THE RELATIONSHIP OF CORONARY ATHEROSCLEROSIS PROGRESSION TO COGNITION

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DEDICATION

This is dedicated to George.

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THE RELATIONSHIP OF CORONARY ATHEROSCLEROSIS PROGRESSION TO COGNITION: THE DALLAS HEART STUDY

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Subclinical atherosclerosis has been linked to poorer cognitive performance. Most of the literature investigating the relationship between atherosclerosis and cognitive functioning has utilized the carotid artery as an indicator. Few studies have examined the association between cognitive performance and atherosclerosis in areas where it accumulates early in the progression process, such as the coronary artery. This project aimed to examine the relationship between change in subclinical coronary atherosclerosis and cognitive performance in a large, community-based sample. Participants included 1,386 individuals

with Dallas Heart Study data for coronary artery calcium (CAC) levels obtained at two time points (DHS-1 and DHS-2, approximately 7 years later) and Montreal Cognitive Assessment (MoCA) scores at DHS-2 (mean age in years (SD)=52 (9.0); 57% female, 48% Black). A subset of DHS participants (N=101, mean age (SD)= 66 (5.1), 58% female, 38% Black) returned 5 years later for comprehensive neuropsychological testing as part of the Dallas Heart and Brain Aging Study (DHBAS) at the UT Southwestern Alzheimer Disease Center. CAC progression was examined as an increase from baseline calcium levels and based on CAC progression groups (i.e., None, Incidence, Non-Progressor, Progressor) in relationship to MoCA Total Score using linear multiple regression and ANOVA to compare MoCA performance between groups. Neuropsychological test data were aggregated into functional domains, and then into a Global Composite Score. The relationship between CAC progression and this global score was examined using linear multiple regression and MANOVA. ANCOVA and MANCOVA were also used to control for sociodemographic variables, traditional vascular risk factors, and baseline CAC. In the DHS sample, CAC progression was weakly but significantly associated with MoCA scores, but this relationship was attenuated by sociodemographic factors. Membership in the CAC Progressor group was significantly associated with poorer MoCA scores after controlling for baseline CAC, race, age, sex, education, hypertension, diabetes, hypercholesterolemia, and waist to hip ratio; however, when participants with stroke were excluded Progressor group membership was no longer a predictor. There was no relationship between CAC change and subsequent cognitive performance on comprehensive neuropsychological testing. Overall, there was

minimal relationship between CAC progression and global cognitive performance in a large, relatively young, community-based sample.

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AD – Alzheimer's Disease

CAC – Coronary Artery Calcium

CHOL – Hypercholesterolemia

cIMT – Carotid Intima Media Thickness

DHS – Dallas Heart Study

DHBAS – Dallas Heart and Brain Aging Study

DM – Diabetes Mellitus

EBCT – Electron-beam Computed Tomography

GCS – Global Composite Score

HTN – Hypertension

MCI – Mild Cognitive Impairment

MDCT – Multi-detector Computed Tomography

MMSE – Mini-Mental State Examination

MoCA – Montreal Cognitive Assessment

WHR – Waist to Hip Ratio

CHAPTER ONE

Introduction

Cardiovascular pathology may aggravate or contribute to the earlier clinical manifestation of neurodegenerative processes, such as Alzheimer's Disease (AD). Atherosclerosis, the principal cause of cardiovascular disease and cerebrovascular disease in adults, is a chronic inflammatory process whose end results may be decreased cerebral perfusion, impaired cognition, and stroke. There is evidence that even subclinical, or asymptomatic, atherosclerosis can have a detrimental effect on cognitive functioning. Atherosclerosis develops throughout the entire body, and can accumulate in more blood vessels than others (Johnston et al., 2004). Atherosclerosis tends to develop extracranially prior to developing intracranially (D'Armiento et al., 2004). There is limited information about the effect of change in atherosclerosis levels on cognitive functioning using other sites, such as the coronary artery.

