CHA_2DS_2-VASC-HSF STROKE RISK INDEX, WHITE MATTER LESIONS, CORTICAL THICKNESS, AND COGNITIVE FUNCTION IN OLDER ADULTS

by

SHANNON MCNALLY

(Under the Direction of Lawrence H. Sweet)

ABSTRACT

CHA_2DS_2-VASc-HSF is a stroke risk stratification system for cardiovascular disease. While it has utility in predicting overt stroke, it is unclear whether CHA_2DS_2-VASc-HSF is associated with subtle sequelae in covert stroke, which has implications for future stroke and cognitive decline. The current study examined associations between CHA_2DS_2-VASc-HSF, white matter lesions (WMH), cortical thickness, and cognition (executive function and processing speed) in 83 older adults. It was hypothesized that greater WMH and cortical thinning would be associated with higher stroke risk; CHA_2DS_2-VASc-HSF would be associated with worse cognitive performance; and there would be an indirect effect between CHA_2DS_2-VASc-HSF and cognitive performance via WMH and cortical thinning. We found stroke risk to be associated with worse cognitive performance and cortical thinning. WMH was not associated with stroke risk. WMH volume was associated with worse cognitive function and cortical thinning. Overall, these findings support the validity of the CHA_2DS_2-VASc-HSF in lower-risk older adults.

INDEX WORDS: Cardiovascular disease, Cerebrovascular disease/accident and stroke, Cortical thickness, Aging, Executive functions, White matter lesions

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CHAPTER 1

INTRODUCTION

Cardiovascular disease (CVD) is one of the leading preventable causes of premature death worldwide (Perk et al., 2012). Onset and progression of CVD is subtle, and many patients do not present with symptoms until the disease has progressed and serious complications arise. Improvements in quality of life and medical treatment options have led to increased lifespans and the ensuing increase in duration of the aging process has resulted in a higher prevalence of age-related disorders, including cardiovascular-related vascular dementias. In fact, the risk for vascular related dementias in older adults over the age of 65 double every 5.3 years (Lobo et al., 2000; Ganguli, 2011). Cerebral white matter is particularly vulnerable to vascular disorders, and T2-weighted MRI hyperintensities associated with lesions are considered to be markers of this process (Kloppenbort, Nederkoorn, Geerlings, & van den Berg, 2014). Incidents of such lesions become increasingly common with age, increasing from 11% for ages 55-64 to 43% for individuals over the age of 85 (Howard, Wagenknecht, Cai, Cooper, Kraut, & Toole, 1998; Bryan et al., 1997). One reason for this is age-related increases in overt and covert vascular diseases, which in turn increase the risk for additional strokes, vascular cognitive impairment (VCI) and dementias (Abraham, Wolfson, Moscufo, Guttman, Kaplan & White, 2015; King, et al., 2014; O'Brien et al., 2003, Prins & Scheltens, 2015). It has been estimated that a majority of older adults will present with white matter hyperintensities (WMH) by the time they are 80 years old (de Leeuw, et al., 2001), but many early incidents remain asymptomatic (i.e., covert, silent strokes). Due to its progressive nature, vascular related pathology, including silent stroke, is

integral to modeling the development of cognitive dysfunction and late-life neurodegenerative conditions. Because many CVD risk factors are preventable and manageable with appropriate interventions, early detection and risk stratification are critical.

The CHA_2DS_2-VASc-HSF is a risk stratification scheme developed to quantify risk of ischemic stroke and transient ischemic attack (TIA) in order to inform patient intervention. This risk stratification system, and similar predecessors (e.g., $CHADS_2$), has been effective in predicting severity of CVD in high stroke-risk patients with atrial fibrillation, as well as lower risk CVD and chronic heart failure without atrial fibrillation. Despite its effectiveness in detecting CVD severity and in predicting incidence of future overt ischemic strokes, the utility of the risk stratification system to detect silent stroke, as indicated by asymptomatic WMH, has not been determined. This is critical because, although silent strokes may not result in immediately apparent symptoms, undetected subtle and insidious symptoms may develop (e.g., slowed processing speed, personality changes), and they indicate increased risk for subsequent changes to white matter and overall structural and functional integrity of the brain (e.g., atrophy). For instance, presence of WMH is a known risk factor for the occurrence of future strokes, and changes to white matter microstructure in regions associated with CVD have been shown to negatively affect cognitive function and precipitate vascular dementia (Vermeer, Prins, den Heijer, Hofman, Koudstaal, & Breteler, 2003). Thus, determining whether the CHA_2DS_2-VASc-HSF predicts WMH volume and associated brain atrophy, indicators of silent stroke, and the subsequent effects on cognitive function, is an important step in improving early identification of stroke risk and inform decisions about preventative intervention.

Development of CHA_2DS_2-VASc-HSF Stroke Risk Index

There have been marked efforts to refine our ability to quantify stroke risk, mortality, and other significant secondary outcomes (e.g., cognitive decline, vascular cognitive impairment, dementia). The Stroke Prevention in Atrial Fibrillation group developed $CHADS_2$, a stroke risk scoring system, in a cohort of hospitalized patients with atrial fibrillation (Gage, Waterman, Shannon, Boechler, Rich & Radford, 2001). The multifactorial approach utilized by the $CHADS_2$ rested on the understanding that stroke prediction is most effective when multiple risk factors are considered. Adverse outcomes of stroke have both been linked to age, female sex, hypertension, diabetes mellitus, congestive heart failure, previous stroke, and other vascular disease (Gage et al., 2001). As such, the $CHADS_2$ attempted to capture the most strongly implicated risk factors. The rubric addressed limitations in predominant existing models for stroke (i.e., Systematic Coronary Risk Evaluation, SCORE; Framingham Risk Score, FRS) by describing its efficacy in clinical practice, attempting to address long-term risk, minimizing the necessity of detailed medical charts, and, most importantly, increasing predictive reliability. Moreover, the development of the $CHADS_2$ acknowledged the practical shortcomings of previous risk scores, including multiplicity and complexity, by minimizing costs associated with risk assessment and being relatively easy for physicians to utilize. Since its original validation in predicting stroke in patients with atrial fibrillation, the $CHADS_2$ scoring system has also demonstrated utility in predicting future stroke in patients with acute ischemic stroke, arrhythmias, interatrial block, and flutter (Ntaios et al., 2013; Paoletti Perini et al., 2013). It has also been determined to be an effective tool in long-term prognosis for coronary artery disease (CAD) patients (Li, Wang, Ly, Xu, & Liu, 2018). Elevations in $CHADS_2$ scores in older adults with atrial fibrillation and stroke were also found to be strongly associated with reductions in cognitive functioning and mild

cognitive impairment (Cerit, Kema, Günsel, & Duygu, 2016; Graff-Radford et al., 2016; Washida, Kowa, Hamaguchi, Kanda & Toda, 2017). Its validation in multiple populations and outcomes, ease of use, and demonstrated utility led to its status as the most commonly used risk stratification tool in clinical practice (Lip, Nieuwlaat, Pisters, Lane, & Crijns, 2010).

Subsequent studies of stroke risk shifted the focus of stroke prevention from high-risk patients to improving identification of at-risk patients who exhibit less obvious markers of stroke risk (Olesen, Torp-Pedersen, Hansen, & Lip, 2012). In addition to the original major risk factors included in the $CHADS_2$, the new proposal updated the score so that it could be used in a range of patients with nonvalvular atrial fibrillation by incorporating "clinically relevant non-major" risk factors (Lip et al., 2010). Subsequently, the stratification system was expanded to include vascular disease, age range 65-75 years, and sex category. These factors appeared to improve the instrument's stratification of low risk patients (i.e., those who have not suffered a previous stroke or TIA), which is critical in order to implement preventative measures before progression to severe CVD and stroke (Piyaskulkaew, Singh, Szpunar, Saravolatz II, & Rosman, 2014). The improvements made in the CHA_2DS_2-VASc were apparent, as sensitivity and negative predictive value were found to be superior to both the $CHADS_2$ and the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) risk stratification schemes (Kim et al., 2017). Moreover, the CHA_2DS_2-VASc score has been shown to predict ischemic stroke in individuals with CAD and chronic heart failure without atrial fibrillation, exceeding the predictive power of other stroke risk scores (Kondo et al., 2017; Welles, Whooley, Na, Ganz, Schiller, & Turakhia, 2011).

To further expand the stroke risk index's validity to detect severity of CAD, Cetin and colleagues (2014) formulated the CHA_2DS_2-VASc-HS score. This updated score is comprised of the previous risk factors with the addition of hyperlipidemia and smoking. The addition of these

variables significantly improved detection of CAD severity when compared to previous iterations among a sample of patients with CAD with and without stenosis (Cetin et al., 2014). When stratification of risk was compared to previous iterations of the $CHADS_2$ in hospitalized CAD patients, the differences were less pronounced. Thus, it appears that this refinement is most relevant to low-risk/lower severity CAD patients.

Most recently, Modi and colleagues (2017) formulated the CHA_2DS_2-VASc-HSF to further refine stratification in CAD. The CHA_2DS_2-VASc-HSF score consists of congestive cardiac failure (C), hypertension (H), age >75 years (A), diabetes mellitus (D), stroke (S), vascular diseases (V), age 67-75 years (A), and sex category (Sc), hyperlipidemia (H), smoking (S), and family history of CAD (F). This iteration was determined to be an effective tool in differentiating between individuals of differing coronary artery disease in a large sample of adults (ages 51-60), above and beyond the predictive value of $CHADS_2$ and CHA_2DS_2-VASc. While its utility in predicting severity of CAD via its association with number of diseased coronary vessels has been determined, it's association with indicators of silent stroke (e.g., WMH) in generally healthy older adults has yet to be described.

Cardiovascular Mechanisms for Stroke Risk and Cognitive Function

Consideration of the brain's vasculature is important in determining the link between stroke risk, white matter lesions, atrophy, and cognitive function. There is growing evidence that events such as heart failure and aortic stiffness are associated with TIA and stroke, which often precede onset of vascular cognitive disorders, memory disorders, mild cognitive impairment, and dementia (Chui & Ramirez Gomez, 2017; Wu et al., 2016). The brain is organized from the "outside in," in that critical arteries (i.e., pial arterioles) that control cerebral blood flow are outside the brain parenchyma (Bagher & Segal., 2011; Iadecola, 2013). Due to this organization,

penetrating arterioles cannot be compensated if they are occluded, leaving the subcortical white matter susceptible to ischemia (Blinder, Tsai, Kaufhold, Knutsen, Suhl, & Kleinfeld, 2013). Reductions in blood flow have the potential to produce small ischemic lesions in white matter, and subsequently affects connecting cortical regions, critical for cognitive function (Nguyen, Nishimura, Fetcho, Iadecola, & Schaffer, 2011; Nishimura, Rosidi, Iadecola, & Schaffer, 2010; Shih et al., 2013). This is because white matter is critical for communication among brain regions, including between cortical and subcortical structures, cortico-cortical intrahemispheric projections, and cortico-cortical interhemispheric pathways connecting the two hemispheres (Dan & Poo, 2004; Nave, 2010; Stone & Tesche, 2013).

There are many distinct ways in which arterial changes can affect structural integrity, and subsequently cognitive function, from global cerebral perfusion to acute alterations in cerebral blood vessels (Iadecola, 2013). Arrhythmias, hypotension, cardiac arrest, and cardiac failure have been linked to global cerebral perfusion reductions, which can have acute or permanent impacts on function (Alosco et al., 2013; Justin, Turek, & Hakim., 2013; Marshall, 2012; Stefansdottir et al., 2013). Marked reductions in global cerebral perfusion significantly increase the risk for ischemic stroke, which subsequently increases risk of future stroke (Moskowitz, Lo, & Iadecola, 2010). Additionally, white matter lesions that contribute to such processes can expand over time, which has implications for the development of new lacunes and the progression of cognitive impairment, particularly in the domains of executive function (EF) and processing speed (Gouw et al., 2011; Jokinen et al., 2011; Maillard, Carmichael, Fletcher, Reed, Mungas, & DeCarli, 2012). Vascular lesions associated with cognitive impairment are often associated with subtle alterations in white matter small vessels, particularly in deep cerebral white matter, demonstrating the impact of even small vascular changes (Jellinger, 2013). These

changes have not been found to be necessarily specific to a particular lesion presentation. Microvascular changes often yield different neuropathological lesions that coexist in the brain. For example, leukoaraiosis (confluent white matter lesions) and lacunes (small white matter infarcts) are often both found in subcortical regions, and have been strongly implicated in CVD risk factors such as hypertension, hyperlipidemia, smoking, and diabetes (Gorelick, et al., 2011; Wardlaw et al., 2013a, 2013b).

Despite the effects that the described processes have on neural integrity, many cardiovascular events go undetected, causing damage to the brain that is not immediately apparent. Early studies have found that 11% of community-dwelling adults between 55 to 64 years, 22% for those aged 65 to 69 years, and 43% for individuals older than 85 years had cerebral infarctions on MRI, despite a history negative for overt stroke or TAI (Howard, Wagenknecht, Cai, Cooper, Kraut, & Toole, 1998; Bryan et al., 1997). Importantly, these processes do not appear to be isolated to late life. The progression of cognitive decline following silent stroke has been detected in patients younger than 50 years, reinforcing the notion that CVD processes may affect the trajectory of neuronal changes beyond the effect of age-related dementia and impairments (Schaapsmeerders et al., 2013).

The white matter tracts at distal blood supply boundaries between arterial territories (e.g., periventricular watershed areas) renders these regions especially vulnerable to hypoperfusion and, subsequently, ischemic lesions (De Reuck, 1971; Miklossy, 2003; Suter et al., 2002). Importantly, this vulnerability does not appear to be unique to individuals with severe CVD, as findings in healthy individuals with hypercapnia have reduced cerebral blood flow in the periventricular white matter (Mandell et al., 2008). This underscores the notion that white matter is vulnerable in the absence of overt vascular events. In further support of this vulnerability is the

finding that lower global cerebral blood flow has been associated with greater white matter lesion load in individuals without history of overt strokes (Bakker, de Leeuw, de Groot, Hofman, Koudstaal, & Breteler, 1999; Vernooij et al., 2008).

