto et al., 2015; Whitmer et al., 2007; Elias, Goodell, & Dore, 2012; Awad, Gagnon, & Messier, 2004; Singer, Trollor, Baune, Sachdev, & Smith, 2014). Particularly, poor glycemic control and its associated conditions, including type 2 diabetes
mellitus and prediabetes, are prevalent in individuals with obesity (Galioto et al., 2015; Mayega et al., 2013, Field et al., 2001). Individuals with diabetes demonstrate impairments in cognitive function and longitudinal declines at a rate much higher than their peers with normal glycemic control (Convit, Wolf, Tarshish, & de Leon, 2003; Fontbonne, Berr, Ducimetiere, & Alperovitch, 2001).

Inflammation, glycemic control, medical comorbidities, and cognitive function all commonly improve following weight loss surgery in individuals with severe obesity, further supporting a link between these conditions and the relationship between obesity and cognitive function (Gunstad et al., 2011; Galioto et al., 2015; Hawkins et al., 2014). While these mechanisms are still under exploration, research suggests they only partially account for the relationship between obesity and cognitive function. For example, cognitive deficits are present in individuals with obesity, even in the absence of comorbid medical conditions (Gunstad et al., 2007). Further, previous work has found that reduced inflammation and improved glycemic control following weight loss confers inconsistent effects on cognitive function (Galioto et al., 2015; Hawkins et al., 2014). Converging lines of research suggest that a less explored potential mechanism, cerebrovascular risk, may be the most important contributor to obesity-related cognitive impairment.

**Cerebrovascular Burden: A Potential Mechanism Underlying Obesity and Cognitive Function**

Growing evidence implicates pathological changes in cerebral vasculature as a likely mechanism linking obesity with cognitive decline and subsequent dementia. This process is thought to begin in the endothelia, the interior lining of blood vessels. Specifically, obesity leads to increased oxidative stress in the vascular walls, which disrupts the production and functionality of endothelial nitric oxide, a molecule essential for vasodilation and defense against
atherosclerosis, thrombosis, and infarct (Forstermann & Munzel, 2006; Toda, Ayajiki, & Okamura, 2014). Cerebral vessels become narrow and stiff over time and these alterations result in decreased cerebral blood flow (Toda, Ayajiki, & Okamura, 2014). Chronic insufficiencies in supply of oxygen and glucose throughout the brain then lead to neuronal cell damage and death (de la Torre, 2000).

Supporting these hypothesized pathways, individuals with obesity demonstrate global decreases in cerebral blood flow compared to their normal weight peers and animal research indicates that impaired cerebral blood flow in the brain triggers the accumulation of Aβ (Willeumier, Taylor, & Amen, 2011; Toda, Ayajiki, & Okamura, 2014). Hypoperfusion is observed in the context of both Alzheimer’s disease and mild cognitive impairment in humans and severity of cognitive impairment is proportional to the degree of hypoperfusion (Binnewijzend et al., 2013). As Aβ accumulates in the brain, it further promotes endothelial dysfunction, contributing to a cycle of pathological brain alterations (Chisari, Merlo, Sortino, & Salomone, 2010; Toda, Ayajiki, & Okamura, 2014).

While obesity is an independent risk factor for poor neurocognitive outcomes, the presence of multiple vascular risk factors is known to compound the likelihood of adverse brain outcomes. For instance, midlife obesity, elevated systolic blood pressure, and high cholesterol each contribute to cerebrovascular pathology and are risk factors for later dementia, with individual odds ratios of around 2.0 (Daulatzai, 2016; Hughes, Craft, & Lopez, 2015; Martin, Pfrieger, & Dotti, 2014; Kivipelto et al., 2005); however, when present simultaneously, these factors increase the risk of cognitive decline additively, with a combined odds ratio of 6.2 (Kivipelto et al., 2005). Moreover, imaging research indicates that obesity, hypertension, diabetes, and hyperlipidemia are each independently associated with adverse structural and
functional brain changes, such as brain atrophy and reduced cerebral blood flow, prior to the development of vascular disease or a major vascular event. However, the presence of multiple risk factors amplified these changes. Specifically, individuals with metabolic syndrome (defined as a combination of at least 3 of the following 5 metabolic risk factors: excess abdominal adiposity, high triglycerides, low high-density lipo-protein cholesterol, high blood pressure, or high fasting blood sugar) demonstrate greater numbers of silent brain infarcts with increasing numbers of metabolic risk factors (Mottillo et al., 2010; Friedman et al., 2014).

Based on such findings, researchers suggest that individual variations in cognitive function may be clinical expressions of underlying differences in cerebrovascular structure and function caused by presence of vascular risk factors (Llewellyn et al., 2008). This recognition of a cumulative “cerebrovascular burden” accompanying multiple vascular risk factors and its association with poor neurocognitive outcomes has led to the use of traditional stroke risk algorithms to predict differences in cognitive function and dementia risk in other populations (Llewellyn et al., 2008; Bhat, Yost, & Mahoney, 2015; Ball, Carrington, & Stewart, 2013). Stroke risk algorithms calculate risk of future stroke by assigning points for presence of stroke risk factors, including many vascular risk factors (Lip et al., 2010). Given that severe obesity is associated with a high number of comorbid vascular risk factors, stroke risk algorithms may be particularly applicable in this population.

**CHA$_2$DS$_2$-VASc**

The CHA$_2$DS$_2$-VASc is a clinical composite score originally developed to assess stroke risk using information commonly-found in patient records. This point-based system assigns a score ranging from 0 to 9 by allocating two points for prior stroke or transient ischemic attack, two points for age of 75 years or older, and one point for presence of each of the following...
factors: congestive heart failure, hypertension, diabetes, vascular disease, age between 65 and 74 years, and female gender (See Table 1; Lip et al., 2010). Since its development, research has demonstrated the utility of the CHA₂DS₂-VASc in predicting vascular events, including stroke, myocardial infarction, congestive heart failure, and cardiovascular death in high-vascular-risk patients without atrial fibrillation (Chan et al., 2014).