Atherosclerosis can develop as early as adolescence and may progress for years before resulting in overt symptoms that may warrant treatment (i.e., stroke). The relationship between subclinical atherosclerosis and cognitive performance has been examined in older adults and in clinical populations; however, there are not many community-based studies and even fewer reporting on the effect of subclinical atherosclerosis progression on cognitive performance. Furthermore, few investigations have utilized an ethnically diverse sample with a wide age range. Coronary artery calcification (CAC) is used as a surrogate measure for atherosclerosis and has been associated with brain pathology (Beeri et al., 2006; Rosano, Naydek, Kuller, Longstreth, & Newman, 2005). The purpose of this study was to explore the effect of subclinical

atherosclerosis progression, using CAC as the measure of generalized atherosclerosis, on cognitive performance in an ethnically diverse, community-based sample with a wide age range.

Atherosclerosis

Atherosclerosis occurs in arterial blood vessels and results from damage to endothelial cells that allow low-density lipoproteins to enter blood vessel walls. Low-density lipoprotein, a molecule that transfers lipid in the blood stream, triggers an immune response that leads to an accumulation of monocytes in the lumen. Monocytes then undergo apoptosis and begin a process that eventually results in atherosclerotic plaque formation (Fuster, Lois, & Franco, 2010; Ross, 1999), with subsequent stenosis (narrowing) of the arterial lumen and clot formation (Sanz & Fayad, 2008). Subclinical atherosclerosis refers to the presence of atherosclerotic plaque in the absence of clinical manifestation such as stroke (Novo et al., 2012).

Atherosclerosis is present at a subclinical level as early as 15 years of age (McGill et al., 2002; Strong et al., 1999) and subclinical atherosclerosis appears to be prevalent in young adults. In a large community-based autopsy study (N=2,876, ages 15-34, 24% women, 52% African American), 5% or more of the intimal surface of the thoracic aorta and abdominal aorta had atherosclerotic lesions in 89% or more of all age groups in both Caucasian and African American groups (Strong et al., 1999). In community-dwelling individuals (N=15,792, ages 45-64), average annual progression for combined common carotid intima media thickness (cIMT; another index of atherosclerosis) over 9 years was 8.4 micrometers for African American women, 7.4 micrometers for African American men, 9.1 micrometers for Caucasian women, and 8.6 micrometers for Caucasian men (Chambless et al., 2002).

Risk Factors Related to Atherosclerosis and Cognition

Historically, hypertension (HTN), diabetes mellitus (DM), hypercholesterolemia (CHOL), and obesity served as proxy estimates of atherosclerosis. Current research supports the connection between these indirect measures and the presence of atherosclerosis. For example, DM has been associated with subclinical levels of coronary atherosclerosis (Jin et al., 2012), and waist-to-hip ratio has been independently associated with coronary artery calcium (See et al., 2007). DM and HTN have been independently linked to CAC progression (Yoon, Emerick, Hill, Gjertson, & Goldin, 2002). Additionally, atherosclerosis and HTN have a mutually reinforcing relationship. Atherosclerotic accumulation in the blood vessels exacerbates HTN, and HTN makes blood vessel walls more susceptible to damage, increasing the risk for further progression of atherosclerosis (Hollander, 1976).

There is evidence that HTN is related to cognitive impairment independent of stroke (Hanon & Forette, 2005). In a group of 93 adults aged 52-96 divided into two groups based on level of white matter changes in the brain (high and low), individuals with high volume of white matter hyperintensities had higher levels of HTN and lower cognitive performance even though the groups were similar in age, gender, education level, DM, and hyperlipidemia status (Oh et al., 2012). Cardiovascular risk factors, such as obesity, HTN, and DM, have each been associated with cognitive decline (Leritz, McGlinchey, Kellison, Rudolph, & Milberg, 2011). Knopman, Mosley, Catellier, and Coker (2009) followed community dwelling adults (aged 47-80) with a neuropsychological evaluation and cardiovascular risk assessment at baseline and a repeat neuropsychological evaluation conducted 14 years later. At follow-up, HTN and DM at baseline were associated with declines in verbal fluency and processing speed. Metabolic

syndrome, a cluster of disorders including increased abdominal adiposity, high levels of cholesterol, HTN, and high blood sugar, was associated with a decline in verbal fluency.