By definition, silent infarcts do not exhibit the typical stroke symptoms (e.g., lateralized weakness, numbness, loss of vision, comprehension and speech deficits). The absence of noticeable acute symptoms is not necessarily indicative of better prognosis, as silent stroke can contribute to cognitive dysfunction, future stroke, and overall mortality (Gupta 2016; Sacco, et al., 2013). In fact, one longitudinal study of a sample of 3,697 older adults found that the presence of silent brain infarcts doubled the risk of developing dementia, as determined by assessment at a 3-year follow-up evaluation (Vermeer et al., 2003). The described lesions not only disrupted white matter connectivity, but was also associated with cerebral atrophy (Appelman, Exalto, van der Graaf, Biessels, Mali, & Geerlings, 2009).

Attempts to describe cardiovascular risk factors, stroke, and ensuing cognitive dysfunction have implicated both white matter lesions and cortical thinning as possible mechanisms, as they share cardiovascular disease risk factors and yield similar outcomes in cognitive function (Dickie et al., 2016). Total white matter lesion burden has been linked to total grey matter atrophy (Appelman et al., 2009; Aribisala et al., 2013; Wang et al., 2014). While the nature of this association is not definitively known, it has been hypothesized that damage to white matter disrupts axonal connections and the subsequent cortical-subcortical disruption results in degeneration of cortical grey matter (Du et al., 2005). More simply, cell body death in the cortex is often secondary to axonal death. Cortical thickness has been linked to severity of disease and the progression of dementias (Hartikainen et al., 2012; Lerch and Evans, 2005). Leukoaraiosis, for example, has been found to be associated with focal cortical thinning in the frontal cortex,

which is critical for executive function (Seo et al., 2012). Moreover, patients with leukoaraiosis experience brain volume loss at twice the rate (i.e., 1% per year) of age-matched controls (Nitkunan, Lanfranconi, Charlton, Barrick & Markus, 2011). Both cortical atrophy and thinning has also been linked to greater general CVD, as measured by the Framingham Cardiovascular Risk Profile, and atherosclerosis (Cardenas et al., 2012; Geerlings et al., 2010). Cortical thickness as a marker for potential stroke has been understudied in stroke populations due, in part, to traditional clinical decisions to prioritize more feasible qualitative and ordinal visual MRI image quantification systems over newer and more sophisticated dimensional quantification of high-resolution T1 and T2 MR images (An et al., 2011; Lee et al., 2010; Rohrer et al., 2009). Thus, studies that directly evaluate the associations between stroke risk, WMH, cortical thickness, and cognitive function are needed.

It is well-accepted that higher-level cognitive processing is reliant on frontal lobe integrity, and that insult or degeneration of frontal regions contributes to cognitive decline in aging (Wen & Sachdev, 2004). However, studies have demonstrated that WMHs are associated with frontal lobe functions, regardless of their location (Tullbert et al., 2004). To this end, the current study will evaluate total brain lesion burden and the effects on frontal cortical thickness as they relate to stroke risk and cognitive function.

Cognitive Function

CVD is the second most common etiological factor in vascular cognitive impairment and dementia worldwide (Gorelick, et al., 2011). CVD encompasses many disorders with overlapping risk factors, associated neuropathology, and impact on cognitive function, prompting many researchers to combine various subtypes (Brady, Spiro, McGlinchey-Berroth, Milberg & Gaziano, 2001; Dregan, Stewart, & Gulliford, 2013; Liebel & Sweet, 2019). There is

a general consensus that overall cumulative neural tissue damage and total lesion burden contributes to brain and subsequently cognitive dysfunction (Black, Gao, & Bilbao, 2009; Brickman et al., 2011; Gelber et al., 2012; Gorelick et al., 2011; Inzitari et al., 2009; Marshall, 2012; Tomlinson et al., 1970). As described, small vessel disease affects the arteries, arterioles, and capillaries, all of which have the potential to alter microstructure and contribute to stroke and dementia (Meissner, 2016). Even before CVD progresses to a degree of severity that results in overt stroke or dementia, changes to the brain's microstructure and gray matter can impart changes in cognitive functioning.

Studies that have sought to delineate the cognitive domains implicated in CVD-associated cognitive decline have consistently found EF and processing speed to be most prominent, with the two rarely being affected in isolation of one another (Cannon et al., 2017; De Right et al., 2015; Eggermont, de Boer, Muller, Jaschke, Kamp & Scherder, 2012; Liebel et al., 2017; Pantoni, 2010; Roman, 2003). EF is a complex, multicomponent domain of cognitive function. Intact EF is dependent on the interplay between fundamental, core cognitive skills (e.g., attention, language, visuospatial perception, processing speed) and higher-order cognitive functions (e.g., concept formation, planning, cognitive flexibility, and inhibition). Thus, inefficient EF can result from any individual or combination of deficits in these contributing domains. Consideration of the mechanisms by which CVD can impact vascular and, subsequently, neuronal integrity may clarify the vulnerability of executive functions to CVD. Extant literature reflects this conceptualization, as findings have primarily yielded change in executive functions and its contributing domains, particularly processing speed (for reviews, see Liebel & Sweet, 2019). For instance, geriatric cardiac patients with lower cardiac output exhibit worse performance on tests of problem solving and cognitive flexibility compared to healthy

controls (Jefferson, Poppas, Paul, & Cohen, 2007). Risk factors for CVD in older adults have been associated with executive functioning, attention, and processing speed (Cohen et al., 2009; Duda, Keith, & Sweet, 2019). More specifically, EF subdomains of cognitive flexibility and inhibition, in conjunction with processing speed, have been most strongly implicated in CVD (Liebel et al., 2017).

The $CHADS_2$ scoring systems have been shown to be sensitive to cognitive function. Early versions of the scoring system (i.e., $CHADS_2$) have been shown to predict post-stroke cognitive impairment. Specifically, visuo-executive performance has been associated with $CHADS_2$ after cardioembolic stroke (Washida et al., 2017). Using the newer score, reductions in global cognitive function have been documented in older adults with atrial fibrillation with higher CHA_2DS_2-VASc scores (Meyre et al., 2017). Many studies have further specified this by demonstrating that EF is related to this updated index. The risk factors encompassed in the $CHADS_2$-VASc score, such as cardiac failure, hypertension, and overt stroke, have been linked to EF and processing speed (Debette et al., 2011; Duda et al., 2019; Gottesman et al., 2017; Hoth, Poppas, Moser, Paul & Cohen, 2008; Nishtala et al., 2015; Waldstein , Giggey, Thayer, & Zonderman, 2006).

Aims and Hypotheses for the Current Study

The overall goal of the current study was to clarify the association between stroke risk, total WMH volume, frontal lobe cortical thickness, and cognitive function (EF and processing speed) in a sample of low-risk older adults without history of overt stroke. While iterations of the CHA_2DS_2-VASc-HSF have been determined to be an effective predictor of overt stroke risk in less severe CVD patients, it is unclear whether elevated scores are associated with covert white matter lesions and cortical thinning. Additionally, studies that directly assess the roles of white

matter and cortical thickness as mechanisms for cognitive dysfunction related to stroke risk are scarce. Thus, the current study first aimed to determine whether stroke risk (i.e., CHA_2DS_2-VASc-HSF) scores are associated with white matter lesions (i.e., MRI lesion volumes as indicated by WMH) and frontal cortical thickness. We hypothesized that higher WMH load and thinner frontal cortex would be associated with higher CHA_2DS_2-VASc-HSF scores, which are indicative of higher risk. Second, we aimed to determine whether there is a significant association between total WMH load and frontal cortical thickness. Since total WMH burden is associated with frontal brain integrity, we expected that higher load would be associated with greater frontal cortical thinning (Tullbert et al., 2014). Our third aim was to determine the association between the CHA_2DS_2-VASc-HSF and cognitive function (i.e., EF and processing speed, Figure 1). A latent variable that captures cognitive skills affected in CVD was used, as studies have not found either EF or processing speed to be affected in isolation of one another. While this variable will be referred to as cognitive function, it is important to note that this is specifically in reference to the cognitive domains most strongly implicated in CVD (cognitive flexibility, inhibition, and processing speed). We expected higher stroke risk scores to be associated with worse cognitive function. Finally, we aimed to determine whether structural brain integrity (i.e., WMH and cortical atrophy) is a significant indirect mechanistic link between stroke risk (CHA_2DS_2-VASc-HSF) and cognitive function.

CHAPTER 2

METHOD

Participants

Participants in the current study were 83 community-dwelling older adults (mean age = 63.8 years, range 50-85; 70% female) who were recruited via newspaper ads and flyers from cardiology clinics and the community in the Providence, RI catchment area to participate in a study of the impact of cardiovascular health on neurocognitive and neuroimaging markers (i.e., MRI, fMRI, perfusion). Both CVD patients and typically-aging older adults were recruited for the parent study. Full demographic information for the sample is available in Table 1. Participants were excluded if they had a significant history of neurological disorders (e.g., overt stroke or transient ischemic event, multiple sclerosis, Alzheimer's disease, traumatic brain injury with loss of consciousness), a current diagnosis of psychiatric disorder (e.g., schizophrenia, mood disorder), hospitalization due to substance abuse, major medical disorders (e.g., cardiac arrest, coronary artery bypass graft surgery), or contraindication for MRI (e.g., ferrous metal implant). To improve generalizability, the sample included patients with prevalent forms of mild CVD (e.g., hypertension, atrial fibrillation) when heart health and disability indictors were with in normal limits (i.e., mean left ventricular ejection fraction cutoff <55%, Ueda et al., 2015). We also examined the New York Heart Association (NYHA) Classification to confirm that individuals with severe cardiac failure were not included.

Procedures

Participants underwent telephone screening and provided written informed consent prior to enrollment. They were subsequently assessed over the course of three visits. The assessments comprised of a comprehensive neuropsychological battery, a cardiology assessment, and an MRI of the brain. The three-hour neuropsychological battery assessed all major cognitive domains (i.e., global function, attention, language, visuospatial ability, executive function, learning and memory, motor function) and evaluations were supervised by a licensed clinical neuropsychologist. A licensed cardiologist conducted echocardiogram assessments, including CVD status, severity, and risk factors. Participants received monetary compensation for their visits. The study was approved by the Butler Hospital and Brown University (Providence, RI) Institutional Review Boards.

Measures

CHA_2DS_2-VASc-HSF. The CHA_2DS_2-VASc-HSF score was developed to stratify stroke risk in individuals with cardiovascular disease (Gage et al., 2001; Modi et al., 2017). The most recent iteration improved risk stratification for lower stroke risk CAD patients without atrial fibrillation. The CHA_2DS_2-VASc-HSF is calculated by allotting 1 point for the presence of congestive heart failure (C), hypertension (H), diabetes mellitus (D), vascular disease (V), sex category (Sc), hyperlipidemia (H), smoking (S), family history (F), and age between 65-74 years (A). Age >75 years (A_2 instead of A) and history of stroke or TIA (S_2) are each assigned 2 points. The points are summed for a total possible score of 12, with higher scores indicative of greater risk of stroke. Currently, sensitivity and specificity are not available for the CHA_2DS_2-VASc-HSF for healthy older adults, but a cutoff of 3 is used for CAD. Guidelines for the CHA_2DS_2-VASc suggest that 0 constitutes "low" risk of stroke, 1 is “moderate” and scores greater than 1

constitute “high” risk, with the exception of a score of 1 due solely to gender. In individuals with atrial fibrillation, “moderate” or “high” risk are considered candidates for full oral anticoagulation (Camm, et al., 2012). While specificity for predicting ischemic stroke and thromboembolism (stroke, TIA, or systemic embolism) was lower at .06 and .07, respectively, sensitivity of the CHA_2DS_2-VASc was 1.00, and was overall found to be an effective predictor of truly low-risk individuals (Friberg, Rosenqvist, Lip, 2012; Kim et al., 2017).

Delis-Kaplan Executive Function System (D-KEFS). The D-KEFS is a set of standardized tests designed to comprehensively assess higher level cognitive functions (i.e., executive functions). Executive functions require fundamental cognitive skills, including attention, language, and perception, in order to achieve abstract and integrative thinking. The D-KEFS was standardized using a national dataset of over 1,700 adults and children. Normative data is available for ages 8 to 89 years, and reflects the demographic distribution of the U.S. population. Its reliability and validity are well-established (Delis, Kramer, Kaplan, & Holdnack, 2004).

The D-KEFS is composed of nine tests that assess cognitive areas that contribute to executive function. Each test was developed to give the examiner the option to administer a stand-alone test or administer the tests along with other D-KEFS tests. For the current study, Color-Word Interference, Trail Making Test, and Verbal Fluency were selected to represent components of EF (i.e., cognitive flexibility and inhibition) most strongly implicated in prior CVD literature (Liebel et al., 2017).

Color-Word Interference (CWI) Test. This task was developed based on the Stroop Test (Stroop, 1935). To successfully complete this task, examinees must inhibit word reading (overlearned, automatic response tendency), and instead name the incongruent ink color (i.e.,

generate a conflicting response). There are four conditions in the D-KEFS CWI, with two serving as baseline conditions that assess foundational skills (i.e., Color Naming, condition 1, and Word Reading, condition 2) necessary for the higher-order tasks (i.e., Inhibition, condition 3, and Cognitive Flexibility, condition 4). For the current study, condition 3 (Inhibition) will be used to assess inhibitory control performance in isolation. In this condition participants are instructed to name the color of the ink, rather than read the word. They are instructed to complete two lines of words to practice. Following successful completion of practice items, participants are instructed to complete the stimuli page as quickly and accurately as possible. The time (in seconds) that it takes for the participant to complete the page is recorded, and serves as their raw score for the subtest.