Given the growing recognition of a relationship between vascular risk factors and adverse neurological outcomes (Chan et al., 2014), researchers have also begun to examine the utility of the CHA₂DS₂-VASc in predicting neurocognitive measures. For example, researchers have found associations between higher CHA₂DS₂-VASc and CHADS₂ (the predecessor to the CHA₂DS₂-VASc) scores and a greater number of cortical and subcortical silent cerebral infarcts and the presence and severity of white matter hyperintensities in individuals with atrial fibrillation (Kobayashi, Iguchi, Shimizu, & Uchiyama, 2012; Wieczorek et al., 2016). The CHA₂DS₂-VASc and its predecessor have also been shown to predict mild cognitive impairment (as measured by the Montreal Cognitive Assessment) in both persons with atrial fibrillation and advanced heart failure (Ball, Carrington, & Stewart, 2013; Bhat, Yost, & Mahoney, 2015). In combination, these findings suggest that higher CHA₂DS₂-VASc scores are associated with poorer cognitive function, even in individuals without stroke or dementia, and this association likely reflects differences in underlying cerebrovascular burden. Such findings also suggest that cerebrovascular function may be a useful target for intervention research for individuals at high risk of developing dementia, such as persons with severe obesity. However, no study has examined the CHA₂DS₂-VASc in this population.

*Neurocognitive Outcomes in the Context of Bariatric Surgery*
Bariatric surgery is approved for persons with severe obesity (Gastrointestinal Surgery for Severe Obesity, 1991) and offers a unique opportunity to investigate mechanisms linking severe obesity and poor neurocognitive outcomes in this population. It allows for evaluation of both the impact of severe obesity and its comorbidities on cognitive function prior to surgery and the mechanisms associated with post-operative improvements. Bariatric surgery results in significant weight loss, with an average 14.5 unit drop in BMI one year following Roux-en-y gastric bypass surgery (Chang et al., 2014). In addition to weight reduction, individuals undergoing bariatric surgery exhibit decreased mortality and frequent resolution of obesity-related comorbidities, including many of the vascular risk factors associated with severe obesity (Sjostrom et al., 2007; Chang et al., 2014). For example, post-operative remission rates for diabetes have been estimated at 92%, while remission rates for hypertension and dyslipidemia are estimated at around 75% (Chang et al., 2014). Further, bariatric surgery results in improved endothelium function and vasodilation, raising the possibility that bariatric surgery improves the function of the cerebral vasculature (Gokce et al., 2005).

Bariatric surgery also leads to improvements in cognitive function. Research from the Longitudinal Assessment of Bariatric Surgery-2 (LABS-2) project indicates that improvements in cognitive domains of memory, attention, and executive functioning can be seen as early as 12 weeks post-bariatric surgery and gains in performance may continue to be made up to 24 months following surgery (Gunstad et al., 2011; Alosco et al., 2014). However, some individuals continue to exhibit cognitive deficits after surgery. For instance, previous work found that approximately 25% of individuals exhibit clinically-meaningful impairments in cognitive function 12 months following surgery, regardless of age, amount of weight loss, or resolution of common comorbidities (Rochette et al., 2016).
It is possible that individual differences in cognitive function following bariatric surgery may be partly explained by degree of cerebrovascular pathology. Given the improvements seen in endothelial function and vasodilation following bariatric surgery, it is expected that impairments in cerebrovascular function may also improve with weight loss and the resolution of vascular risk factors following bariatric surgery (Willeumier, Taylor, & Amen, 2011; Gokce et al., 2005). Further, other interventions known to improve cerebrovascular function, such as physical activity, also improve cognitive function in domains commonly impaired in individuals with obesity, such as memory, attention, and processing speed (Gertz et al., 2006; Lautenschlager et al., 2008; Weuve et al., 2004; Angevaren, Aufdemkampe, Verhaar, Aleman, & Vanhees, 2008; Gunstad et al., 2011; Alosco et al., 2014;). However, both BMI and presence of vascular risk factors are inversely associated with decrements in structural brain integrity (Taki et al., 2008; Raz, Rodrigue, Acker, & Kennedy, 2007). It is expected that any structural brain alterations incurred by disease prior to surgery would result in lasting cognitive deficits, regardless of weight loss and resolution of comorbidities.

Weight Outcomes following Bariatric Surgery

Should a relationship between the CHA₂DS₂-VASc and cognitive function exist, cerebrovascular pathology may also impact weight loss success after bariatric surgery indirectly through cognitive function. Despite the overall success of bariatric surgery in the treatment of severe obesity, approximately 30% of individuals either fail to lose or re-gain a considerable amount of weight post-surgery (Karlsson, Taft, Ryden, Sjostrom, & Sullivan, 2007). Several factors related to insufficient weight loss have been identified, including demographic variables, psychosocial factors, and comorbid medical conditions, including diabetes, and dyslipidemia

However, pre- and post-operative cognitive function has been shown to predict excess weight loss one year after surgery (Spitznagel et al., 2013a). As a result, it is possible that degree of cerebrovascular pathology may help to explain post-operative weight loss in this population. Given the known link between cerebrovascular disease and impairments on tests of attention and executive function (Forman et al., 2008), algorithms like the CHA\textsubscript{2}DS\textsubscript{2}-VASc could potentially identify those patients at elevated risk for suboptimal weight loss outcomes following bariatric surgery. No study has examined this possibility.

**Present Study**

The present study examined the association between pre-operative CHA\textsubscript{2}DS\textsubscript{2}-VASc risk score and cognitive function before and after bariatric surgery. Given the relationship between the CHA\textsubscript{2}DS\textsubscript{2}-VASc and cognitive function in other populations, we expected that the presence of greater risk for cerebrovascular events (as indicated by a higher CHA\textsubscript{2}DS\textsubscript{2}-VASc score) would be associated with lower cognitive test performance before and after surgery. Should this relationship between cerebrovascular burden and cognitive function exist, we hypothesize that it would also contribute to post-operative weight loss. Specific aims and hypotheses include:

**Aim 1:** Determine whether the presence of multiple vascular risk factors predicts cognitive dysfunction prior to bariatric surgery.

**Hypothesis 1:** Individuals with more vascular risk factors, operationalized by higher CHA\textsubscript{2}DS\textsubscript{2}-VASc scores, will exhibit poorer cognitive test performance at baseline.

**Aim 2:** Determine whether the presence of multiple vascular risk factors at baseline predicts cognitive function 12 months post-bariatric surgery.
Hypothesis 2: Individuals with the presence of more vascular risk factors at baseline, operationalized by higher CHA\textsubscript{2}DS\textsubscript{2}-VASc scores, will exhibit poorer global cognitive test performance 12 months post-bariatric surgery.

Aim 3: Determine whether the presence of multiple vascular risk factors at baseline predicts weight loss success 12 months post-bariatric surgery.