Direct Measures of Atherosclerosis

Direct measures of atherosclerosis include coronary artery calcification (CAC), abdominal aortic plaque, and aortic wall thickness. The focus of the current study is coronary artery calcification. Electron-beam computed tomography (EBCT) is a reliable, non-invasive tool for quantifying CAC (Schmermund et al., 2000). Of late, multi-detector computed tomography (MDCT) has become the new gold standard because it is more sensitive than EBCT (Hamon et al., 2006) and it has the capability of ruling out the presence of coronary artery disease, or stenosis of the coronary artery (Budoff et al., 2006). These tools make it possible to study the manifestation of atherosclerosis in vivo.

Coronary Artery Calcium

Coronary calcification is a widely accepted measure of atherosclerosis (Henein et al., 2013). Degree of calcification is a measured in Agatston units, a score used to measure density of calcium using computed tomography. Coronary artery calcification (CAC) has been linked to brain pathology. For example, the severity of coronary artery disease is independently associated with the development of neuritic plaques and tangles in apolipoprotein-E_4 allele carriers with Alzheimer's disease (Beeri et al., 2006). This association is also apparent when atherosclerosis is at subclinical levels. Higher levels of subclinical CAC were associated with abnormal brain MRIs and poorer cognitive status in older community dwelling individuals (N=409); in contrast, low levels of coronary artery atherosclerosis were associated with fewer brain abnormalities in healthier older adults (Rosano, Naydeck, Kuller, Longstreth & Newman,

2005). Greater amounts of CAC were also independently associated with brain vascular disease in a community-based sample (N=855) (Bos et al., 2011). Despite the evidence linking CAC and brain pathology, surprisingly few studies have examined the relationship between CAC and cognitive performance.

CAC Progression

Coronary artery calcification is an organized and regulated process. Calcification can be observed as early as the 2nd and 3rd decade, and CAC progresses for quite some time before coronary atherosclerosis reaches a clinical level (Wexler et al., 1996).

> "In vivo epidemiological evidence and postmortem studies show that the prevalence of coronary artery calcium deposits in a given decade of life is 10 to 100 times higher than the expected 10-year incidence of coronary heart disease events for individuals of the same age. This disparity is less evident in the elderly and symptomatic than in the young and asymptomatic." (Wexler et al., 1996)

This suggests that subclinical CAC progression has an opportunity to affect cognitive processes before cardiac and cerebrovascular events. As much as a 24% annual increase in CAC levels may be observed in the general population (Maher et al., 1999) and a 9-22% increase each year in asymptomatic individuals (Janowtiz, Agatston, & Viamonte, 1991; Budoff et al., 2000).

Subclinical Atherosclerosis and Cognition

The relationship between clinical levels of atherosclerosis and poorer cognitive performance is well established. For example, myocardial infarction, high-grade carotid artery stenosis, and history of cardiovascular disease have been associated with declines in global cognition, verbal memory, nonverbal memory, attention, executive functioning, and psychomotor speed among older adults (Johnston et al., 2004; Vinkers et al. 2005; Zheng et al., 2012). These associations have been demonstrated in patients with AD (Silvestrini et al., 2009)

and mild cognitive impairment (MCI; Lo et al., 2012), as well as in a middle-aged community-based sample (Romero et al., 2009) though the effect was small in these studies.