Verbal Fluency Test. In this task, participants are asked to generate words according to a given rule as quickly as possible. The Verbal Fluency Test is comprised of three conditions, for which participants must generate words that begin with a specified letter (Letter Fluency, condition 1), words that belong to a designated semantic category (Category Fluency, condition 2), and then switch between generating words belonging to two different semantic categories (Category Switching, condition 3). These subtests primarily measure phonemic fluency, semantic fluency, and category shifting, respectively. Category Switching (condition 3) involves the simultaneous engagement of rapid retrieval skills from semantic knowledge and cognitive flexibility, increasing its sensitivity to frontal dysfunction when compared to condition 2. To assess the degree to which individuals are able to switch between cognitive sets, the switching accuracy score was used, which is a raw sum of the total number of correct switches (i.e., category 1 followed by category 2, etc.) achieved during the 60 second time limit.

Trail Making Test. Five conditions comprise the Trail Making Test (TMT). These are a visual cancellation task and four connect-the-circle tasks requiring the examinee to sequence numbers, letters, and demonstrate motor speed. Visual Scanning (condition 1) and Number Sequencing (condition 2) taps visual attention and processing speed, while Letter Sequencing (condition 3) and Motor Speed (condition 5) are assessed to ensure that visual attention, and alphabet sequence skills were intact. Number-Letter Switching (condition 4) is the primary executive-function task. This task taps cognitive flexibility skills, which are central for executive functions, by requiring individuals to connect circles using a pencil by switching between numbers and letters, in order. The Number-Letter Switching condition has been found to be sensitive both to frontal lobe and diffuse brain dysfunction (Delis et al., 2004). Moreover, the D-KEFS TMT was specifically designed to improve sensitivity to milder cognitive deficits by increasing visual scanning demands (i.e., expanding stimuli to two pages) and introducing "capture stimuli" (i.e., placing two stimuli of the same set, such as 3 and 4, near each other to increase the chance of a set-loss error; Delis et al., 2004). The Letter-Number Sequencing completion time in seconds was used as a measure of cognitive flexibility in this study.

Wechsler Adult Intelligence Scale (WAIS-IV) Symbol Search. The WAIS-IV (Wechsler, 2008) is the most recent iteration of a series of intelligence scales stemming from the Wechsler-Bellevue Intelligence Scale (Wechsler, 1939). It is one of the most frequently used measures of intelligence and its Processing Speed Index (PSI) has been well validated as a reliable measure of processing speed (Benson, Hulac, & Kranzler, 2010; Kaufman & Lichtenberger, 2006). The Symbol Search Task is one of the subtests of the WAIS-IV that contributes to the Processing Speed Index (PSI). During this task, participants are presented with pages on which two target symbols appear to the left of an array of five symbols. They are to

find one of the two target symbols among this array of five. To respond, participants mark the identical symbol, or mark the "no" box if neither of the target symbols match any of the five in the array. Participants are instructed to work as quickly and accurately as possible. Performance is quantified as the correct number of responses minus the number of incorrect responses in a two-minute time period.

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Coding. The RBANS is a well-established, brief, screening tool that measures multiple neurocognitive domains, including attention, language, visuospatial abilities, memory, and processing speed (Randolph 1998). The RBANS's test-retest reliability, split-half reliability, and validity have been well-established (Carlozzi, Horner, Yang, & Tilley, 2015; Duff et al., 2006; Randolph, 1998). In the Coding subtest, participants are presented with a key at the top of the page, in which corresponding numbers and a unique symbol are paired. During this task, participants are asked to copy the appropriate response in the empty box beneath the stimulus-items. Performance is quantified as the number of items correctly copied within the time limit.

Latent Cognitive Function. A latent variable comprised of raw values for EF and processing speed measures was used in analysis. The decision to combine these measures into a latent factor was based on existing research literature that consistently implicates EF subdomains, cognitive flexibility and inhibition, and processing speed as affected in CVD (e.g., Cannon et al., 2017; Cohen et al., 2009; Duda et al., 2019; Liebel et al., 2017). Importantly, mechanisms for CVD-related declines in EF and processing speed overlap in that white matter damage influences frontal lobe cell body death (Wen & Sachdev, 2004). This, combined with the fact that stroke risk factors often co-occur, reinforces the notion that individuals with CVD seldom exhibit a single type of MRI finding that would affect EF or processing speed in isolation

(Gorelick, et al., 2011; Wardlaw et al., 2013a, 2013b). Thus, a latent variable is likely to best capture the underlying processes that manifest as performance deficits in tasks of EF (cognitive flexibility and inhibition) and processing speed in individuals with stroke risk factors.

As a post-hoc follow-up analysis, a second model where EF and processing speed were entered as separate latent factors was estimated. This is because EF and processing speed, although highly related (Liebel et al., 2017), are considered separate domains by clinicians and may reflect different neuropathological mechanisms (e.g., gray matter atrophy, white matter lesions).

MRI Acquisition and Processing

Acquisition. Images were acquired on a 3T Siemens Tim Trio scanner with a 32-channel head coil. Volumetric imaging analysis was performed using whole-brain high-resolution T1-weighted magnetization prepared rapid gradient echo (MPRAGE) images (TR =1900 ms, TE = 2.98 ms, TI = 900 ms, flip angle = 9°, FOV = 256 x 256 mm, voxel size =1mm isotropic, scan duration = 240 seconds). Whole-brain high-resolution T2-weighted fluid attenuated inversion recovery (FLAIR) images, which are highly sensitive to white matter abnormalities, were also included in analysis (TR = 6000ms, TE = 408 ms, slice thickness = 1mm, FOV = 240 x 256 mm, matrix = 240 x 256, scan duration = 388 seconds).

FreeSurfer. Neuroanatomical segmentation, parcellation (i.e., cortical thickness), and lesion quantification was performed using the FreeSurfer software package (version 6.0). FreeSurfer has been validated as a robust tool for segmentation of cortical ischemic strokes, subcortical strokes, and as a stable measure in stroke populations (Li et al., 2015).

Both T1-weighted MPRAGE and T2-weighted FLAIR images were used in the FreeSurfer recon-all pipeline in an effort to refine white matter delineations (Fischl et al., 2002;

2004). All images were visually inspected for errors in skull stripping, segmentation, intensity normalization, pial surface demarcation, and topological surfaces problems. FreeSurfer yields an extensive number of subcortical segmentations, surface area, and cortical thickness outputs. Volume of total white matter hyperintensities (in mm^3) and frontal mean cortical thickness (in mm), as defined by the Desikan-Killiany atlas (2006), were used in data analyses. Hereafter, WMH refers to abnormal intensity on MRI indicative of lesions. Specifically, this will be the convergence of volumes of T2 hyperintensity and T1 hypointensity as determined by the FreeSurfer Pipeline. Total intracranial volume (ICV), also quantified by FreeSurfer, was used as a control for head size. Prefrontal lobe regions were examined in the present study, as they have been associated with executive function in previous research literature. These include the gray matter of the superior frontal, middle frontal, inferior frontal (i.e., pars opercularis, pars triangularis, pars orbitalis), medial frontal, orbitofrontal, paracentral, and frontal pole (Desikan et al., 2006). To account for head size and ensure that WMH and cortical thickness were not simply reflective of general atrophy, both variables were represented as a percentage of ICV.

Data Analysis

MPlus version 8.2 (Muthén & Muthén) was used for structural equation model (SEM) analyses. Data was checked for normality and product coefficients derived in the estimation of mediation models seldom meet the assumption or normality, which is a core assumption in traditional maximum-likelihood estimation methods (Preacher & Hayes, 2008; Shrout & Bolger, 2002). To reconcile this concern, nonnormality of data was accounted for via bootstrapping techniques (Preacher & Hayes, 2008). The full information maximum likelihood method was used to estimate missing data from the model. Missing data was quantified and assumed to be missing at random (i.e., missing variables would be related to observed variables but unrelated to

the missing values themselves; Shafer & Graham, 2002). Fit indices were reviewed to assess model fit. It is generally recommended that indices from each category are represented, including absolute (i.e., chi-square test of model fit; standardized root mean square residual, SRMR; root mean square error of approximation, RMSEA), relative fit (Tucker-Lewis Index, TLI), and noncentrality-based indices (the comparative fit index, CFI). Fit indices were selected based on their appropriateness for the given sample size of this study. For example, chi-square is artificially inflated for large sample sizes but is appropriate for sample sizes of approximately 75 (Schermelleh-Engel, Moosbrugger, & Müller, 2003). TLI, SRMR, and RMSEA are relatively independent of sample size (Chen, 2007; Ding, Velicer & Harlow, 1995; Gerbing & Anderson, 1992). CFI specifically performs better for studies with small sample sizes (Chen, 2007; Hu and Bentler, 1998). In general, SRMR values close to or below .06, RMSEA values close to or below .05, and CFI and TLI values close to or greater than .95 indicate good fit (Hu and Bentler, 1999).

Confirmatory factor analysis (CFA) was used to confirm the factor structure for cognitive function, which included the described D-KEFS measures of executive function and WAIS-IV and RBANS measures of processing speed (Figure 1). RBANS Coding, WAIS-IV Symbol Search, and D-KEFS Verbal Fluency Switching were reverse coded so that higher values for cognitive variables uniformly reflected worse performance. Next, SEM was used to estimate the associations among the CHA_2DS_2-VASc-HSF, WMH, frontal cortical thickness, and cognitive function (Figure 2). We considered using age as a covariate in the model; however, due to its inclusion in the CHA_2DS_2-VASc-HSF score, it was left out of the model. Since age is a component of the risk stratification score, controlling for the variance associated with age would in effect control for variance that we are interested in examining. A serial mediation model was

selected, as there is evidence that WMH precipitates cell body death (Du et al., 2005). The indirect effects via total WMH and frontal cortical thickness between CHA_2DS_2-VASc-HSF and cognitive function was tested. Standardized effects and 95% confidence intervals were examined, and all statistical tests were conducted using a two-tailed $p<.05$ threshold. Specifically, the estimated SEM model addressed the following aims:

1. To determine whether CHA_2DS_2-VASc-HSF scores are associated with total WMH and cortical thickness.
2. To determine whether there is an association between total WMH and frontal cortical thickness.
3. To determine whether there is an association between the CHA_2DS_2-VASc-HSF and a latent cognitive function variable that encompasses EF and processing speed.
4. To determine whether WMH and frontal cortical thickness are important mechanistic links for an indirect effect between stroke risk (CHA_2DS_2-VASc-HSF) and cognitive function.

Power Analysis

The data for the current study was collected as a part of a larger study. As such, power analyses have been conducted to ensure that the proposed model is appropriate for available sample size (83). In SEM, it has traditionally been recommended that there are at least five observations per observed variable (Bentler & Chou, 1987). In the proposed model with nine observed variables, the sample size for the current study is sufficient. However, these are broadly seen as rules of thumb, and are subject to over- or underestimate sample size requirements. Therefore, a Monte Carlo procedure in MPlus was used to conduct power analyses (Muthén and Muthén, 2002). The Monte Carlo approach to power analysis repeatedly samples the proposed

serial mediation model under a given population model with specific parameter values. The specific parameter values were determined by expected population estimates (i.e., the theoretical true relationships between variables), as determined by existing literature. This approach was selected based on its ability to handle measurement models, nonnormality, and estimate power under missing data conditions (Davey & Salva, 2009). This approach to power analysis in SEM yields estimates of power to detect the effects of interest within the model.

Effect sizes parameters used to estimate statistical power were expected to be between small to moderate based on available literature. For example, the association between WMH and cortical gray matter, and their association with cognitive function have been found to be in small-moderate (e.g., Tullberg et al., 2014). Associations between WMH and brain morphometry has been found to be moderately associated with CVD (e.g., Geerlings et al., 2009). Thus, an analysis was conducted to determine if the proposed model could detect effect sizes in the small to medium rage (i.e., .2-.5). 10,000 successful replications with 83 observations were conducted. The RMSEA indicated close fit (.027), which suggests that the model as a whole is appropriate for the given sample size (MacCallum, Browne, & Sugawara, 1996). The power was greater than .80 for all paths of interest in the proposed serial mediation model.

CHAPTER 3

RESULTS

Data was inspected for normality and individual outliers (i.e., >3 standard deviations) were removed (<.1%). Natural logarithmic transformations were performed to reduce skewed data for WMH and cognitive variables. Demographic and descriptive characteristics are presented in Table 1. While both raw and standardized cognitive performance are reported, note that raw values, where higher values equate to worse performance (i.e., task completion times and reverse coded Coding, Symbol Search, and Verbal Fluency total correct scores), were used in the analysis. Clinical characteristics for the present sample were relatively consistent with incidents observed in the older adult population (Yazdanyar and Newman, 2009). Bivariate zero-order correlations between stroke risk, brain morphometry, and cognitive performance were generally in the hypothesized directions (Table 2).

The latent cognitive function factor was comprised of D-KEFS measures of executive function (CWI, TMT Number-Letter Switching, and Verbal Fluency Category Switching) and processing speed (WAIS-IV Symbol Search and RBANS Coding) (Figure 1). Model fit was in the close to exact range, $\chi^2(5)=3.666$, p=.594, CFI=1.000, RMSEA=.000, SRMR=.023. Since indicators were not cross-loaded, factor loadings may be interpreted as correlations between the indicator and factor. All factor loadings were greater than .40, which is the recommended guideline for substantively meaningful magnitudes for parameter estimates, and significant at a two-tailed significance of p<.001 (Brown, 2015).

Hypotheses were tested using SEM serial mediation models to evaluate associations among CHA_2DS_2-VASc-HSF, WMH, frontal cortical thickness, and cognitive function (Figure 2). The SEM model exhibited good fit overall: $\chi^2(17)=21.028$, p=.225, CFI=.979, TLI=.965, RMSEA=.053, SRMR=.054. Results indicated a significant negative association between CHA_2DS_2-VASc-HSF and frontal cortical thickness (β = -.241 , p=.025), and WMH and frontal cortical thickness (β = -.344 , p=.015). There were significant associations between CHA_2DS_2-VASc-HSF and cognitive function (β = .330, p=.004), and WMH and cognitive function (β =.526 , p<.001), where higher risk and WMH burden were associated with worse cognitive performance. There was no significant association between CHA_2DS_2-VASc-HSF and WMH (β =.174, p=.100), and indirect effects were nonsignificant (Table 3).