Hypothesis 3: Higher CHA\textsubscript{2}DS\textsubscript{2}-VASc scores at baseline will predict poorer weight loss 12 months post-bariatric surgery.

Aim 4: If significant effects are found for a relationship between number of vascular risk factors at baseline and weight loss success at 12 months post-surgery, determine if cognitive function mediates this relationship.

Hypothesis 4: Cognitive function will mediate the relationship between vascular risk factors and weight loss success at 12 months post-surgery.
Method

Participants

Cognitive test performance and medical history information for 88 participants was extracted from a larger National Institutes of Health study exploring the effects of bariatric surgery on cognitive function. All participants were involved in a multi-site parent project, entitled the Longitudinal Assessment of Bariatric Surgery (LABS), and were recruited by research assistants from the following sites: the Neuropsychiatric Research Institute in Fargo, North Dakota, and both Cornell Weill Medical Center and Columbia University in New York, New York. All participants were electively undergoing bariatric surgery and were required to be between the ages of 18 and 70 and English speaking. Individuals were ineligible if they had a past or current history of severe psychiatric illness (e.g., bipolar disorder, schizophrenia), history of neurological disorder or injury (e.g., stroke, seizure, dementia), moderate to severe head injury (loss of consciousness for more than 10 minutes), past or current history of alcohol or drug abuse (defined by DSM-IV criteria), history of impaired sensory function, and history of a learning or developmental disability (defined by DSM-IV criteria). The present study included all participants undergoing Roux-en-Y gastric bypass surgery with complete medical history at baseline and cognitive data prior to surgery and 12-months post-surgery. See Table 2 for demographic and medical characteristics.

Measures

Modified CHA2DS2-VASc scores. Stroke risk scores were calculated for each individual by assigning points based on age, gender, and self-reported medical history at baseline. One
point was given for individuals between the ages of 65 and 74, while 2 points were assigned for ages of 75 or higher. One point was assigned for female gender. Two points were assigned for history of a past stroke or transient ischemic attack. One point was assigned for the presence of each of the following reported diagnoses: congestive heart, hypertension, and myocardial infarction.

The risk score used in the current study is considered a modified version of the CHA\textsubscript{2}DS\textsubscript{2}-VASc due to deviations in score calculations based on availability of data from the parent LABS project. First, vascular disease was defined only by myocardial infarction, whereas the CHA\textsubscript{2}DS\textsubscript{2}-VASc risk score also includes peripheral artery disease and aortic plaque in the definition. Additionally, the CHA\textsubscript{2}DS\textsubscript{2}-VASc risk score assigns a point for left ventricular systolic dysfunction OR congestive heart failure, whereas the current study only used congestive heart failure (Lip et al., 2010).

**Neuropsychological Testing.** Cognitive performance was assessed using alternate versions of the *IntegNeuro* cognitive test battery at baseline and 12-months post-surgery. The *IntegNeuro* is a computerized battery requiring 45 to 60 minutes for completion and easily administered by a trained research assistant. The battery was scored by an automated software program. The battery has been shown to have sound psychometric properties, including test-retest reliability between 0.52 and 0.89 and convergent validity with other neurocognitive measures ($r = 0.53$ to 0.77) (Paul et al., 2005; Williams et al., 2005). Cognitive domains assessed include: memory, language, attention, and executive functioning. Tests for each domain were chosen based on their known sensitivity to the cognitive changes seen in individuals with excess weight (Gunstad et al., 2007). Procedures for composite score
calculations are presented below (see Analytic Strategy). Specific measures used to assess these domains include:

**Memory**

*Verbal List Learning:* This task required learning, recall, and recognition of a 12-item word list. The word list was presented 4 times and the total number of words recalled after each presentation was summed and used to quantify learning. A distractor word list was presented after the learning trials and before the first recall of the word list. Number of words recalled at the first recall and words recalled 20 minutes later were each used as dependent variables. On a final recognition trial, words from the list and new words were presented and participants were asked to identify words from the original word list. A discrimination score (number true positives minus number of false positives) was calculated and used as a measure of word recognition.

**Attention**

*Digit Span:* This task presents a sequence of digits on a computer screen with a one-second interval between digits. Participants are then asked to immediately recall the sequence by entering them into a touch-screen keypad. The task contains two sections: first, participants are asked to recall each sequence in the same order they were presented (Digits Forward) and second, they are instructed to recall the digits in reverse order (Digits Backward). For both sections, the digit span begins with 3 numbers and increases by one number after every two series, with an upper limit of 9 digits. The longest digit span correctly recalled for Digits Forward is used as a measure of basic auditory attention and the longest span correctly recalled for Digits Backward is used to assess working memory.
Switching of Attention-Digits: Psychomotor speed was measured using a computerized version of the Trail Making Test A (Reitan, 1958). In this task, participants are shown 25 numbered circles on the screen and asked to touch the numbers in ascending order. As each number is touched on the screen, a line appears to allow visualization of the path. Completion time was used as the dependent variable.

Verbal Interference-Word: Similar to the Stroop task, this task presents a series of individual words written in one of the following font colors: red, yellow, green, or blue (Golden, 1978). The words presented also include color names: red, yellow, green, and blue. Below the presented word, the four words are listed in black font and participants are instructed to select the name of each word that appears on the screen, while ignoring the color of the font. Participants are instructed to work as quickly as possible and are presented words for a total of 1 minute. The number of words correctly named in 1 minute was used as a measure of selective attention.

Executive Function

Switching of Attention-Mixed: Ability to shift between mental sets was measured using a computerized version of the Trail Making Test B (Reitan, 1958). In this task, participants are shown 13 numbers and 12 letters on the screen and asked to touch the numbers and letters in alternative and ascending order (i.e., 1-A-2-B, etc.) Again, as each number is touched on the screen, a line appears to allow visualization of the path. Completion time was used as the dependent variable.

Verbal Interference-Color-Word: This task presents a series of individual words written in one of the following font colors: red, yellow, green, or blue. The words presented also include color names: red, yellow, green, and blue. Below the presented word, the four words are listed in black font and participants are instructed to select the color of the font the word is written in,
while ignoring the actual word. Participants are instructed to work as quickly as possible and are presented words for a total of 1 minute. The number of colors correctly named in 1 minute was used as a measure of mental flexibility and inhibition.