Although clinically significant levels of atherosclerosis have been associated with poorer cognitive performance, this relationship can also be observed with subclinical atherosclerosis. In non-demented cardiology outpatients (N=109, ages 55-85), cIMT was modestly inversely related to attention, executive functioning, and psychomotor speed (β= -0.26), but not global cognition, language abilities, visuospatial skills, or memory (Haley et al., 2007). The Beaver Dam Offspring Study, an investigation of 1,651 middle-aged to older cognitively intact participants, evaluated carotid atherosclerosis at baseline and cognitive data obtained 10 years later. In this study, higher cIMT was associated with poorer subsequent performance on a timed task involving mental set-shifting, but was not associated with verbal fluency or verbal memory (Zhong et al., 2012). In a cross-sectional study of 51-79-year olds (N=1,279), only men demonstrated a modest association between higher levels of cIMT and lower global cognitive scores, mental set-shifting, psychomotor speed, and sustained auditory attention, but not memory or verbal fluency (Auperin et al., 1996). Subclinical atherosclerosis appears to affect cognition in women as well. Levels of carotid atherosclerosis were inversely related to future performance on a global cognitive measure in a sample of community dwelling women (N=91, ages 60-70) (Komulainen et al., 2007). In contrast, Knopman et al. (2009) found that baseline measures of cIMT did not predict risk for cognitive decline after a 14-year follow-up in a middle to older-aged community-based sample (N=1,130).

In addition to these studies of older adults, evidence for a relationship between subclinical atherosclerosis, cognitive performance, and later cognitive decline has been shown in

studies with wide age ranges. In men aged 40-80 with subclinical levels of atherosclerosis, a higher level of cIMT was associated with lower scores on memory measures (Muller, Grobbee, Aleman, Bots, & ver der Schouw, 2006). In a community-based sample spanning a wide age range (N=538, ages 20-93), cIMT at baseline was associated with prospective decline in visual memory, delayed verbal memory, and semantic fluency, but not with confrontation-naming, executive functioning, attention, and immediate verbal memory (Wendell 2009). In another large, primarily Caucasian sample (n=2,794), adults ranging in age from 21-84, carotid plaques and cIMT were inversely related to measures of fine motor speed, global functioning and aspects of executive functioning (Zhong et al., 2011). In a prospective, community-based study with 4,371 mainly Caucasian subjects ages 25 to 78, the number of atherosclerotic plaques and total plaque area in the carotid artery were modestly inversely associated with verbal memory and processing speed performance after a 7-year follow-up (Arntzen, Schirmer, Johnsen, Wilsgaard, & Mathiesen, 2012).

A few community-based studies have utilized CAC to examine the association between the presence of subclinical atherosclerosis and cognitive performance. The Rotterdam Study examined the relationship between subclinical atherosclerosis at three sites (coronary arteries, aortic arch, and extra and intracranial carotid arteries) and cognitive performance in a community-based sample of non-demented adults, aged 55 and older (N=2,417). CAC was inversely related to information processing and fine motor speed, while extra and intracranial calcification was associated with processing speed, inhibition, verbal fluency, and fine motor skills, and calcification in the aortic arch was associated with all domains examined (e.g., verbal memory, information processing, motor speed, inhibition, verbal fluency) (Bos et al., 2012). The

Dallas Heart Study, a large, relatively young, ethnically diverse, community-based project, recently examined the relationship between baseline CAC as well as two measures of abdominal atherosclerosis and later performance on a cognitive screening measure, the Montreal Cognitive Assessment (MoCA) (Rossetti et al., in preparation). Individuals in the lowest MoCA tertile had significantly higher CAC, abdominal aortic plaque, and aortic wall thickness levels compared to those with MoCA scores in the middle and highest tertile. The effect was small, perhaps because the sample was relatively young, and the use of a cognitive screening measure instead of a more detailed neuropsychological battery may have limited the detection of minor changes in cognitive performance. The Coronary Artery Risk Development in Young Adults (CARDIA) study, which is similar to the Dallas Heart Study in focus and design, examined the relationship between subclinical atherosclerosis and concurrent cognitive performance using comprehensive neuropsychological testing (Reis et al., 2013). Participants (N=2,510, ages 43-55, 46% African American) were stratified based on degree of CAC. Higher levels of CAC, were associated with poorer performance in verbal learning, psychomotor speed and aspects of executive functioning. After controlling for age, education, race, and study center, the effect was attenuated but remained significant. After controlling for adiposity, smoking, alcohol use, dyslipidemia, HTN, DM, the effect was further attenuated but remained significant for psychomotor speed and verbal learning (Reis et al., 2013).