Exploratory Analysis

The latent factor for EF was comprised of CWI, TMT Number-Letter Switching, and Verbal Fluency Category Switching. The latent factor for processing speed was comprised of Coding, Symbol Search, and TMT Number Sequencing. The SEM model exhibited close fit: $\chi^2(19)=20.028$, p=.393, CFI=.996, TLI=.992, RMSEA=.026, SRMR=.056. There were significant negative associations between CHA_2DS_2-VASc-HSF and cortical thickness (β = -.240, p=.024) and WMH and cortical thickness (β = -.336, p=.018). There were significant associations between CHA_2DS_2-VASc-HSF and EF (β = .335, p=.003), CHA_2DS_2-VASc-HSF and processing speed (β = .319, p=.009), WMH and EF (β = .511, p<.001), WMH and processing speed (β = .535, p<.001), and cortical thickness and processing speed (β = .254, p=.035). There were no significant associations between CHA_2DS_2-VASc-HSF and WMH (β = .168, p=.113), cortical thickness and EF (β = .028, p=.864), or indirect effects (Table 4).

Table 1. Participant Characteristics

	Mean (SD)	Median	Range
Age	63.8 (8.7)	62.5	50 – 85
Female N (%)	56 (70.0%)		
Education	15.6 (2.2)	16	11 – 21
Race N (%)			
African American	2 (2.5%)		
Asian	1 (1.2%)		
Caucasian	80 (96.3%)		
Clinical Characteristics			
Left Ventricular Ejection Fraction	60.8% (4.4%)		
NYHA Classification			
None	21 (25.3%)		
Class I	29 (34.9%)		
Class II	10 (12.0%)		
Class III	3 (3.6%)		
Class IV	0 (0%)		
Missing data	20 (24.1%)		
Arrhythmia	10 (12.1%)		
Atrial Fibrillation	6 (7.2%)		
Blood Pressure	27 (32.5%)		
Cardiac Arrest	0 (0%)		
Coronary Artery Disease	3 (3.6%)		
CABG Heart Bypass Surgery	0 (0%)		
Diabetes	6 (7.2%)		
High Cholesterol	31 (37.3%)		
Heart Attack	5 (6.0%)		
Stent Insertion	2 (2.4%)		
Thyroid	9 (10.8%)		
Stroke/TIA	0 (0%)		
CHA_2DS_2-VASc-HSF	2.7 (1.9)	2.0	0 – 8
White Matter Hyperintensities	1614.2 (1649.3)	1025.3	274.6 – 8384.0
Frontal Cortical Thickness	2.7 (.25)	2.7	1.6 – 3.2
Cognitive Performance	**Scaled Score**	**Raw**	
Color Word Interference	11.4 (2.7)	61.2 (18.6)	
Trails NL	11.5 (2.6)	91.3 (42.5)	
Verbal Fluency Category Switching	12.1 (3.3)	13.3 (3.4)	
Trails NS	11.7 (3.0)	39.5 (21.2)	
Coding	10.5 (3.2)	45.9 (10.2)	
Symbol Search	11.2 (2.6)	29.5 (7.4)	

Note: Clinical characteristics are overlapping, with many participants possessing more than one clinical symptom; NYHA = New York Heart Association; Class I= No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath); Class II= Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath); Class III= Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea; Class IV= Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Table 2. Zero-order correlations

	CHA_2DS_2-VASc-HSF	WMH	Cortical Thickness	CWI	NL	VF	SS	NS
CHA_2DS_2-VASc-HSF								
WMH	.186							
Cortical Thickness	-.291	-.382						
CWI	.395	.470	-.291					
NL	.197	.369	-.084	.612				
VF	.210	.117	.063	.362	.281			
SS	.308	.457	-.035	.599	.609	.307		
NS	.063	.197	.074	.448	.622	.342	.481	
CD	.282	.329	-.032	.566	.638	.308	.684	.502

Note. WMH=white matter hyperintensities; CWI= D-KEFS Color Word Identification; NL=D-KEFS Trail Making Test Number Letter Sequencing; VF=D-KEFS Verbal Fluency Category Switching; SS=WAIS-IV Symbol Search; NS=D-KEFS Trail Making Test Trail Making Test Number Sequencing; CD=RBANS Coding.

Table 3. Standardized SEM results, full cognition model

				95% C.I.	
	B(S.E.)	β	*p*	*Lower*	*Upper*
CHA_2DS_2-VASc-HSF → WMH	.075(.049)	.174	.100	-.033	.382
CHA_2DS_2-VASc-HSF → Cortical Thickness	-.032(.014)	-.241	.025*	-.451	-.030
CHA_2DS_2-VASc-HSF → Cognition	.055(.019)	.330	.004**	.103	.557
WMH → Cognition	.206(.055)	.526	<.001**	.281	.771
WMH → Cortical Thickness	-.105(.044)	-.344	.015*	-.622	-.066
Cortical Thickness → Cognition	.185(.203)	.144	.341	-.153	.442
CHA_2DS_2-VASc-HSF → WMH → Cognition	.015(.012)	.092	.150	-.033	.216
CHA_2DS_2-VASc-HSF → Cortical Thickness → Cognition	-.006(.008)	-.035	.464	-.128	.058
CHA_2DS_2-VASc-HSF → WMH → Thickness → Cognition	-.001(.002)	-.009	.481	-.033	.015

** p<.01; *p<.05

Table 4. Standardized SEM results, EF and PS

				95% C.I.	
	B(S.E.)	β	*p*	*Lower*	*Upper*
CHA_2DS_2-VASc-HSF → WMH	.072(.049)	.168	.113	-.040	.376
CHA_2DS_2-VASc-HSF → Cortical Thickness	-.031(.014)	-.240	.024*	-.448	-.031
CHA_2DS_2-VASc-HSF → EF	.056(.018)	.335	.003**	.117	.554
CHA_2DS_2-VASc-HSF → PS	1.056(.419)	.319	.009**	.080	.558
WMH → EF	.198(.060)	.511	<.001**	.242	.780
WMH → PS	4.124(1.136)	.535	<.001**	.286	.784
WMH → Cortical Thickness	-.102(.044)	-.336	.018*	-.613	-.059
Cortical Thickness → EF	.036(.228)	.028	.864	-.297	.353
Cortical Thickness → PS	6.431(3.621)	.254	.035*	.018	.491
CHA_2DS_2-VASc-HSF → WMH → EF	.014(.011)	.086	.168	-.036	.208
CHA_2DS_2-VASc-HSF → Cortical Thickness → EF	-.001(.009)	-.007	.885	-.099	.085
CHA_2DS_2-VASc-HSF →WMH → PS	.298(.235)	.090	.165	-.037	.217
CHA_2DS_2-VASc-HSF → Cortical Thickness → PS	-.202(.154)	-.061	.196	-.153	.031
CHA_2DS_2-VASc-HSF → WMH → Thickness → EF	.000(.002)	-.002	.893	-.025	.022
CHA_2DS_2-VASc-HSF → WMH → Thickness → PS	-.048(.050)	-.014	.319	-.043	.014

** p<.01; *p<.05

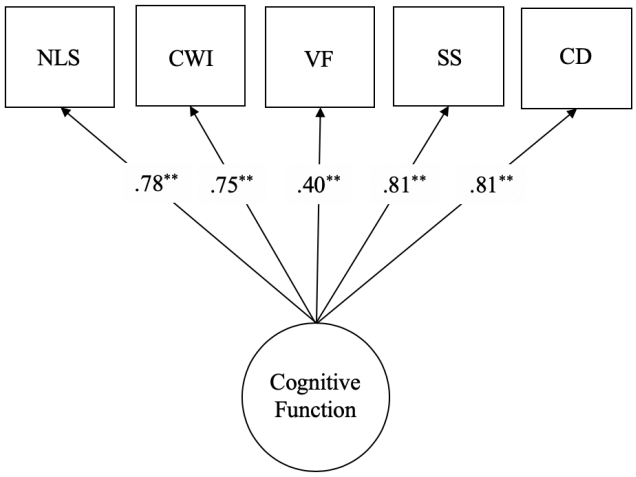

Figure 1. Measurement model for cognitive function.
Note. NLS = D-KEFS TMT Number-Letter Switching; CWI= D-KEFS Color Word Identification; VF=D-KEFS Verbal Fluency Category Switching; SS=WAIS-IV Symbol Search; CD=RBANS Coding
*p<.05, **p<.001

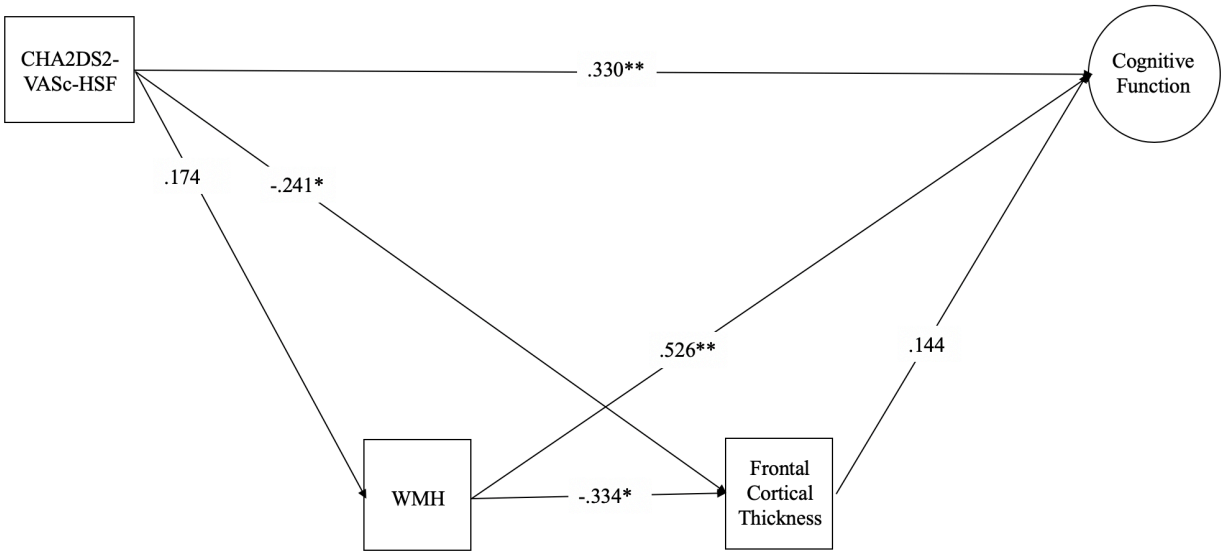

Figure 2. Standardized estimates for SEM model.
Note. WMH= white matter hyperintensities.
*p<.05, **p<.001

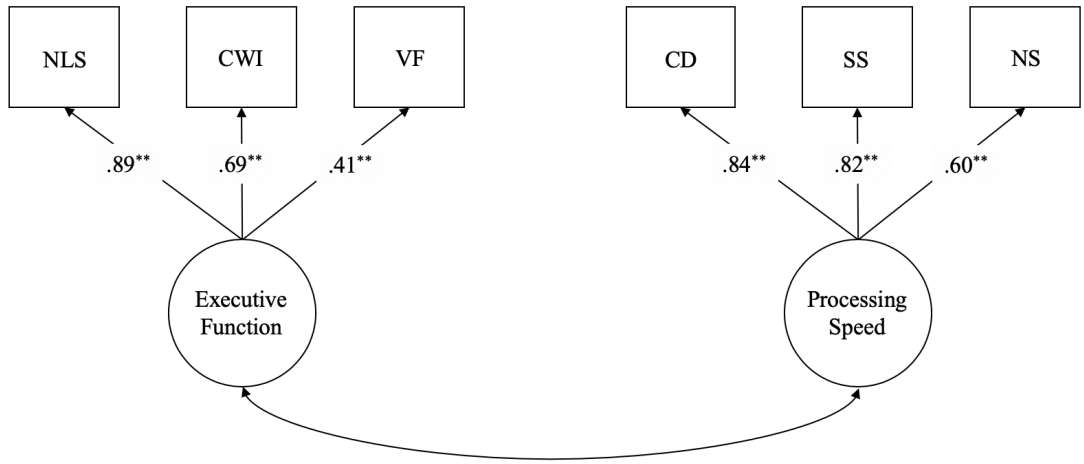

Figure 3. Measurement models for EF and processing speed.
Note. NLS = D-KEFS TMT Number-Letter Switching; CWI= D-KEFS Color Word Identification; VF=D-KEFS Verbal Fluency Category Switching; CD=RBANS Coding; SS=WAIS-IV Symbol Search; NS=D-KEFS TMT Number Sequencing
*p<.05, **p<.001

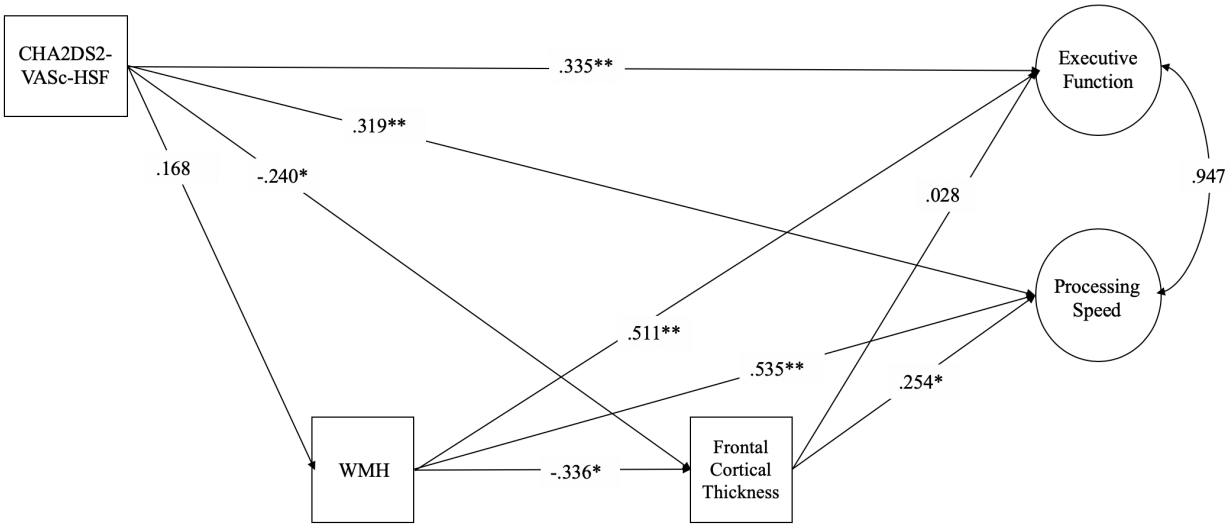

Figure 4. Standardized estimates for EF and processing speed SEM model.
Note. WMH= white matter hyperintensities.
*p<.05, **p<.001

CHAPTER 4

DISCUSSION

We tested the associations among CHA_2DS_2-VASc-HSF, WMH, frontal lobe cortical thickness, and cognitive function in a sample of generally healthy older adults. Specifically, we evaluated whether structural integrity (WMH and frontal cortical thickness) mediated the link between stroke risk (CHA_2DS_2-VASc-HSF) and cognitive function. CFA supported the classification of EF and processing speed, domains commonly associated with CVD status, into a latent factor reflecting variance in cognitive performance. There were three main findings of this study. The first was a significant association between CHA_2DS_2-VASc-HSF and cognitive function, where higher stroke risk was associated with poorer cognitive performance. Second, CHA_2DS_2-VASc-HSF was significantly negatively associated with frontal cortical thickness, but not WMH, with higher risk linked to cortical thinning. Third, greater WMH burden was associated with worse cognitive function and cortical thinning. There were no significant indirect effects via structural brain indices (WMH or frontal lobe cortical thickness). Extant literature posits both EF and processing speed as domains susceptible to vascular risk factors (Gorelick, et al., 2011; Wardlaw et al., 2013a, 2013b). However, there is some evidence that they represent different levels of cognitive function, and may reflect different neuropathological mechanisms. Thus, in an exploratory analysis, we tested a model where EF and processing speed effects were separately estimated. The CHA_2DS_2-VASc-HSF exhibited similar patterns with WMH and frontal cortical thickness, as would be expected from the primary analyses, and a higher risk score was significantly associated with both worse EF and worse processing speed performance.