*Maze Task:* This test is a computerized version of the Austin Maze (Walsh, 1991). Participants are asked to identify a hidden path on an 8x8 matrix grid of circles. Participants are informed of correctness via unique auditory and visual cues for correct and incorrect answers. The trial continues for 10 minutes or until the participant completes the maze twice with no mistakes. The dependent variables for this task are the number of maze errors and maze overruns.

**Language**

*Phonemic Fluency:* This task measures phonemic word fluency and asks participants to generate as many words as possible that begin with a certain letter in 1 minute. Participants generate words for the letters F, A, and S. Word generation was recorded and scored by hand. Scores were totaled across the three trials and the total number was used as the dependent variable.

*Semantic Fluency:* This task measures semantic fluency and asks participants to generate as many animal names as possible in 1 minute. The total number of words generated was used as the dependent variable.

**Weight Variables.** Height and weight were measured at baseline and 12-month follow-up and used to calculate BMI using the formula kg/m^2_. Percent weight loss (%WL) was then calculated using the formula: ((baseline weight – 12-month weight)/ baseline weight) * 100. Consistent with previous literature, baseline BMI was used as a covariate when predicting weight loss following surgery and %WL was used as the dependent variable (Spitznagel et al., 2013b).
**Procedure**

All study procedures were approved by the Institutional Review Boards at each site and all procedures were standardized across testing locations. Research assistants obtained written informed consent from each participant prior to study participation. Participants completed self-report medical history questionnaires and computerized cognitive testing in the month prior to surgery and again 12 months post-surgery (SD = 14 days). Research assistants also reviewed medical records to confirm self-reported medical history and to gain additional medical information.

**Statistical Power**

Because data for the current study was extracted from a larger parent project, there is a pre-determined sample size of 88 individuals. However, one participant was removed due to violation of normality, resulting in a final sample size of 87 (See Preliminary statistical analyses section). Power analyses were conducted and found a power of 0.97 to find a medium effect size (.25) if one exists or power of 0.82 to detect a small effect size of 0.1 in a sample of 87 participants. Even with a Bonferroni correction (alpha = 0.013), an effect size of .25 could be found with a sample size of 48.

**Analytic Strategy**

**Preliminary statistical analyses.** SPSS version 20 was used to run all statistical analyses. To facilitate interpretation, raw scores for cognitive test data were transformed to T-scores using normative data to correct for age, gender and premorbid intelligence. These scores were then averaged within each cognitive domain to create a composite score for memory, language, attention, and executive function. Preliminary analyses were then conducted to examine the data for violations of regression assumptions. Descriptive statistics were used to
observe sample characteristics and check for univariate normality (skewness < 3 and kurtosis < 7). Multivariate outliers were examined using Mahalanobis distance and removed if exceeding the specified critical value of 16.266 (3 degrees of freedom, .001 p value). This resulted in the removal of 1 participant from analyses, resulting in a sample size of 87. No other assumptions were violated and no transformations were necessary. Repeated-measures analysis of variance (ANOVA) was utilized to determine change in cognitive domain performances from baseline to 12 months. All missing data were excluded listwise.

**Primary statistical analyses.** Linear regression analyses were used to analyze the potential contribution of the CHA$_2$DS$_2$-VASc scores to baseline cognitive test performance. Separate analyses were performed for each cognitive domain and cognitive composite scores for each domain served as the dependent variables. Hierarchical multiple regression was then used to examine the potential contribution of the CHA$_2$DS$_2$-VASc scores to 1) 12-month test performance, while controlling for baseline scores in Block 1, and 2) 12-month %WL, while controlling for baseline BMI in Block 1. Separate analyses were conducted for each 12-month cognitive domain and cognitive composite scores for each domain served as the dependent variables. CHA$_2$DS$_2$-VASc scores served as the independent variable in all analyses.
Results

Preliminary Analyses

Sample Characteristics

The final sample consisted of 87 bariatric surgery patients. Average age was 44.09 ± 10.60 years and the sample was predominately female (81.6%). Average BMI was 46.84 ± 5.74 prior to surgery and 29.94 ± 5.19 at 12-month follow-up. Average percent weight loss from baseline to 12-months was 34.67% ± 7.83 (See Table 2). Prevalence rates for medical characteristics and distribution of CHA₂DS₂-VASc scores are presented in Table 2. Performance in cognitive domains generally fell in the average range, though 51% and 35% of individuals had at least one task performance falling more than 1.5 standard deviations below the normative mean at pre-operative baseline and 12 months post-surgery, respectively.

Comparison of Baseline to 12-Month Cognitive Function

Significant post-operative changes emerged in the domains of memory [F(1,86) = 67.14, p < .001], attention [F(1,86) = 31.00, p < .001], and executive function [F(1,86) = 52.52, p < .001]. Specifically, scores improved from baseline to 12-month follow-up in each domain. However, analyses revealed no change in language composite scores from baseline to 12-month follow-up [F(1,86) = .54, p = .46] and thus, language was dropped from the 12-month cognitive analyses in Aim 2. See Table 3 for changes in individual tasks from baseline to 12-month follow-up.

Primary Analyses
**Aim 1.** Determine whether the presence of multiple vascular risk factors predicts cognitive dysfunction prior to bariatric surgery. Hypothesis 1 - Individuals with more vascular risk factors, operationalized by higher CHA$_2$DS$_2$-VASc scores, will exhibit poorer cognitive test performance at baseline.

*Memory:* The regression model predicting memory performance at baseline based on CHA$_2$DS$_2$-VASc scores was nonsignificant and predicted 3% of the variability in memory performance at baseline ($R^2 = .03$, $F (1,85) = 2.71$, $p = .10$). See Table 4 for a summary of Aim 1 results. CHA$_2$DS$_2$-VASc scores were negatively but not significantly associated with memory performance, with individuals’ memory composite scores decreasing by 1.66 for every one point increase on the CHA$_2$DS$_2$-VASc ($\beta = -.18$, $p = .10$).

*Attention:* Regression analysis revealed that CHA$_2$DS$_2$-VASc scores were not associated with baseline attention ($R^2 = .01$, $F (1,85) = .73$, $p = .40$). CHA$_2$DS$_2$-VASc scores were negatively but not significantly associated with attention, with participants’ attention composite scores decreasing by .76 for every one point increase on the CHA$_2$DS$_2$-VASc ($\beta = -.09$, $p = .40$).