Overall, the literature suggests that subclinical atherosclerosis has a subtle effect on several cognitive domains. The association appears to be modest but there is evidence to suggest higher levels of subclinical atherosclerosis have a detectable effect on cognitive performance in middle-aged individuals. It appears comprehensive measures of cognitive performance may be

more sensitive to this modest relationship (Bos et al., 2012; Reis et al., 2013) than global measures. There is limited literature specific to CAC and cognitive performance. However, there is evidence to suggest higher levels of CAC are associated with poorer global functioning (Rossetti et al., in preparation), aspects of executive functioning, fine motor speed, psychomotor speed, and verbal learning (Bos et al., 2012; Reis et al., 2013).

Subclinical Atherosclerosis Progression and Cognitive Performance

To date, very little is known about the relationship between subclinical atherosclerosis *progression* and cognitive function. However, progression of indirect indicators of atherosclerosis has been linked to poorer cognitive outcomes. In fact, the persistent presence (Leritz et al., 2011) or an increase in severity of cardiovascular risk factors as measured by the Framingham Risk score may increase the risk of later cognitive decrements (Lo et al., 2012). The relationship between atherosclerosis and cognition is likely complicated and may involve thresholds above or below which cognition is affected, which underscores the need to examine subclinical atherosclerosis progression. For example, in older adults who received magnetic resonance imaging brain scans (N=409), researchers observed a threshold CAC level effect between 333 and 917 Agatston units for the presence of brain abnormalities and cognitive impairment as measured by neuropsychological and neurological examination (Rosano et al., 2005). Progression of subclinical atherosclerosis needs to be examined in order to learn how and when atherosclerosis affects cognition. While there is no literature regarding progression of CAC and cognitive performance, areas of executive functioning, processing speed, and verbal learning have been identified as areas that may be affected by CAC levels; thus, these areas may be affected by subclinical CAC progression.

Subclinical Atherosclerosis and Demographic Variables

There is evidence to suggest CAC is affected by sociodemographic variables, such as age, gender and ethnicity, and the interactions of these variables (McClelland, Chung, Detrano, Post & Kronmal, 2006). For this reason, it is important to examine these factors in relation to subclinical atherosclerosis and cognitive performance in a large, diverse sample with a wide age range.

Age

An increase in age is associated with an increase in atherosclerosis (Chen et al., 2013) and the prevalence and incidence of cardiovascular factors also increase with age (DeCarli, 2003). Age may be a risk factor for the presence of CAC (Wexler et al., 1996), but it may not be a risk factor for CAC progression (Yoon et al., 2002; Budoff et al., 2000). Although there is evidence to suggest subclinical levels of atherosclerosis have an inverse relationship with cognitive performance (Rossetti et al., in preparation), this effect disappeared after controlling for age. However, age did not attenuate the relationship between atherosclerosis and cognitive performance in other community-based studies (Muller et. al., 2006; Breteler et al., 1994; Reis et al., 2013). While changes in cognitive performance are associated with normal aging, the effect of age on the relationship between subclinical atherosclerosis progression and cognitive performance is unclear.

Sex

Atherosclerosis may manifest differently depending on sex. Male sex may be a predictor for subclinical atherosclerosis (Jin et. al., 2012; Wexler et al., 1996), though it may not be a predictor of CAC progression (Budoff et al., 2000; Yoon et al., 2002). Community-dwelling

males had higher CAC at baseline compared to females, but progression in atherosclerosis between the sexes over a year to two-year follow-up was not significantly different regardless of age (Henein et al., 2013); however, this may be reversed in older age. In community-dwelling older women, plaque burden was greater compared to older men, and the rate of progression was greater in women (Jaffer et al., 2002). More information about potential sex differences in the relationship between subclinical atherosclerosis and cognition is needed.