Higher WMH burden was also associated with poorer performance in both EF and processing speed. Interestingly, greater frontal cortical thickness was significantly associated with slower processing speed but there was no association with EF. There were no significant indirect effects via either index of brain integrity.

Stroke risk was found to be associated with worse cognitive function both when estimated as an overall latent construct and when broken into EF and processing speed factors. These findings are consistent with the current literature and theories regarding cognitive outcomes related to CVD risk factors. There is a general consensus that risk factors associated with CVD and stroke are linked to poor cognitive outcomes, particularly in the domains of EF and processing speed (Duda et al., 2019; Eggermont et al., 2012; Vermeer et al., 2003). Our findings supported this notion by confirming links between the CHA_2DS_2-VASc-HSF and EF and processing speed by domain, but also by demonstrating that there is utility in considering latent commonalities underlying both of these cognitive domains. Importantly, our results extend the current research literature to demonstrate that EF and processing speed are linked to stroke risk factors even in the absence of stroke, significant CVD, or other neurological processes. The majority of studies to date have linked these stroke risk factors to cognitive function in populations with diagnosed pathology, such as overt stroke and chronic heart failure (Graff-Radford et al., 2016; Washida, Kowa, Hamaguchi, Kanda & Toda, 2017). Therefore, it was unclear whether cognitive differences associated with previous iterations of the CHA_2DS_2-VASc-HSF were due to vascular effects related to the risk factors or vascular accidents secondary to those risk factors. Because we restricted our sample to individuals without significant neurological and cardiovascular disease, findings extend the utility of this constellation of stroke risk factors in predicting cognitive function among generally healthy older adults.

In contrast to cognitive function, which exhibited consistent associations with stroke risk across domains, structural brain indices exhibited different patterns. In line with previous findings that frontal lobe regions are most greatly impacted by vascular risk (e.g., Seo et al., 2012), we found that greater CHA_2DS_2-VASc-HSF stroke risk was associated with frontal cortical thinning. However, we did not find WMH burden to be associated with stroke risk, as would have been expected based on prior literature (Gorelick, et al., 2011; Wardlaw et al., 2013a, 2013b). Prior work has shown WMH to be robustly associated with stroke risk factors due to vascular organization and mechanisms (Iadecola, 2013). However, there is still some ambiguity, particularly in older adults without severe CVD-related diagnoses. For example, a relatively recent study of a large community-based sample of older adults found diastolic and systolic blood pressure and high-density lipoprotein cholesterol to predict WMH, but diabetes, high blood pressure diagnosis, total cholesterol, and smoking did not (Dickie et al., 2016). Attempts to reconcile discordant conclusions about vascular risk factors and WMH have led some groups to classify WMH lesions according to location. For instance, deep WMH, as opposed to periventricular WMH load, has been shown to better differentiate between vascular dementia and Alzheimer's disease (Smith et al., 2016). Another study found frontal WMH to be highest in a group with vascular risk (Raz, Rodrigue, Kennedy, Acker, 2007). They also found that the fastest cortical shrinkage occurred in the prefrontal cortex. Based on the findings regarding frontal WMH in these studies, as well as the frontal cortical thickness results from the current study, it is possible that frontal lobe WMH may be more specifically related to the CHA_2DS_2-VASc-HSF stroke risk index.

In addition to WMH location, medication use has been found to have important implications for vascular-related neural consequences. In a recent study, angiotensin receptor blockers (ARB),

more so than angiotensin-converting enzyme (ACE) inhibitors, were predictive of vascular risk-related WMHs. Specifically, ARB use was associated with lower WMH burden in patients with Alzheimer's Disease; however, there was no protective effect for brain volume (Edwards et al., 2017). While this study found the effect to be specific to ARBs, researchers continue to longitudinally investigate the effect of treatment with ACE inhibitors and ARBs on progression of small vessel disease markers, including WMHs (Yamano et al., 2013). In the current study, 19% of the sample reported use of an ACE inhibitor and 2% reported ARB use. An additional 20% reported use of medications commonly associated with vascular risk factors (e.g., cholesterol, blood pressure, arrhythmia medications). While the protective role of medications in the progression of WMHs remains a topic of continued investigation, it is plausible that medication effects may protect specifically against marked WMH progression secondary to vascular risk. This may help to elucidate the observed association between the CHA_2DS_2-VASc-HSF and cortical thickness, but not WMH.

Pathways to cerebrovascular-related decline in brain structure are multifactorial, and other factors may have contributed to our findings. As described, occlusion via ischemic stroke contributes to cerebral hypoperfusion, which in turn precipitates the development of white matter lesions and cerebral atrophy often linked to cognitive dysfunction (Dichgans & Leys, 2017; Iadecola, 2013). However, it is clear that the factors described in this pathway do not fully explain association between vascular risk and outcomes. Animal models investigating molecular mechanisms have contributed to a more comprehensive understanding of the many pathways to cognitive decline. One useful model highlights several distinct processes that may precede neuronal atrophy and cell death (Hort, J, Vališ, M., Kuča, K., Angelucci, 2019). Common to these pathways is the initial role of hypoxia and ischemia. Oxidative stress has been shown to be

a key factor in precipitating cognitive decline (Liu & Zhang, 2012). Oxidative stress also triggers inflammatory processes in VCI (Wang, Norma, Srinivasan, & Rutledge, 2016). Animal models have shown that metalloproteinases released secondary to hypoxia causes damage to the blood-brain barrier and myelinated axons (Sood et al., 2009; Zhang, Chen, Ren, & Bao, 2006). Neuroinflammation contributes to chronic activation of microglia, subsequent increases in cytokines, and damage to astrocyte endfeet critical for cytoarchitecture in key brain regions, which have been associated with neuronal atrophy and cognitive impairment (Miwa, Okazaki, Sakaguchi, Mochizuki, & Kitagawa, 2016; Xu et al., 2016). Oxidative stress causing damage to endothelial cells that are central in secreting nitric oxide has been proposed as a separate pathway to cognitive dysfunction via vascular lesions (Stephan, Harrison, Keage, Babateen, Robinson, Siervo, 2017; Wang, Cao, Ma, Pei, Rausch, Li, 2018). Importantly, the mechanisms by which oxidative stress affects cognitive function may first be evident in alterations in synaptic activity and neurotransmission, rather than structural integrity (Tönnies & Trushina, 2017). Finally, there is evidence that decline in insulin-like growth factor-1 (IFG-1) due to age may cause vascular pathologies, triggering this cascade of events, and simultaneously directly impair synaptic activity leading to cognitive decline (Sonntag et al., 2013). Consideration of these alternative mechanisms may provide further insight regarding the association between the CHA_2DS_2-VASc-HSF and cortical thickness, independent of WMH. Further, steps that precede the development of markers observable on MRI may provide mechanistic targets for investigation in populations earlier in the progression of aging.

Regarding structural brain indices and cognitive function, findings for WMH were consistent across domains, while findings for cortical thickness were not. The observed associations between WMH and the full latent cognitive factor, as well as both EF and processing speed, fits

well with neural models for cognition. Both EF and processing speed are cognitive domains that are not localized to a particular brain region, but instead dependent on communication among brain regions subserved by white matter pathways. Thus, our findings bolster existing literature that posits the role of white matter integrity as a critical substrate of cognitive function. While we did not observe significant associations between cortical thickness and the full cognitive latent factor, our exploratory analysis revealed that there was a significant association with latent processing speed but not EF. Prior studies have implicated processing speed to be inversely associated with frontal cortical thickness due to the region's role in error correction, reaction time, initiation, and response adjustment (Alexander et al., 2007; Chee et al., 2009; Modirrousta and Fellows, 2008; Righart et al., 2013). Our findings, however, showed slower processing speed to be associated with greater cortical thickness. While this may initially appear to be counterintuitive, there is a growing body of literature that contests the notion that optimal cognitive functioning is reliant on greater cortical thickness. A recent study showed that better global cognition was associated with greater cortical surface area in prefrontal, lateral temporal and parietal regions and reduced surface area in medial temporal and occipital regions (Vuoksimaa et al., 2016). The opposite was true for cortical thickness, and frontal cortical thickness was found to be inversely associated with global cognition. Moreover, they found that in high-expanded regions (i.e., those that are lightly myelinated and myelinated later in life) such as the prefrontal cortex, cortical thickness and surface area are inversely related. Greater cortical gyrification has been theorized to be reflective of greater surface area expansion, which subsequently results in thinner cortex due to mechanical pressure associated with folding (Tallinen et al., 2013). Thus, particularly in healthy, high-functioning samples such as that of the

current study, cortical configuration may be important to examine when connecting findings to domains of cognitive function.

While the association of frontal cortical thickness with processing speed was not unexpected, it is surprising that EF was not similarly related since EFs are often thought of as frontal systems (Wen & Sachdev, 2004). Recent work in a sample of healthy adults has shown executive functioning to no longer significantly relate to cortical thickness once processing speed was controlled (MacPherson et al., 2017). Alternatively, rates of cortical thinning for different populations may provide additional insight. While frontal lobe thinning is predominant in CVD, studies in healthy older adults have found that, with the exception of the prefrontal cortex, thinning is concentrated in sensory and motor association areas (Artero et al., 2004; Raz et al., 2007; Ziegler et al 2010). Since healthy older adults appear to exhibit proportionally more thinning in sensory and motor areas, EF found to be associated with vascular-risk factors in this population may be more reflective of general neuronal changes. In other words, the multifaceted domain of EF is subserved by a complex network of brain regions not limited to frontal lobe, and subtle changes in any one lobe may not be substantial enough to impede compensatory processes. WMH, however, interrupts communication among critical brain regions in a way that may disrupt compensatory processes. Thus, WMH may be a more sensitive marker for higher-order cognitive functions in healthy, low-risk individuals.

There are clearly many factors that differentially impact trajectories for neuronal structure alterations and cognitive decline that may be more relevant for individuals with low vascular risk or are at early stages of vascular-related neuronal progression. As a group, cognitive performance was in the average range when participants were compared to their same-age peers, despite the presence vascular-related risk factors. One possible explanation is that the

participants with stroke risk factors simply have not experienced chronic exposure to a degree that would result in cognitive decline. Alternatively, protective factors often associated with reserve may be promoting preservation of cognitive functioning for these individuals. Studies have suggested that brain reserve prior to the onset of aging processes and cognitive reserve may play protective roles as individuals age (Brickman et al., 2011). Brain reserve refers to the brain's capacity to afford more substantial pathological damage, while cognitive reserve refers to one's ability to cope with brain pathology due to factors such as education, occupational attainment, and social engagement (Brickman et al., 2009; Richards and Sacker, 2003; Stern 2009). Our sample was highly educated (M= 15.6 years), which is a key factor in the preservation of cognitive function despite risk and pathology. Unfortunately, investigation of factors promoting brain reserve and other markers of cognitive reserve was not feasible for this study. While the cross-sectional design and power of the current study does not allow us to address this potential explanation, it is important to consider protective factors when interpreting these results.

Several limitations are important to note. First, this study had a relatively low sample size and may not have had sufficient power to detect small effects (i.e., <0.1), particularly with regard to indirect effects. This sample size also limited the inclusion of additional possible mechanisms (e.g., inflammatory markers) in our model that may have been more sensitive in relatively healthy populations and for those at earlier stages of vascular-related processes. Additionally, the sample was highly educated and ethnically homogenous, limiting the generalizability of these findings. The age range of this sample was relatively young when compared to typical studies of older adults, and may not be the appropriate range to capture changes in brain structure in

healthy individuals. Finally, this study was cross-sectional in design. As a result, we were unable to investigate causal effects of stroke risk factors, structural changes and cognitive decline.