*Executive Function:* The regression model predicting executive functioning at baseline based on CHA$_2$DS$_2$-VASc scores was not significant and predicted 3% of the variability in performance at baseline, ($R^2 = .03$, $F (1,85) = 2.60$, $p = .11$). CHA$_2$DS$_2$-VASc scores were negatively but not significantly associated with executive function, with individuals’ executive function composite scores decreasing by 1.93 for every one point increase on the CHA$_2$DS$_2$-VASc ($\beta = -.17$, $p=.11$).

*Language:* Analysis revealed that CHA$_2$DS$_2$-VASc scores were not associated with baseline language performance ($R^2 = .00$, $F (1,85) = .32$, $p = .58$). CHA$_2$DS$_2$-VASc scores were
negatively but not significantly associated with language, with individuals’ attention composite scores decreasing by .63 for every one point increase on the CHA$_2$DS$_2$-VASc ($\beta = -.06$, $p=.32$).

**Aim 2.** Determine whether the presence of multiple vascular risk factors at baseline predicts cognitive function 12 months post-bariatric surgery. Hypothesis 2 - Individuals with the presence of more vascular risk factors at baseline, operationalized by higher CHA$_2$DS$_2$-VASc scores, will exhibit poorer global cognitive test performance 12 months post-bariatric surgery.

*Memory:* The first step of the hierarchical multiple linear regression revealed that baseline memory performance significantly predicted 12-month memory performance ($R^2 = .35$, $F (1,85) = 45.94$, $p < .001$). See Table 5 for a summary of Aim 2 results. Specifically, better memory at baseline was associated with better memory at follow-up ($\beta = .59$, $p < .001$). However, adding CHA$_2$DS$_2$-VASc scores to the model did not predict additional variance in 12-month memory performance, ($\Delta F(1,84) = .17$, $\Delta R^2 = .001$, $p = .68$).

*Attention:* The first step revealed that baseline attention significantly predicted 12-month attention ($R^2 = .36$, $F (1,85) = 47.03$, $p < .001$). Better attention at baseline was associated with better attention at follow-up ($\beta = .60$, $p < .001$). However, adding CHA$_2$DS$_2$-VASc scores to the model did not improve model fit, ($\Delta F(1,84) = .001$, $\Delta R^2 = .00$, $p = .98$).

*Executive Function:* In the first step, baseline executive function significantly predicted 12-month performance in executive function ($R^2 = .62$, $F (1,85) = 136.32$, $p < .001$). Specifically, better baseline performance was associated with better 12-month performance ($\beta = .79$, $p < .001$). However, adding CHA$_2$DS$_2$-VASc scores to the model did not predict additional variance in 12-month performance, ($\Delta F(1,84) = .65$, $\Delta R^2 = .003$, $p = .42$).
Aim 3. Determine whether the presence of multiple vascular risk factors at baseline predicts weight loss success 12 months post-bariatric surgery. Hypothesis 3 - Higher CHA\textsubscript{2}DS\textsubscript{2}-VASc scores at baseline will predict poorer weight loss 12 months post-bariatric surgery.

In the first step of the hierarchical multiple regression, baseline BMI was added as a control variable, but did not significantly predict 12-month percent weight loss ($R^2 = .00$, $F(1,85) = .22$, $p = .64$). However, adding CHA\textsubscript{2}DS\textsubscript{2}-VASc scores explained a significant amount of additional variance in percent weight loss at 12-month follow-up ($\Delta F(1,84) = 5.60$, $\Delta R^2 = .06$, $p < 0.05$). Higher CHA\textsubscript{2}DS\textsubscript{2}-VASc scores were negatively associated with percent weight loss, with individuals’ percent weight loss decreasing by 2.09 percentage points for every one point increase on the CHA\textsubscript{2}DS\textsubscript{2}-VASc ($\beta = -.25$, $p < .05$).

Aim 4. If significant effects are found for a relationship between number of vascular risk factors at baseline and weight loss success at 12 months post-surgery, determine if cognitive function mediates this relationship. Hypothesis 4 - Cognitive function will mediate the relationship between vascular risk factors and weight loss success at 12 months post-surgery.

Given that CHA\textsubscript{2}DS\textsubscript{2}-VASc scores did not predict cognitive function for any domain or at either time point, aim 4 was dropped from analyses.

Exploratory Analyses

Additional exploratory analyses were ran to clarify the nonsignificant findings in aim 3 and the potential link between the CHA\textsubscript{2}DS\textsubscript{2}-VASc and improvements in cognitive function from baseline to 12-months post-surgery. Specifically, past work aimed at establishing guidelines for treating individuals with atrial fibrillation suggests that persons surpassing a categorical cut-off of 1 on the CHA\textsubscript{2}DS\textsubscript{2}-VASc be categorized as high-risk for future stroke (January et al., 2014). This guideline suggests a possible nonlinear relationship between
CHA2DS2-VASc scores and underlying cerebrovascular pathology may exist, where risk of adverse outcomes increases more steeply beyond a certain threshold. Therefore, exploratory analyses sought to examine whether changes in cognitive test performance from pre- to post-surgery were a function of high vs. low CHA2DS2-VASc scores.

Additional repeated measures ANOVA analyses were conducted to determine whether changes in cognitive function from baseline to 12-months post-surgery is a function of high vs. low CHA2DS2-VASc scores. Scores of 0 and 1 were considered low scores and a score of 2 or higher was considered a high score. This approach was made based on established guidelines from past work in which individuals with a CHA2DS2-VASc score greater than 1 were considered in the high-risk category for future stroke (January et al., 2014). Tests of equality of covariance indicated that sample sizes of CHA2DS2-VASc scores were balanced (n = 38 vs 49) and therefore, the Wilks’ Lambda statistic was utilized for each analysis.

Multivariate F tests revealed significant main effect of time for domains of memory \[F(1,85) = 64.30, p < .001, \eta_p^2 = .43\], attention \[F(1,85) = 29.47, p < .001, \eta_p^2 = .26\], and executive function \[F(1,85) = 49.73, p < .001, \eta_p^2 = .37\]. However, there was no significant main effect of high vs. low CHA2DS2-VASc score on domains of memory \[F(1,85) = 2.81, p = .10, \eta_p^2 = .03\], attention \[F(1,85) = 22.25, p = .65, \eta_p^2 = .00\], or executive function \[F(1,85) = .06, p = .81, \eta_p^2 = .00\]. Additionally, there were no significant differences in change in memory \[F(1,85) = .42, p = .52, \eta_p^2 = .01\], attention \[F(1,85) = .34, p = .56, \eta_p^2 = .00\], or executive function \[F(1,85) = 1.86, p = .18, \eta_p^2 = .02\] as a function of high vs. low CHA2DS2-VASc scores, suggesting no interaction between stroke risk score and changes over time.
Discussion

The current study had two primary goals. The first objective was to examine the relationships between baseline CHA$_2$DS$_2$-VASc scores and cognitive function in persons before and after bariatric surgery. The second goal was to assess the relationship between CHA$_2$DS$_2$-VASc scores and weight loss 12-months post-bariatric surgery. Significant improvements in cognitive function were noted in multiple domains 12 months following bariatric surgery, including memory, attention, and executive function. Regression analyses showed that CHA$_2$DS$_2$-VASc scores were not associated with performance in any cognitive domain at baseline or the improvements in cognitive function at follow-up. However, this stroke risk score did explain a significant amount of the variance in %WL at 12 months post-surgery, even when controlling for baseline BMI. Several aspects of these findings merit further discussion.