Ethnicity

In the only study available, CAC was similar among African Americans and Caucasians in a large, ethnically diverse community based sample (N=1,289, 59% African American) (Arthur et al., 2003). Carotid artery plaques and cIMT were compared in community-dwelling individuals (N=587, aged 35-85, 52% African American) and Blacks had increased carotid bifurcation and cIMT compared to Whites after controlling for SES, HTN, DM, and body mass index. However, in the same sample greater levels of carotid plaque in Whites were observed relative to Blacks (MacKinnon et al., 2010). Some ethnic groups may have more atherosclerotic burden than others, which could have implications for vulnerability to cognitive decline.

Socioeconomic Status and Education

There are no data concerning the association of socioeconomic status or education on CAC. However, in a cross-sectional sample of community dwellers (N=666, ages 35-64), those with a greater deprivation index (which included income, employment status, health, education, skills, training, housing, as well as geographical and telecommunication access) had greater levels of cIMT and carotid plaques (Deans et al., 2009). In a community based sample of young adults (N=1,813, ages 24-39 at baseline), baseline levels of cIMT were not significantly different

based on low, intermediate and high SES; however, after a six-year follow-up the low SES group had significantly higher cIMT (Kestila et al., 2012). However, education may be more influential than income. Nash et al. (2011) observed that older adults with less than 12 years of education had significantly larger cIMT than participants with low SES during childhood and high SES during adulthood, as well as participants who had high SES in both childhood and adulthood. The relationship between level of education and cognitive performance is well established, as individuals with higher education level tend to perform better on formal cognitive testing than less educated individuals and education may help compensate for cognitive deficits (Christensen et al., 1997; Stern, 2009).

Summary

There is evidence that subclinical atherosclerosis is associated with poorer cognitive performance. To date, few studies have used CAC to examine this relationship. Those that have examined the relationship between subclinical CAC and cognitive performance observed small but inverse relationships between CAC levels and global cognitive abilities, information processing speed, psychomotor speed, and verbal learning (Bos et al., 2012; Reis et al., 2013; Rossetti, in preparation). Although the literature regarding the relationship between direct measures of atherosclerosis progression and cognitive performance is scant, there is evidence that the longstanding presence (Leritz et al., 2011) or an increase of severity of cardiovascular risk factors may increase the risk of later cognitive decrements (Lo et al., 2012).

There appear to be differences in atherosclerosis manifestation based on age (DeCarli, 2003; Wexler et al., 1996), sex (Jin et al., 2012; Wexler et al., 1996; Arthur et al., 2003; Jeltsch et al., 2009; Rosero et al., 2011), race (Arthur et al., 2003; Jain et al., 2004; Rosero et al., 2011;

MacKinnon et al., 2010), and education (Deans et al., 2009; Nash 2011). It would be important to analyze the relationship between atherosclerosis change and cognitive function while considering sociodemographic variables to determine whether atherosclerotic change exerts a differential effect on cognition based on group membership.

The proposed study examined the relationship of CAC progression and cognitive function using a global cognitive screening tool (MoCA) and neuropsychological measures from several domains. The relationship between atherosclerotic change and cognitive performance was examined in different sociodemographic groups, including factors such as age, sex, race, and education.

CHAPTER TWO

Aims and Hypotheses

Overall Aim: To explore the relationship between coronary atherosclerosis progression and cognitive function.

Aim 1: To investigate the relationship between coronary atherosclerotic change over 7 years and global cognitive function.