Despite these limitations, the findings from the present study lend important contributions to the literature and considerations for future work. Due to its ease of use and cost-effectiveness, earlier iterations of the CHA_2DS_2-VASc-HSF have already proven to be an effective tool in clinical practice (Lip, Nieuwlaat, Pisters, Lane, & Crijns, 2010). Validation of the CHA_2DS_2-VASc-HSF stratification index, and its association with cognitive outcomes and cortical thickness suggests that vascular risk factors can have effects even in the absence of overt diagnoses and vascular events. Thus, the CHA_2DS_2-VASc-HSF may have utility in informing need for early intervention in non-clinical older adults. Still, further investigation is warranted before the CHA_2DS_2-VASc-HSF index is utilized in non-clinical samples. First, longitudinal investigations are needed in order to determine whether the CHA_2DS_2-VASc-HSF is predictive of cognitive outcomes and neural changes. Longitudinal studies, particularly those with larger sample sizes, would allow more comprehensive investigation of vascular risk and alternative neural mechanisms (e.g., frontal WMH, inflammatory markers, cortical configuration) that precede changes in cognitive function. Specifically, studies that determine the most effective markers at various stages of aging have great potential to improve risk identification. Additionally, studies that determine more specific risk stratification scoring classifications for low-risk samples are needed. Recommended cutoffs for older adults without clinical diagnoses are currently unclear. Appropriate classification of risk through studies that investigate longitudinal outcomes and promote precision in risk stratification are critical in determining the extent of intervention required. For example, while individuals without atrial fibrillation, stroke risk, or other diagnosis may have exposure to vascular risk factors that warrant anticoagulation

therapy, others may benefit from lower levels of interventions and/or preventative measures such as physical activity, diet modifications, or cognitive training interventions (Bahar-Fuchs et al., 2013; Psaltopoulou et al., 2013; Schmidt et al., 2013). Future work investigating the generalizability of the CHA_2DS_2-VASc-HSF, not only in its application to non-clinical samples, but across age and other demographic factors including race, ethnicity, socioeconomic status, and education levels is needed.

In conclusion, the results of this study highlight the impact of stroke risk factors on neuronal structural integrity and cognitive function in a sample of relatively low-risk, community-dwelling older adults. Our findings support the notion that EF and processing speed may be susceptible to vascular-related processes in the absence of overt stroke or significant CVD diagnoses. While structural integrity was not a mechanism for this association in our sample, direct effects among stroke risk, structural integrity, and cognitive function may implicate the role of processes not accounted for in this model. Still, our study offers support for the utility of the recently updated CHA_2DS_2-VASc-HSF in identifying sequelae related to vascular processes, and the critical need to continue research that attempts to improve early identification of risk.

REFERENCES

Abraham, H.M.A., Wolfson, L., Moscufo, N., Guttmann, C.R., Kaplan, R.F., & White, W.B. (2015). Cardiovascular risk factors and small vessel disease of the brain: Blood pressure, white matter lesions, and functional decline in older persons. *Journal of Cerebral Blood Flow & Metabolism, 36*, 132–142.

Alexander, M.P., Stuss, D.T., Picton, T., Shallice, T., Gillingham, S. (2007). Regional frontal injuries cause distinct impairments in cognitive control. *Neurology, 68,* 1515-1523.

Allan, L.M., Rowan, E.N., Firbank, M.J., Thomas, A.J., Parry, S.W., Polvikoski, T.M., … Kalaria, R.N. (2011). Long term incidence of dementia, predictors of mortality and pathological diagnosis in older stroke survivors. *Brain, 134,* 3716–3727.

Alosco, M.L., Brickman, A.M., Spitznagel, M.B., Garcia, S.L., Narkhede, A., Griffith, E.Y., … Gunstad, J. (2013). Cerebral perfusion is associated with white matter hyperintensities in older adults with heart failure. *Congest. Heart Fail., 19,* E29–E34.

An, H., Ford, A.L., Vo, K., Eldeniz, C., Ponisio, R., Zhu, H., … Lin,W. (2011). Early changes of tissue perfusion after tissue plasminogen activator in hyperacute ischemic stroke. *Stroke; a Journal of Cerebral Circulation 42,* 65–72.

Appelman, A.P.A., Exalto, L.G., van der Graaf, Y., Biessels, G.J., Mali, W.P.T.M., & Geerlings, M.I. (2009). White matter lesions and brain atrophy: more than shared risk factors? A systematic review. *Cerebrovasc. Dis. 28*, 227–242.

Aribisala, B.S., Valdes Hernandez, M.C., Royle, N.A., Morris, Z., Munoz Maniega, S., Bastin, M.E., … Wardlaw, J.M. (2013). Brain atrophy associations with white matter lesions in the ageing brain: the Lothian Birth Cohort 1936. *European Radiology, 23*, 1084-1092.

Artero, S., Tiemeier, H., Prins, N.D., Sabatier, R., Breteler, M.M., Ritchie, K. (2004). Neuroanatomical localization and clinical correlates of white matter lesions in the elderly. *J. Neurol. Neurosurg. Psychiatry, 75*, 1304-1308.

Ashrafi, F., Taheri, M.S., Farzaneh, A., Behnam, B., & Ahmadi, M.A. (2019). Cognitive functions and white matter lesions on magnetic resonance images in a sample of normal Iranian population with cardiovascular risk factors. *The Neuroradiology Journal, 32,* 108-114.

Bagher, P. & Segal, S.S. (2011). Regulation of blood flow in the microcirculation: role of conducted vasodilation. *Acta Physiol. (Oxf.) 202*, 271–284.

Bahar-Fuchs, A., Clare, L., &Woods, B. (2013). Cognitive training and cognitive rehabilitation for mild to moderate Alzheimer's disease and vascular dementia. Cochrane database of systematic reviews, 2013 (6), CD003260.

Bakker, S.L., de Leeuw, F.E., de Groot, J.C., Hofman, A., Koudstaal, P.J., & Breteler, M.M. (1999). Cerebral vasomotor reactivity and cerebral white matter lesions in the elderly. *Neurology, 52,* 578–583.

Benson, N., Hulac, D.M., & Kranzler, J.H. (2010). Independent Examination of the Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV): What Does the WAIS-IV Measure? *Psychological Assessment, 22,* 121-130.

Bentler, P.M. & Chou, C. (1987) Practical Issues in Structural Modeling. *Sociological Methods and Research, 16,* 78- 117.

Black, S., Gao, F., & Bilbao, J. (2009). Understanding white matter disease: imaging-pathological correlations in vascular cognitive impairment. *Stroke 40 (Suppl),* S48–S52.

Blinder, P., Tsai, P.S., Kaufhold, J.P., Knutsen, P.M., Suhl, H., & Kleinfeld, D. (2013). The cortical angiome: an interconnected vascular network with noncolumnar patterns of blood flow. *Nat. Neurosci. 16,* 889–897.

Brady, C. B., Spiro, A., III, McGlinchey-Berroth, R., Milberg, W., & Gaziano, J. M. (2001). Stroke risk predicts verbal fluency decline in healthy older men: Evidence from the Normative Aging Study. *Journals of Gerontology Series B, 56,* 340–346.

Brickman, A.M., Siedlecki, K.L., Muraskin, J., Manly, J.J., Luchsinger, J.A., Yeung, L.-K., … Stern, Y. (2011). White matter hyperintensities and cognition: testing the reserve hypothesis. *Neurobiol. Aging, 32,* 1588–1598.

Bryan, R.N., Wells, S.W., Miller, T.J., Elster, A.D., Jungreis, C.A., Poirier, V.C., … Manolio, T.A. (1997). Infarct-like lesions in the brain: prevalence and anatomic characteristics at MR imaging of the elderly--data from the Cardiovascular Health Study. *Radiology, 202,* 47-54.

Camm, A.J., Lip, G.Y., De Caterina, R., Savelieva, I., Atar, D., Hohnloser, S.H; ESC Committee for Practice Guidelines (CPG). (2012). 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J, 33,* 2719-47. doi: 10.1093/eurheartj/ehs253.

Cardenas, B.A., Reed, B., Chao, L.L., Chui, H., Sanossian, N., DeCarli, C.C., … Weiner, M.W. (2012). Associations Among Vascular Risk Factors, Carotid Atherosclerosis, and Cortical Volume and Thickness in Older Adults. *Stroke, 43*, 2865-2870.

Carlozzi, N.E., Horner, M.D., Yang, C., & Tilley, B.C. (2015). Factor Analysis of the Repeatable Battery for the Assessment of Neuropsychological Status. *Applied Neuropsychology, 17,* 8-17.

Cerit, L., Kemal, H., Günsel, A., & Duygu, H. (2016). Double-edged blind, hemorrhagic or cardioembolic cognitive impairment. *Journal of geriatric cardiology: JGC, 13*, 724–726.

Cetin, M., Cakaci, M., Zencir, C., Tasolar, H., Baysal, E., Balli, M., & Akturk, E. (2014). Prediction and Coronary Artery Disease Severity Using CHADS2 and CHA2DS2-VASc and a Newly Defined CHA2DS2-VASc-HS score. *Am J Cardiol, 113*, 950-956.

Chee, M.W.L., Chen, K.H.M., Zheng, H., Chan, K.P.L., Issac, V., Sim, S.K.Y., … Ng, T.P. (2009). Cognitive function and brain structure correlations in healthy elderly East Asians. *NeuroImage, 46*, 257-*269.*

Chen, F.F. (2007). Sensitivity of Goodness of Fit Indexes to Lack of Measurement Invariance. *Structural Equation Modeling: A Multidisciplinary Journal, 14*, 464-504.

Chui, H.C. & Ramirez-Gomez, L. (2015). Clinical and imaging features of mixed Alzheimer and vascular pathologies. *Alzheimers Res Ther, 7*.

Chui, H.C. & Ramirez Gomez, L. (2017). Vascular contributions to cognitive impairment in late life. *Neurologic Clinics, 35,* 295–323.

Cohen, R. A., Poppas, A., Forman, D. E., Hoth, K. F., Haley, A. P., Gunstad, J., et al. (2009). Vascular and cognitive functions associated with cardiovascular disease in the elderly. *Journal of Clinical and Experimental Neuropsychology, 31,* 96–110.

Dan, Y., & Poo, M.M. (2004). Spike timing-dependent plasticity of neural circuits. *Neuron 44,* 23–30.

Davey, A. & Salva, J. (2009). Statistical power analysis with missing data: A structural equation modeling approach. New York, NY: Routledge.

Debette, S., Seshadri, S., Beiser, A., Au, R., Himali, J. J., Palumbo, C., et al. (2011). Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. *Neurology, 77*, 461–468.

de Leeuw, F.E., de Groot, J.C., Achten, E., Oudkerk, M., Ramos, LM., Heijboer, R., … Breteler, M.M. (2001). Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam Scan Study. *J Neurol Neurosurg Psychiatry, 70,* 9–14.

Delis, D.C., Kramer, J.H., Kaplan, E., & Holdnack, J., (2004). Reliability and validity of the Delis-Kaplan Executive Function System: an update. *Journal of the International Neuropsychological Society, 10*, 310-313.

De Right, J., Jorgensen, R. S., & Cabral, M. J. (2015). Composite cardiovascular risk scores and neuropsychological functioning: A meta-analytic review. *Annals of Behavioral Medicine, 49*, 344–357.

De Reuck, J. (1971). The human periventricular arterial blood supply and the anatomy of cerebral infarctions. *Eur. Neurol. 5,* 321–334.

Desikan, R.S., Segonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., … Killiany, R.J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage, 31*, 968-980.

Dichgans, M. and Leys, D. (2017). Vascular Cognitive Impairment. *Circulation Research, 120,* 573-591.

Dickie, D.A., Karama, S., Ritchie, S.J., Cox, S.R., Sakka, E., Royle, N.A., … Wardlaw, J.M. (2016). Progression of White Matter Disease and Cortical Thinning Are Not Related in Older Community-Dwelling Subjects. *Stroke, 47*, 410-416.

Ding, L., Velicer, W.F., & Harlow, L.L. (1995). Effects of estimation methods, number of indicators per factor, and improper solutions on structural equation modeling fit indices. *Structural Equation Modeling: A Multidisciplinary Journal, 2*, 119-143,

Dregan, A., Stewart, R., & Gulliford, M. C. (2013). Cardiovascular risk factors and cognitive decline in adults aged 50 and over: A population-based cohort study. *Age and Ageing, 42*, 338–45.

Duda, B.M., Keith, C.M., & Sweet, L.H. (2019). CHA2DS2-VASc Stroke Risk Index and Executive Functioning in Older Adults. *Archives of Clinical Neuropsychology*, acz031.

Duff, K., Langbehn, D.R., Schoenberg, M.R., Moser, D.J., Baade, L.E., Mold, J., … Adams, R.L. (2007). The repeatable battery for the assessment of neuropsychological status: factor analytic studies in an elderly sample. *Am J Geriatric Psychiatry, 14*, 976-979.

Edwards, J.D., Ramirez, J., Callahan, B.L., Tobe, S.W., Oh, P., Berezuk, C., … Black, S.E.; Alzheimer's Disease Neuroimaging Initiative. (2017). Antihypertensive Treatment is associated with MRI-Derived Markers of Neurodegeneration and Impaired Cognition: A Propensity-Weighted Cohort Study. *Journal of Alzheimer's Disease, 59,* 1113-1122.

Eggermont, L.H.P., de Boer, K.., Muller, M., Jaschke, A.C., Kamp, O., & Scherder, E.J.A. (2012). Cardiac disease and cognitive impairment: A systematic review. *Heart, 98*, 1334–1340.

Evans, T.E., O'Sullivan, M.J., de Groot, M., Niessen, W.J., Hofman, A., Krestin, G.P., … Ikram, M.A. (2016). White matter microstructure improves stroke risk prediction in the general population. *Stroke, 47*, 2756–2762.

Fernando, M.S., Simpson, J.E., Matthews, F., Brayne, C., Lewis, C.E., Barber, R., … Wharton, S.B. (2006). White matter lesions in an unselected cohort of the elderly molecular pathology suggests origin from chronic hypoperfusion injury. *Stroke, 37*, 1391–1398.

Fischl, B., Salat, D.H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., … Dale, A.M. (2002). Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron, 33*, 341-355.

Fischl, B., van der Kouwe, A., Destrieux, C., Halgren, E., Segonne, F., Salat, D.H., … Dale, A.M. (2004). Automatically Parcellating the Human Cerebral Cortex. *Cerebral Cortex, 14*, 11-22.