Cognitive Function from Pre- to Post-Bariatric Surgery

Cognitive function significantly improved from pre- to post-bariatric surgery in the domains of memory, attention, and executive function. However, no significant improvement was noted for language. These findings are consistent with previous work using this sample, but with slightly different inclusion/exclusion criteria (Miller et al., 2013). That work also found improved attention and executive function in non-surgery controls (Miller et al., 2013), raising the possibility of practice effects rather than true cognitive improvements. However, the utilized cognitive test battery has shown adequate psychometric properties (including test-retest reliability), used alternate forms, and had a longer testing interval of 12 months (Beglinger et al.,
2005; Williams et al., 2005). Each of these factors should limit the possible impact of practice effects, though more work is needed.

**CHA\textsubscript{2}DS\textsubscript{2}-VASc scores and Cognitive Function**

Contrary to hypotheses, analyses found that the CHA\textsubscript{2}DS\textsubscript{2}-VASc does not predict performance in domains of memory, attention, language, or executive function, at baseline or post-surgery. This finding is somewhat surprising, given the known association between obesity and both cerebrovascular pathology and cognitive function (Kurth et al., 2002; Willeumier, Taylor, & Amen, 2011; Rochette et al., 2016). Obesity has been linked to global compromises in white matter integrity, decreases in cerebral blood flow, and deficits in multiple domains of cognitive function (Verstynen et al., 2012; Willeumier, Taylor, & Amen, 2011; Gunstad et al., 2007; Rochette et al., 2016). CHA\textsubscript{2}DS\textsubscript{2}-VASc scores have been linked to each of these outcomes in other populations, and therefore, was expected to be linked in individuals with severe obesity, as well (Wieczorek et al., 2016; Ball, Carrington, & Stewart, 2013; Bhat, Yost, & Mahoney, 2015; Chan et al., 2014; Kurth et al., 2002; Willeumier, Taylor, & Amen, 2011). Specifically, the CHA\textsubscript{2}DS\textsubscript{2}-VASc has been shown to be positively correlated with the presence and severity of white matter hyperintensities in a sample of individuals with atrial fibrillation and to predict mild cognitive impairment in both persons with atrial fibrillation and heart failure (Wieczorek et al., 2016; Ball, Carrington, & Stewart, 2013; Bhat, Yost, & Mahoney, 2015).

There are several possible explanations for the lack of association between the CHA\textsubscript{2}DS\textsubscript{2}-VASc and cognitive function in the current study. One possibility involves the strict inclusion/exclusion criteria in the parent study from which data for the current study was extracted. That larger project excluded individuals with heart failure, stroke, and other conditions known to complicate bariatric surgery or to cause cognitive deficits independent of
obesity (Mechanick et al., 2008). This likely resulted in a relatively healthier sample with less severe cerebrovascular pathology and better cognitive function than is found in a more representative sample of individuals with severe obesity. This restricted variability in CHA$_2$DS$_2$-VASc scores and cognitive impairment may have obscured possible relationships. Similarly, the operational definition of the CHA$_2$DS$_2$-VASc in the current study was modified due to availability of data from the LABS parent project. For example, the current study defined the criterion for vascular disease (the V of the CHA$_2$DS$_2$-VASc, see table 1) as a history of myocardial infarction or heart surgery. However, the developers of the CHA$_2$DS$_2$-VASc risk score define this criterion as myocardial infarction OR aortic plaque OR peripheral artery disease (Lip et al., 2010). Unfortunately, this additional information was unavailable for the current study and therefore, not included in the calculation.

Despite these possible limitations, it appears likely that such data would not have influenced overall findings. For example, the current sample was relatively young (44.09 ± 10.60) and peripheral artery disease and aortic plaque are rare prior to age 60, with prevalence estimates of less than 5% and 10%, respectively (Allison et al., 2007; Coffey, Cox, & Williams, 2014). Similarly, persons with peripheral artery disease are 2.5 times more likely to have history of myocardial infarctions and thus, persons with peripheral artery disease would likely have already been assigned a point in the CHA$_2$DS$_2$-VASc (Criqui & Aboyans, 2015). Nonetheless, individuals with obesity have an elevated prevalence of comorbid vascular pathology than their normal weight peers and thus, the prevalence of individuals in the current sample with peripheral artery disease or aortic plaque could be higher than the overall population estimates (Kivipelto et al., 2005). Future studies should include these pathologies in the definition of vascular disease to better understand the contribution of these risk factors to cognitive impairment in this population.
The current findings are consistent with some past work in bariatric surgery patients indicating that medical comorbidities do not account for the changes seen in cognitive function post-surgery, but require further clarification (Alosco et al., 2014; Rochette et al., 2016). In each of these studies, medical comorbidities were measured as the categorical presence or absence of the condition, which likely limited the ability to find an association (Alosco et al., 2014; Rochette et al., 2016). More precise measurement of these conditions may help to clarify their impact on cognitive function in the context of severe obesity and their mechanistic role in the cognitive improvements seen after bariatric surgery. However, the CHA₂DS₂-VASc risk score does not take into account these more precise measures, and therefore, having better measurements of these conditions would not have influenced findings in the current study.