Hypothesis 1: Atherosclerotic progression, as measured by coronary artery calcification difference between Dallas Heart Study phase 1 (DHS-1) and phase 2 (DHS-2) will have an inverse relationship with scores on a cognitive screening tool (Montreal Cognitive Assessment administered in DHS-2) and the effect size will be small.

Aim 2: To examine the relationship between atherosclerotic change and subsequent performance on a comprehensive neuropsychological battery and to determine if the association varies by cognitive domain.

Hypothesis 2: There will be a stronger relationship between CAC change and performance on tests of attention/processing speed (Digit Span, Digit Symbol Coding, Trail Making, Part A) and executive functioning (WCST, Block Design, Trail Making, Part B) compared to other cognitive domains (e.g., language).

Hypothesis 3: There will be a significant inverse relationship between CAC change (DHS-1 to DHS-2) and a Global Composite Score derived from a comprehensive

neuropsychological battery, and the effect size will be greater than the observed relationship between atherosclerotic change and the cognitive screening tool (MoCA).

Aim 3: To investigate the relationship between CAC and subsequent change in cognitive performance (MoCA at DHS-2 and DHBAS Visit 1).

Hypothesis 4: There will be a significant, inverse relationship between CAC levels at DHS-2 and subsequent change in MoCA scores (DHS-2 to DHBAS-1), and CAC Progressors will demonstrate significantly greater change in MoCA than Non-Progressors. There will also be a significant inverse relationship between CAC change (DHS-1 to DHS-2) and subsequent change in MoCA scores (DHS-2 to DHBAS-1).

Exploratory Aim 1: To determine if CAC progression (DHS-1 to DHS-2) is associated with subsequent diagnosis of cognitive impairment.

Hypothesis 5: CAC Progressors will be more likely to be diagnosed with cognitive impairment than Non-Progressors.

Exploratory Aim 2: To determine if the aforementioned relationship between CAC progression and cognitive functioning is attenuated after accounting for demographic and traditional risk factors, specifically, in relation to age, sex, race/ethnicity, hypertension, diabetes, high cholesterol, and waist-to-hip ratio.

Hypothesis 6: The relationship between CAC progression and cognitive functioning will be attenuated by sociodemographic variables and traditional risk factors, but the relationship will remain significant.

CHAPTER THREE

Method

Dallas Heart Study

The Dallas Heart Study (DHS) is a longitudinal project developed to examine cardiovascular risk factors in a multiethnic, population-based sample. Procedures for data collection have been described elsewhere (Victor et. al., 2004). The DHS includes an initial phase (DHS-1) and a second phase (DHS-2) conducted approximately 7 years later and was funded by UT-STAR and NIH/NCATS Grant UL1RR024982. After completion of DHS-2, a subset of DHS participants was recruited to participate in the Dallas Heart and Brain Aging Study (DHBAS) as part of the UT Southwestern Medical Center Alzheimer's Disease Center (NIA AG12300).

DHS-1

In DHS-1, participants completed three sequential visits from 2000 to 2002. The first in-home visit (n=6,101) included a 60-minute interview, a computer-assisted health interview, and measurements of blood pressure, heart rate, and weight. Participants reported demographic data, such as age, race/ethnicity, and sex. Visit two (n=3,398) included the collection of blood and urine from participants. During visit three (n=2,971), participants completed thoracic and abdominal magnetic resonance imaging, a cardiac EBCT scan, proton magnetic resonance imaging of the liver and dual energy x-ray to measure regional adiposity. Blood pressure was also collected and trained personnel collected medical history data (Victor et. al., 2004).

DHS-2

DHS-2 (2007-2009; n=3,401) included returning DHS-1 participants as well as their spouses or family members. Participants completed a health questionnaire, laboratory testing, magnetic resonance imaging of the abdominal aorta, CT scans of the coronary arteries, brain MRI, and the Montreal Cognitive Assessment (MoCA). In the health questionnaire, participants reported stroke history (Paixao et al., in preparation).