Friberg, L., Rosenqvist, M., and Lip, G.Y.H. (2012). Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *European Heart Journal, 33*, 1500-1510.

Gage, B.F., Waterman, A.D., Shannon, W., Boechler, M., Rich, M., & Radford, M.J. (2001). Validation of clinical classification schemes for predicting stroke: Results from the National Registry of atrial fibrillation. *JAMA, 285*, 2864-2870.

Ganguli, M. (2011). Epidemiology of dementia. Abou-Saleh, M.T., Katona, C., Kumar, A. (Ed). Hoboken, NJ: Wiley.

Geerlings, M.I., Appelman, A.P.A., Vincken, K.L., Algra, A., Witkamp, T.D., Mali, W.P.T.M., & the SMART Study Group. (2010). Brian volumes and cerebrovascular lesions on MRI

in patients with atherosclerotic disease. The SMART-MR study. *Atherosclerosis, 210*, 130-136.

Gelber, R.P., Launer, L.J., & White, L.R. (2012). The Honolulu-Asia Aging Study: epidemiologic and neuropathologic research on cognitive impairment. *Curr. Alzheimer Res. 9,* 664–672.

Gerbing, D. W. & Anderson, J. (1992). Monte Carlo Evaluations of Goodness of Fit Indices for Structural Equation Models. *Sociological Methods & Research, 21,* 132-160.

Gorelick, P.B., Scuteri, A., Black, S.E., Decarli, C., Greenberg, S.M., Iadecola, C., … American Heart Association Stroke Council, Council on Epidemiology and Prevention, Council on Cardiovascular Nursing, Council on Cardiovascular Radiology and Intervention, and Council on Cardiovascular Surgery and Anesthesia (2011). Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American heart association/American stroke association. *Stroke, 42*, 2672–2713.

Gottesman, R.F., Albert, M.S., Alonso, A., Coker, L.H., Coresh, J., Davis, S.M., et al. (2017). Associations between midlife vascular risk factors and 25-year incident dementia in the atherosclerosis risk in communities (ARIC) cohort. *JAMA Neurology, 74*, 1246–1254.

Gouw, A.A., Seewann, A., Van Der Flier, W.M., Barkhof, F., Rozemuller, A.M., Scheltens, P., & Geurts, J.J. (2011). Heterogeneity of small vessel disease: A systematic review of MRI and histopathology correlations. *Journal of Neurology, Neurosurgery & Psychiatry, 82*, 126–135.

Graff-Radford, J., Madhavan, M., Vemuri, P., Rabinstein, A.A., Cha, R. H., Mielke, M.M., … Roberts, R.O. (2016). Atrial fibrillation, cognitive impairment, and neuroimaging. *Alzheimer's & Dementia, 12,* 391–398.

Gupta, A., Giambrone, A.E., Gialdini, G., Finn, C., Delgado, D., Gutierrez, J., … Kamel, H. (2016). Silent Brain Infarction and Risk of Future Stroke: A Systematic Review and Meta-Analysis. *Stroke, 47,* 719-725.

Hartikainen, P., Räsänen, J., Julkunen, V., Niskanen, E., Hallikainen, M., Kivipelto, M., … Soininen, H. (2012). Cortical thickness in frontotemporal dementia, mild cognitive impairment, and Alzheimer's disease. *Journal of Alzheimer's Disease: JAD, 30,* 857–874.

Hort, J., Vališ, M., Kuča, K., and Angelucci, F. (2019). Vascular Cognitive Impairment: Information from Animal Models on the Pathogenic Mechanisms of Cognitive Deficits. Int J Mol Sci, 20, 2405.

Hoth, K. F., Poppas, A., Moser, D. J., Paul, R. H., & Cohen, R. A. (2008). Cardiac dysfunction and cognition in older adults with heart failure. *Cognitive and Behavioral Neurology, 21*, 65–72.

Howard, G., Wagenknecht, L.E., Cai, J., Cooper, L., Kraut, M.A., & Toole, J.F. (1998). Cigarette smoking and other risk factors for silent cerebral infarction in the general population. *Stroke, 29*, 913–17.

Hu, L. & Bentler, P.M. (1998). Fit Indies in Covariance Structure Modeling: Sensitivity to Underparameterized Model Misspecification. *Psychological Methods, 3,* 424-453.

Hu, L. & Bentler, P.M. (1999). Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria vs new alternatives. *Structural Equation Modeling, 6,* 1-55.

Iadecola, C. (2013). The Pathobiology of Vascular Dementia. *Neuron Review, 80*, 844-866.

Inzitari, D., Pracucci, G., Poggesi, A., Carlucci, G., Barkhof, F., Chabriat, H., … LADIS Study Group (2009). Changes in white matter as determinant of global functional decline in

older independent outpatients: three year follow-up of LADIS (leukoaraiosis and disability) study cohort. *BMJ, 339,* b2477.

Jefferson, A. L., Poppas, A., Paul, R. H., & Cohen, R. A. (2007). Systemic hypoperfusion is associated with executive dysfunction in geriatric cardiac patients. *Neurobiology of aging, 28*, 477–483.

Jellinger, K.A. (2013). Pathology and pathogenesis of vascular cognitive impairment-a critical update. *Front Aging Neurosci 5,* 17.

Jokinen, H., Gouw, A.A., Madureira, S., Ylikoski, R., van Straaten, E.C.W., van der Flier, W.M., … LADIS Study Group (2011). Incident lacunes influence cognitive decline: the LADIS study. *Neurology, 76*, 1872–1878.

Justin, B.N., Turek, M., & Hakim, A.M. (2013). Heart disease as a risk factor for dementia. *Clin. Epidemiol. 5*, 135–145.

Kaufman, A. S., & Lichtenberger, E. O. (2006). *Assessing adolescent and adult intelligence*. Hoboken, NJ: Wiley.

Kim, T.H., Yang, P.S., Kim, D., Yu, H.T., Uhm, J.S., Kim, J.Y., … Lip, G.Y.H. (2017). CHA2DS2-VASc Score for Identifying Truly Low-Risk Atrial Fibrillation for Stroke: A Korean Nationwide Cohort Study. *Stroke, 48*, 2984-2990.

King, K.S., Peshock, R.M., Rossetti, H.C., McColl, RW., Ayers, C.R., Hulsey, K.M., & Das, S.R. (2014). Effect of normal aging versus hypertension, abnormal body mass index, and diabetes mellitus on white matter hyperintensity volume. *Stroke, 45,* 255–257.

Kloppenborg, R.P., Nederkoorn, P.J., Geerlings, M.I., & van den Berg, E. (2014). Presence and progression of white matter hyperintensities and cognition a meta-analysis. *Neurology, 82,* 2127–2138.

Kondo, T., Yamada, T., Morita, T., Furukawa, Y., Tamaki, S., Iwasaki, Y., … Fukunami, M. (2017). The CHADS2 score predicts ischemic stroke in chronic heart failure patients without atrial fibrillation: comparison to other stroke risk scores. *Heart Vessels, 32,* 193-200.

Lee, I.H., You, J.H., Lee, J.Y., Whang, K., Kim, M.S., Kim, Y.J., Lee, M.S., Brain Research Group. (2010). Accuracy of the detection of infratentorial stroke lesions using perfusion CT: an experimenter-blinded study. *Neuroradiology, 52*, 1095–1100.

Lerch, J.P., & Evans, A.C. (2005). Cortical thickness analysis examined through power analysis and a population simulation*. Neuroimage 24*, 163–173.

Li, Q., Pardoe, H., Lichter, R., Werden, E., Raffelt, A., Cumming, T., & Brodtmann, A. (2015). Cortical thickness estimation in longitudinal stroke studies: A comparison of 3 measurement methods. *NeuroImage: Clinical, 8,* 526-535.

Li, Y., Wang, J., Lv, L., Xu., C., & Liu, H. (2018). Usefulness of the CHADS2 and R2CHADS scores for prognostic stratification in patients with coronary artery disease. *Clinical Interventions in Aging, 13,* 565-571.

Liebel, S.W., Jones, E. C., Oshri, A., Hallowell, E. S., Jerskey, B. A., Gunstad, J., … Sweet, L.H. (2017). Cognitive processing speed mediates the effects of cardiovascular disease on executive functioning. *Neuropsychology, 31*, 44–51.

Liebel, S. W., & Sweet, L. H. (2019). Effects of cardiovascular disease and related risk factors on neurocognition. In Stern, R. A., & Alosco, M. L. (Eds.), The Oxford Handbook of Adult Cognitive Disorders (pp. 84–116). New York, NY: Oxford University Press.

Lip, G.Y.H., Nieuwlaat, R., Pisters, R., Lane, D.A., & Crijns, H.J. (2010). Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a

novel risk factor-based approach: The Euro Heart Survey on Atrial Fibrillation. *Chest. 137*, 263-272.

Liu, H. and Zhang, J. (2012). Cerebral hypoperfusion and cognitive impairment: the pathogenic role of vascular oxidative stress. *Int J Neurosci, 122,* 494-499.

Lobo, A., Launer, L.J., Fratiglioni, L., Andersen, K., Di Carlo, A., Breteler, M.M., … Hofman, A. (2000). Prevalence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. *Neurology, 54*, S4–S9. 5.

MacCallum, R.C., Browne, M.W., & Sugawara, H.M. (1996). Power analysis and determination of sample size for covariance structural modeling. *Psychological Methods, 1,* 130–149.

MacPherson, S.E., Cox, S.R., Dickie, D.A., Karama, S., Starr, J.M., Evans, A.C., … Deary, I.J. (2017). Processing speed and the relationship between Tail Making Test-B performance, cortical thinning and white matter microstructure in older adults. *Cortex, 95,* 92-103.

Maillard, P., Carmichael, O., Fletcher, E., Reed, B., Mungas, D., & DeCarli, C. (2012). Coevolution of white matter hyperintensities and cognition in the elderly. *Neurology, 79*, 442–448.

Mandell, D.M., Han, J.S., Poublanc, J., Crawley, A.P., Kassner, A., Fisher, J.A., & Mikulis, D.J. (2008). Selective reduction of blood flow to white matter during hypercapnia corresponds with leukoaraiosis. *Stroke, 39,* 1993–1998.

Marshall, R.S. (2012). Effects of altered cerebral hemodynamics on cognitive function. *J. Alzheimers Dis. 32,* 633–642.

Meissner, A. (2016). Hypertension and the Brain: A Risk Factor for More Than Heart Disease. *Cerebrovascular Disease, 42*, 255-262.

Meyre, P., Eggimann, L., Beer, J.H., Bonati, L.H., Di Valentio, M., Kuehne, M., … S. Osswald. (2017). Cognitive function correlates with the CHA2DS2-VASc score in patients with atrial fibrillation: The Swiss atrial fibrillation cohort study. *European Heart Journal, 38.*

Miklossy, J. (2003). Cerebral hypoperfusion induces cortical watershed microinfarcts which may further aggravate cognitive decline in Alzheimer's disease. *Neurol. Res. 25*, 605–610.

Miwa, K., Okazak, S., Sakaguchi, M., Mochizuki, H., Kitagawa, K. (2016). Interleukin-6, interleukin-6 receptor gene variant, small-vessel disease and incident dementia. *Eur J Neurol, 23,* 656-663.

Modi, R., Patted, S.V., Halkati, P.C., Porwal, S., Ambar, S., Prasad, M.R., … Sattur, A. (2017). CHA2DS2-VASc-HSF score – New predictor of severity of coronary artery disease in 2976 patients. *International Journal of Cardiology, 228*, 1002-1006.

Modirrousta, M., Fellows, L.K. (2008). Dorsal medial prefrontal cortex plays a necessary role in rapid error prediction in humans. *Journal of Neuroscience, 28, 14000*-14005.

Moskowitz, M.A., Lo, E.H., & Iadecola, C. (2010). The science of stroke: mechanisms in search of treatments. *Neuron, 67,* 181–198.

Muthén, L.K. & Muthén, B.O. (2002). How to use a Monte Carlo study to decide on sample size and determine power. *Structural Equation Modeling, 9,* 599–620.

Nave, K.-A. (2010). Myelination and the trophic support of long axons. *Nat. Rev. Neurosci. 11*, 275–283.

Nguyen, J., Nishimura, N., Fetcho, R.N., Iadecola, C., & Schaffer, C.B. (2011). Occlusion of cortical ascending venules causes blood flow decreases, reversals in flow direction, and vessel dilation in upstream capillaries. *J. Cereb. Blood Flow Metab. 31*, 2243–2254.

Nishimura, N., Rosidi, N.L., Iadecola, C., & Schaffer, C.B. (2010). Limitations of collateral flow after occlusion of a single cortical penetrating arteriole. *J. Cereb. Blood Flow Metab. 30*, 1914–1927.

Nishtala, A., Himali, J. J., Beiser, A., Murabito, J. M., Seshadri, S., Wolf, P. A., et al. (2015). Midlife hypertension risk and cognition in the non-demented oldest old: Framingham heart study. *Journal of Alzheimer's Disease, 47*, 197–204.

Nitkunan, A., Lanfranconi, S., Charlton, R.A., Barrick, T.R., & Markus, H.S. (2011). Brain atrophy and cerebral small vessel disease: a prospective follow-up study. *Stroke, 42*, 133–138.

Ntaios, G., Lip, G. Y., Makaritsis, K., Papavasileiou, V., Vemmou, A., Koroboki, E., … Vemmos, K. (2013). CHADS2, CHA2DS2-VASc, and long-term stroke outcome in patients without atrial fibrillation. *Neurology, 80,* 1009–1017.

O'Brien J.T., Erkinjuntti T., Reisberg B., Roman, G., Sawada, T., Pantoni, L., … DeKosky, S.T. (2003). Vascular cognitive impairment. *Lancet Neurology, 2*, 89–98.

Olesen, J.B., Torp-Pedersen, C., Hansen, M.L., & Lip, G.Y. (2012). The value of the CHA2DS2-VASc score for refining stroke risk stratification in patients with atrial fibrillation with a CHADS2 score 0–1: A nationwide cohort study. *Thrombosis and haemostasis, 108,* 1172–1179.