While the CHA₂DS₂-VASc lends important insight into the effects of cerebrovascular burden on cognitive function, future work should also include more direct measures of cerebrovascular pathology. Structural neuroimaging can quantify the accumulation of small vessel ischemic disease and arterial spin labeling (ASL) and blood oxygen level dependent (BOLD) functional magnetic resonance imaging techniques provide measurements of cerebrovascular reactivity (Zhou, Rodgers, & Kuo, 2015). Inclusion of these techniques may help to parse out the contribution of structural versus functional changes in cerebral vasculature to the relationship between obesity and cognitive function both pre- and post-bariatric surgery. Past work has found associations between the CHA₂DS₂-VASc and structural brain integrity in individuals with intact cognitive function (Wieczorek et al., 2016). Therefore, given the relatively intact cognitive performance seen in the current sample, imaging may better capture subtle, but meaningful, changes in cerebral vasculature in this population. This detection is
essential for better understanding both the mechanisms contributing to cognitive decline in this population and those underlying improvements seen after bariatric surgery.

**CHA₂DS₂-VASc scores and Weight Loss Following Bariatric Surgery**

As hypothesized, higher CHA₂DS₂-VASc scores predicted lower %WL 12 months following bariatric surgery. This finding was expected, as the CHA₂DS₂-VASc is comprised of factors known to be related to weight loss success, including age, sex, and presence of diabetes (Averbukh et al., 2003; Busetto et al., 2002; Junior, Amaral, & Nonino-Borges, 2011).

However, the extent to which this finding is a function of underlying cerebrovascular pathology rather than reflecting the contribution of these known predictors is unclear. Follow-up studies including imaging techniques would help to clarify the potential mediating role of cerebrovascular pathology in the association found between the CHA₂DS₂-VASc and %WL in the current study.

Other potential mediators accounting for the relationship between CHA₂DS₂-VASc scores and %WL should also be explored. One potential mediator contributing to the current finding is post-operative adherence to bariatric surgery guidelines. For example, research has demonstrated links between cerebral vasculature and cognitive function, and cognitive function and adherence in other populations, and adherence has been linked to weight loss following bariatric surgery (Shim et al., 2015; Raz, Rodrigue, Kennedy, & Acker, 2007; Forman et al., 2008; Spitznagel, Galioto, Limbach, Gunstad, & Heinberg, 2013; Spitznagel et al., 2013a; Spitznagel et al., 2013b). However, no study has explored these relationships together in a single study. Advanced statistical techniques, such as path analysis, should be utilized to explore the potential contribution of these variables to %WL following bariatric surgery.

**Limitations and Future Considerations**
The current study is limited in several ways. First, as mentioned above, this study did not utilize a control group. Future work employing a control group of individuals with severe obesity who do not undergo weight loss surgery is needed to clarify the longitudinal association between the CHA\textsubscript{2}DS\textsubscript{2}-VASc and cognitive function in this population when untreated. In contrast to the finding of improved cognitive function at 12-month follow-up in the current study, past epidemiological research suggests that individuals with higher BMI experience more rapid cognitive decline over time (Gunstad, Lhotsky, Wendell, Ferrucci, & Zonderman, 2010). Therefore, examination of the relationship between the CHA\textsubscript{2}DS\textsubscript{2}-VASc and longitudinal declines in cognitive function in this population is much needed.

Additionally, the current sample was relatively homogenous on key variables included in analyses. For example, individuals were primarily middle aged and female (See Table 2). While the current sample is representative of the population of individuals undergoing bariatric surgery, it may not be representative of the population of individuals with severe obesity (Santry, Gillen, & Lauderdale, 2005; Kruger, Pricolo, Streeter, Colacchio, & Andrade, 2014). Future studies should include more diverse patient populations when possible, though this is somewhat limited by restrictions for undergoing bariatric surgery. For example, individuals can be denied surgery due to advanced age, BMI greater than 70 kg/m\textsuperscript{2}, and severe cardiovascular conditions, such as congestive heart failure and unstable angina (Mechanick et al., 2008; Poirier et al., 2011; Sadhasivam, Larson, Lambert, Mathiason, & Kothari, 2007). Therefore, it is expected that individuals with the highest CHA\textsubscript{2}DS\textsubscript{2}-VASc scores would be denied bariatric surgery, resulting in range restriction. Alternatively, utilizing behavioral weight loss populations may help to elucidate the relationship between the CHA\textsubscript{2}DS\textsubscript{2}-VASc and cognitive function before and after weight loss in individuals with severe obesity and increase generalizability of findings.
Further work is needed to fully elucidate the possible contribution of cerebrovascular burden to the relationship between obesity and adverse brain outcomes. While the CHA₂DS₂-VASc lends important insight into the effects of cerebrovascular burden on cognitive function, future work should include more direct measures of cerebrovascular pathology, such as the aforementioned neuroimaging techniques. Extended follow-up of individuals undergoing bariatric surgery is also much needed, as late follow-up visits (i.e., 10+ years) would allow researchers to evaluate whether the cognitive improvements seen following bariatric surgery extend into older adulthood and reduce the rates of pathological cognitive aging and subsequent dementia.

**Conclusion**

In summary, the current study found no association between CHA₂DS₂-VASc scores and cognitive function pre- or post-bariatric surgery, though CHA₂DS₂-VASc scores were associated with %WL. Future work should investigate possible mechanisms underlying this relationship. Research utilizing advanced neuroimaging techniques may be particularly beneficial for clarifying the influence of cerebrovascular pathology in the relationship between obesity and neurological outcomes.
References


Mayega, R. W., Guwatudde, D., Makumbi, F., Nakwagala, F. N., Peterson, S., Tomson, G., &


Nguyen, N. T., Magno, C. P., Lane, K. T., Hinojosa, M. W., & Lane, J. S. (2008). Association of


Table 1: CHA₂DS₂-VASc Point System (Table adapted from Lip et al., 2010)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Point Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C  Congestive Heart Failure OR Left Ventricular Systolic Dysfunction</td>
<td>1</td>
</tr>
<tr>
<td>H  Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A₂ Age ≥ 75 years</td>
<td>2</td>
</tr>
<tr>
<td>D  Diabetes Mellitus</td>
<td>1</td>
</tr>
<tr>
<td>S₂ Prior Stroke OR Transient Ischemic Attack</td>
<td>2</td>
</tr>
<tr>
<td>V  Vascular Disease (e.g., peripheral artery disease OR myocardial infarction OR aortic plaque)</td>
<td>1</td>
</tr>
<tr>
<td>A  Age between 65 and 74 years</td>
<td>1</td>
</tr>
<tr>
<td>Sc Sex (i.e., female gender)</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 2. Sample Demographic and Medical Characteristics at Baseline \((n = 87)\)

<table>
<thead>
<tr>
<th>Demographic Factors</th>
<th>Mean (SD) or frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>44.09 (10.60)</td>
</tr>
<tr>
<td>Female Gender</td>
<td>71 (81.6)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Medical Factors</th>
<th>Mean (SD) or frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Mass Index (kg/m(^2))</td>
<td>46.84 (5.74)</td>
</tr>
<tr>
<td>Type 2 Diabetes Mellitus</td>
<td>24 (27.6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>51 (58.6)</td>
</tr>
<tr>
<td>Transient Ischemic Attack</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td>Vascular Disease</td>
<td>7 (8.0)</td>
</tr>
</tbody>
</table>

CHA\(_2\)DS\(_2\)-VASc Score Frequency Distribution

<table>
<thead>
<tr>
<th>Score</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td>1</td>
<td>36 (41.4)</td>
</tr>
<tr>
<td>2</td>
<td>30 (34.5)</td>
</tr>
<tr>
<td>3</td>
<td>17 (19.5)</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td></td>
<td>Baseline Mean (SD)</td>
</tr>
<tr>
<td>----------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td><strong>Memory</strong></td>
<td></td>
</tr>
<tr>
<td>List Learning</td>
<td>43.65 (12.42)</td>
</tr>
<tr>
<td>Short Delay Free Recall</td>
<td>46.43 (10.12)</td>
</tr>
<tr>
<td>Long Delay Free Recall</td>
<td>46.17 (10.49)</td>
</tr>
<tr>
<td>Recognition</td>
<td>42.37 (9.69)</td>
</tr>
<tr>
<td><strong>Attention</strong></td>
<td></td>
</tr>
<tr>
<td>Digit Span Forward</td>
<td>50.65 (10.35)</td>
</tr>
<tr>
<td>Digit Span Backward</td>
<td>50.36 (11.56)</td>
</tr>
<tr>
<td>Switching of Attention-Digits</td>
<td>54.70 (14.17)</td>
</tr>
<tr>
<td>Verbal Interference- Word</td>
<td>52.97 (10.82)</td>
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<tr>
<td><strong>Executive Function</strong></td>
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<tr>
<td>Switching of Attention-Mixed</td>
<td>52.91 (15.14)</td>
</tr>
<tr>
<td>Maze Task Errors</td>
<td>49.92 (12.24)</td>
</tr>
<tr>
<td>Maze Task Overruns</td>
<td>51.97 (15.96)</td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td></td>
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<tr>
<td>Phonemic Fluency</td>
<td>46.95 (11.50)</td>
</tr>
<tr>
<td>Semantic Fluency</td>
<td>50.25 (10.58)</td>
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</table>
Table 4: Regression Model Examining the Predictive Validity of CHA₂DS₂-VASc on Cognitive Function at Baseline

<table>
<thead>
<tr>
<th></th>
<th>Memory</th>
<th>Attention</th>
<th>Executive Function</th>
<th>Language</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B (SE B) β</td>
<td>B (SE B) β</td>
<td>B (SE B) β</td>
<td>B (SE B) β</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc</td>
<td>-1.66 (1.01)</td>
<td>-.18</td>
<td>-.76 (.89)</td>
<td>-.09</td>
</tr>
<tr>
<td></td>
<td>-1.93 (1.20)</td>
<td>-.17</td>
<td>-.63 (1.13)</td>
<td>-.06</td>
</tr>
<tr>
<td>$R^2$</td>
<td>.03</td>
<td>.01</td>
<td>.03</td>
<td>.00</td>
</tr>
<tr>
<td>$F$</td>
<td>2.71</td>
<td>.73</td>
<td>2.60</td>
<td>.32</td>
</tr>
</tbody>
</table>

*p < .05, **p < .01, ***p < .001
Table 5: Regression Model Examining the Predictive Validity of CHA₂DS₂-VASc on Cognitive Function at 12-Months Post-Surgery

<table>
<thead>
<tr>
<th></th>
<th>Memory</th>
<th></th>
<th>Attention</th>
<th></th>
<th>Executive Function</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B (SE B)</td>
<td>$\beta$</td>
<td>B (SE B)</td>
<td>$\beta$</td>
<td>B (SE B)</td>
<td>$\beta$</td>
</tr>
<tr>
<td>Block 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Performance</td>
<td>.58 (.09)</td>
<td>.59***</td>
<td>.66 (.10)</td>
<td>.60***</td>
<td>.69 (.06)</td>
<td>.79***</td>
</tr>
<tr>
<td>$R^2$</td>
<td>.35</td>
<td>.36</td>
<td>.36</td>
<td>.36</td>
<td>.62</td>
<td></td>
</tr>
<tr>
<td>$F$</td>
<td>45.94***</td>
<td>47.03***</td>
<td>136.32***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHA₂DS₂-VASc</td>
<td>.35 (.83)</td>
<td>.04</td>
<td>.02 (.81)</td>
<td>.00</td>
<td>-.55 (.68)</td>
<td>-.06</td>
</tr>
<tr>
<td>$R^2$</td>
<td>.35</td>
<td>.36</td>
<td>.36</td>
<td>.36</td>
<td>.62</td>
<td></td>
</tr>
<tr>
<td>$F$ for $\Delta R^2$</td>
<td>.17</td>
<td>.00</td>
<td>.00</td>
<td>.00</td>
<td>.65</td>
<td></td>
</tr>
</tbody>
</table>

*p < .05, **p < .01, ***p < .001
Table 6: Regression Model Examining the Predictive Validity of CHA₂DS₂-VASc on Percent Weight Loss at 12-Months Post-Surgery

<table>
<thead>
<tr>
<th>Percent Weight Loss</th>
<th>B (SE B)</th>
<th>β</th>
</tr>
</thead>
<tbody>
<tr>
<td>Block 1</td>
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<td></td>
</tr>
<tr>
<td>Baseline BMI</td>
<td>-.07 (.15)</td>
<td>-.05</td>
</tr>
<tr>
<td>(R^2)</td>
<td>.00</td>
<td></td>
</tr>
<tr>
<td>(F)</td>
<td>.22</td>
<td></td>
</tr>
<tr>
<td>Block 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHA₂DS₂-VASc</td>
<td>-2.09 (.88)</td>
<td>-.25*</td>
</tr>
<tr>
<td>(R^2)</td>
<td>.07</td>
<td></td>
</tr>
<tr>
<td>(F) for (\Delta R^2)</td>
<td>5.60*</td>
<td></td>
</tr>
</tbody>
</table>

*p < .05, **p < .01, ***p < .001