Pantoni, L. (2010). Cerebral small vessel disease: From pathogenesis and clinical characteristics to therapeutic challenges. *The Lancet Neurology, 9,* 689–701.

Paoletti Perini, A., Bartolini, S., Pieragnoli, P., Ricciardi, G., Perrotta, L., Valleggi, A., … Padeletti, L. (2013). CHADS2 and CHA2DS2-VASc scores to predict morbidity and

mortality in heart failure patients candidates to cardiac resynchronization therapy. *Europace, 16,* 71–80.

Perk, J., De Backer, G., Gohlke, H., Graham, I., Reiner, Z., Verchuren, M., … Zannad, F. (2012). European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *European Heart Journal, 33,* 1635–1701.

Piyaskulkaew, C., Singh, T., Szpunar, S., Saravolatz II., L., & Rosman, H. (2014). CHA_2DS_2-VASc versus $CHADS_2$ for stroke risk assessment in low-risk patients with atrial fibrillation: a pilot study from a single center of the NCDR-PINNACLE registry. *J Thromb Thrombolysis, 37*, 400-403.

Preacher, K.J. & Hayes, A.F. (2008). Asymptotic and Resampling Strategies for Assessing and Comparing Indirect Effects in Multiple Mediator Models. *Behavior Research Methods, 40,* 879-891.

Prins, N.D. & Scheltens, P. (2015). White matter hyperintensities, cognitive impairment and dementia: An update. *Nature Reviews Neurology, 11*, 157–165.

Psaltopoulou, T., Sergentanis, T. N., Panagiotakos, D. B., Sergentanis, I. N., Kosti, R., & Scarmeas, N. (2013).Mediterranean diet, stroke, cognitive impairment, and depression: A meta-analysis. Annals of neurology, 74 (4), 580–591.

Randolph, C. (1998). Repeatable Battery for the Assessment of Neuropsychological Status: Manual. San Antonio, TX: The Psychological Corporation.

Raz, N., Rodrigue, K.M., Kennedy, K.M., and Acker, J.D. (2007). Vascular health and longitudinal changes in brain and cognition in middle-aged and older adults. *Neuropsychology, 21,* 149-147.

Righart, R., Duering, M., Gonik, M., Jouvent, E., Reyes, S., Hervé, D., Chabriat, H., Dichgans, M. (2013). Impact of regional cortical and subcortical changes on processing speed in cerebral small vessel disease. *NeuroImage: Clinical 2,* 854-861.

Rohrer, J.D., Warren, J.D., Modat, M., Ridgway, G.R., Douiri, A., Rossor, M.N., … Fox, N.C. (2009). Patterns of cortical thinning in the language variants of frontotemporal lobar degeneration. *Neurology, 72*, 1562–1569.

Román, G.C. (2003). Vascular dementia: Distinguishing characteristics, treatment, and prevention. *Journal of the American Geriatrics Society, 51*, S296–S304.

Sacco, R.L., Kasner, S.E., Broderick, J.P., Caplan, L.R., Connors, J.J., Culebras, A., … Vinters HV, American Heart Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia, Council on Cardiovascular Radiology and Intervention, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention, Council on Peripheral Vascular Disease, and Council on Nutrition. (2013). Physical activity and Metabolism: An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke, 44*, 2064–2089.

Schaapsmeerders, P., Maaijwee, N.A.M., van Dijk, E.J., Rutten-Jacobs, L.C.A., Arntz, R.M., Schoonderwaldt, H.C., … de Leeuw, F.E. (2013). Long-term cognitive impairment after first-ever ischemic stroke in young adults. *Stroke, 44,* 1621–1628.

Schermelleh-Engel, K., Moosbrugger, H., & Müller, H. (2003). Evaluating the Fit of Structural Equation Models: Tests of Significance and Descriptive Goodness-of-Fit Measures. *Methods of Psychological Research, 8,* 23–74.

Schmidt,W., Endres, M., Dimeo, F., & Jungehulsing, G. J. (2013). Train the vessel, gain the brain: Physical activity and vessel function and the impact on stroke prevention and outcome in cerebrovascular disease. Cerebrovascular diseases, 35 (4), 303–312.

Scuteri, A., Nilsson, P.M., Tzourio, C., Redon, J., and Laurent, S. (2011). Microvascular brain damage with aging and hypertension: pathophysiological consideration and clinical implications. *J. Hypertens. 29,* 1469–1477.

Seo, S.W., Lee, J.M., Im, K., Park, J.-S., Kim, S.-H., Kim, S.T., … Na, D.L. (2012). Cortical thinning related to periventricular and deep white matter hyperintensities. *Neurobiol. Aging, 33,* 1156–1167.

Shih, A.Y., Blinder, P., Tsai, P.S., Friedman, B., Stanley, G., Lyden, P.D., & Kleinfeld, D. (2013). The smallest stroke: occlusion of one penetrating vessel leads to infarction and a cognitive deficit. *Nat. Neurosci. 16,* 55–63.

Shrout, P.E. & Bolger, N. (2002). Mediation in Experimental and Nonexperimental Studies: New Procedures and Recommendations. *Psychological Methods, 7,* 422-445.

Smith, C.D., Johnson, E.S., Eldik, L.J., Jicha, G.A., Schmitt, F.A., Nelson, P.T. … Wellnitz, C.V. (2016). Peripheral (Deep) but not periventricular MRI white matter hyperintensities are increased in clinical vascular dementia compared to Alzheimer's disease. *Brain Behav, 16*, e00438.

Sonntag, W.E., Deak, F., Ashpole, N., Toth, P., Csiszar, A., Freeman, W., Ungvari, Z. (2013). Insulin-like growth factor-1 in CNS and cerebrovascular aging. *Front Aging Neurosci, 5*, 27.

Sood, R., Yang, Y., Taher, S., Candelario-Jalil, E., Estrada, E.Y., Walker, E.J., … Rosenberg, G.A. (2009). Increased apparent diffusion coefficients on MRI linked with matrix metalloproteinases and edema in white matter after bilateral carotid artery occlusion in rats. *J Cereb Blood Flow Metab, 29*, 308-316.

Sörös, P., Whitehead, S., Spence, J.D., & Hachinski, V. (2013). Antihypertensive treatment can prevent stroke and cognitive decline. *Nat. Rev. Neurol. 9,* 174–178.

Stefansdottir, H., Arnar, D.O., Aspelund, T., Sigurdsson, S., Jonsdottir, M.K., Hjaltason, H., … Gudnason, V. (2013). Atrial fibrillation is associated with reduced brain volume and cognitive function independent of cerebral infarcts. *Stroke, 44,* 1020–1025.

Stephan, B.C.M., Harrison, S.L., Keage, H.A.D., Babateen, A., Robinson, L., Siervo, M. (2017). Cardiovascular Disease, the Nitric Oxide Pathway and Risk of Cognitive Impairment and Dementia. *Curr Cardiol Rep, 19,* 87.

Stone, D.B. & Tesche, C.D. (2013). Topological dynamics in spike-timing dependent plastic model neural networks. *Front. Neural Circuits 7,* 70.

Suter, O.-C., Sunthorn, T., Kraftsik, R., Straubel, J., Darekar, P., Khalili, K., & Miklossy, J. (2002). Cerebral hypoperfusion generates cortical watershed microinfarcts in Alzheimer disease. *Stroke 33,* 1986–1992.

Tallinen, T., Chung, J.Y., Biggins, J.S., Mahadevan, L. (2014). Gyrification from constrained cortical expansion. *PNAS, 111,* 12667-12672.

Tomlinson, B.E., Blessed, G., & Roth, M. (1970). Observations on the brains of demented old people. *J. Neurol. Sci. 11*, 205–242.

Tönnies, E. and Trushina, E. (2017). Oxidative Stress, Synaptic Dysfunction, and Alzheimer's Disease. *J Alzheimers Disease, 57*, 1105-1121.

Tsubota-Utsugi, M., Satoh, M., Tomita, N., Hara, A., Kondo, T., Hosaka, M., … Ohkubo, T. (2017). Lacunar infarcts rather than white matter hyperintensity as a predictor of future higher-level functional decline: The Ohasama study. *J Stroke Cerebrovasc Disease, 26*, 376–384.

Tullberg, M., Fletcher, E., DeCarli, C., Mungas, D., Reed, B.R., Harvey, D.J., … Jagust, W.J. (2004). White matter lesions impair frontal lobe function regardless of their location. *Neurology, 63*, 246-253.

Ueda, T., Kawakami, R., Nishida, T., Onoue, K., Soeda, T., Okayama, S., … Saito, Y. (2015). Left Ventricular Ejection Fraction (EF) of 55% as Cutoff for Late Transition from Heart Failure (HF) With Preserved EF to HF With Mildly Reduced EF. *Circulation Journal, 79,* 2209-2215.

Vermeer, S.E., Prins, N.D., den Heijer, T., Hofman, A., Koudstaal, P.J., & Breteler, M.M.B. (2003). Silent Brain Infarcts and the Risk of Dementia and Cognitive Decline. *The New England Journal of Medicine, 348,* 1215-1222.

Vernooij, M.W., van der Lugt, A., Ikram, M.A., Wielopolski, P.A., Vrooman, H.A., Hofman, A., … Breteler, M.M.B. (2008). Total cerebral blood flow and total brain perfusion in the general population: the Rotterdam Scan Study. *J. Cereb. Blood Flow Metab. 28*, 412–419.

Vuoksimaa, E., Panizzon, M.S., Chen, C.H., Fiecas, M., Eyler, L.T., Fennema-Notestine, C., … Kremen, W.S. (2016). Is bigger always better? The importance of cortical configuration with respect to cognitive ability. *Neuroimage, 129,* 356-366.

Waldstein, S. R., Giggey, P. P., Thayer, J. F., & Zonderman, A. B. (2006). Nonlinear relations of blood pressure to cognitive function: The Baltimore longitudinal study of aging. *Hypertension, 45,* 374–379.

Wang, F., Cao, Y., Ma, L., Pei, H., Rausch, W.D., Li, H. (2018). Dysfunction of Cerebrovascular Endothelial Cells: Prelude to Vascular Dementia. *Front Aging Neurosci,* 10.

Wang, R., Fratiglioni, L., Laveskog, A., Kalpouzos, G., Ehrenkrona, C.H., Zhang, Y., … Qiu, C. (2014). Do cardiovascular risk factors explain the link between white matter hyperintensities and brain volumes in old age? A population-based study. *European Journal of Neurology, 21*, 1076-1082.

Wang, M., Norman, J.E., Srinivasan, V.J., Rutledge, J.C. (2016). Metabolic, inflammatory, and microvascular determinants of white matter disease and cognitive decline. *Am J Neurodegener Dis, 5*, 171-177.

Wardlaw, J.M., Smith, C., & Dichgans, M. (2013a). Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. *Lancet Neurol. 12,* 483–497.

Wardlaw, J.M., Smith, E.E., Biessels, G.J., Cordonnier, C., Fazekas, F., Frayne, R., Lindley, R.I., O'Brien, J.T., Barkhof, F., Benavente, O.R., et al.; Standards for Reporting Vascular changes on Neuroimaging (STRIVE v1) (2013b). Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol. 12*, 822–838.

Washida, K., Kowa, H., Hamaguchi, H., Kanda, F., & Toda, T. (2017). Validation of the R2CHADS2 and CHADS2 scores for predicting post-stroke cognitive impairment. *Internal Medicine, 56,* 2719–2725.

Wechsler, D. (1939). *Wechsler–Bellevue Intelligence Scale*. New York, NY: Psychological Corporation.

Wechsler, D. (2008). *Wechsler Adult Intelligence Scale—Fourth Edition: Technical and interpretive manual.* San Antonio, TX: Pearson Assessment.

Welles, C.M.D., Whooley, M., Na, B., Ganz P., Schiller, N.B., & Turakhia, M.P. (2011) The CHADS2 score predicts ischemic stroke in the absence of atrial fibrillation among patients with coronary heart disease: data from the heart and soul study. *Am Heart J, 162*, 555–561.

Wen, W & Sachdev, P. (2004). The topography of white matter hyperintensities on brain MRI in healthy 60- to 64-year-old individuals. *Neuroimage, 22*, 144-154.

Wu, Y.F., Wu, W.B., Liu, Q.P., He, W.H., Ding, H., Nedelska, Z., … Xu, Y. (2016). Presence of lacunar infarctions is associated with the spatial navigation impairment in patients with mild cognitive impairment: A DTI study. *Oncotarget, 7,* 78310–78319.

Xu, X., Zhang, B., Lu, K., Deng, J., Zhao, F., Zhao, B.Q., Zhao, Y. (2016). Prevention of Hippocampal Neuronal Damage and Cognitive Function Deficits in Vascular Dementia by Dextromethorphan. *Mol Neurobiol, 53*, 3494-3502.

Yamano, S., Horii, M., Takami, T., Sakuma, M., Morimoto, T., Okada, S., … Saito, Y. (2015). Comparison between angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on the risk of stroke recurrence and longitudinal progression of white matter

lesions and silent brain infarcts on MRI (CEREBRAL study): rationale, design, and methodology. *Int J Stroke, 10,* 452-456.

Yazdanyar, A. & Newman, A.B. (2009). The Burden of Cardiovascular Disease in the Elderly: Morbidity, Mortality, and Costs. *Clin Geriatr Med, 25,* 563-577.

Zhang, F.Y., Chen, X.C., Ren, H.M., Bao, W.M. (2006). Effects of ischemic preconditioning on blood-brain barrier permeability and MMP-9 expression of ischemic brain. *Neurol Res, 28,* 21-24.

Ziegler, D.A., Piguet, O., Salat, D.H., Prince, K., Connally, e., and Corkin, S. (2010). Cognition in healthy aging is related to regional white matter integrity, but not cortical thickness. *Neurobiology of Aging, 31,* 1912-1926.

Zou, Q., Goryawala, M., Cabrerizo, M., Barker, W., Duara, R., and Adjouadi, M. (2014). Significance of Normalization on Anatomical MRI Measures Predicting Alzheimer's Disease. *The Scientific World Journal.* Article ID 541802.