Dallas Heart/Brain Aging Study (DHBAS)

Individuals who participated in DHS-1 and DHS-2 and were 55 years or older were invited to participate in the DHBAS, which began in 2012 and examines participants annually. The study involves a clinic visit that includes a comprehensive neuropsychological evaluation which includes the MoCA. Data collected in Visit 1 of DHBAS was utilized for this study (n=101). Qualified research assistants administered the neuropsychological measures and the data were double-scored. Unless otherwise indicated, all neuropsychological measures were administered in the standard manner. DHBAS participants were categorized as normal (no cognitive impairment) or cognitively impaired (possible MCI, probable MCI, Alzheimer's disease, or other dementia) based on the consensus diagnosis of a team of neurologists and neuropsychologists.

Participants

All participants met the following inclusion criteria:

1. Completion of a valid MoCA at DHS-2
2. Available CAC data at DHS-1 and DHS-2

The subset of participants followed in the DHBAS was included for Aims 2 and 3. These participants met the following inclusion criteria in addition to those listed above:

1. DHS-2 CAC scores were greater than or equal to DHS-1 CAC scores
2. Completion of all neuropsychological measures for DHBAS

Measures

Coronary Artery Calcium (CAC)

At DHS-1, measures of CAC were collected using electron beam computed tomography (EBCT). An Imatron C-150XP Scanner was used, with 30 CM FOV, 512 matrix sharp reconstruction kernel and 3mm slices. Atherosclerosis within the coronary arteries was characterized by Agatston units. During DHS-2, CAC was collected using multiple-row detector computed tomography (MDCT) on a Toshiba Aquilon 64-slice scanner. Coronary artery calcium scores from DHS-1 were adjusted by utilizing an imaging phantom to make DHS-2 scores comparable. For DHS-1 and DHS-2, two scans were collected 1 to 2 minutes apart to account for instrument error and the average of the 2 consecutive scans is used as the measure of CAC. Imaging data were processed and characterized by experienced, blinded observers (Piaxao et al., 2013).

Quantifying CAC Progression

Characterizing CAC progression is challenging. Image variability due to extraneous factors such as motion, noise, and table positioning can influence rates of yearly progression (Bielak, Sheedy, & Peyser, 2001; Schmermund et al. 2003). In order to capture CAC progression, it is necessary to determine whether change observed is true change or simply error. When characterizing CAC progression, it is also important to consider how atherosclerosis

progresses. Atherosclerosis does not progress linearly, but in an S-shape along the vessel walls, and baseline subclinical CAC increases the chance of CAC progression (Yoon et al., 2002; Schmermund et al., 2003). For these reasons, special care was taken to accurately characterize individuals who have demonstrated CAC progression over time, account for baseline CAC, and reliably capture the progression using imaging tools. In order to address these concerns, formulas were derived by DHS researchers to calculate change between the two DHS time points and to reliably characterized participants into 4 groups (None, Incidence, Non-Progressors, and Progressors) based on CAC change, as follows (Paixao et al., in preparation):

a) The None group had 0 levels of CAC at both DHS-1 and DHS-2.
b) The Incidence group had 0 CAC level at DHS-1 and greater than 2.7 Agatston units at DHS-2.
c) Individuals who accumulated a significant amount of CAC from DHS-1 to DHS-2 were classified as Progressors based on:
    a. DHS-2 CAC level greater than $5.60\sqrt{(\text{Baseline CAC})} + 0.26*\text{Baseline CAC} - 3.09$ if baseline CAC levels were less than or equal to 100 Agatston units or
    b. DHS-2 CAC level greater than $16.14\sqrt{(\text{Baseline CAC})} - 110.4$ or if DHS 1 CAC levels were greater than 100 Agatston units.
d) Non-Progressors were defined as participants who had greater than 0 CAC levels at baseline and DHS-2 CAC levels that did not exceed the thresholds listed above.

In addition to CAC change groups, a continuous CAC change variable was calculated using the difference between the square root of DHS-1 CAC and the square root of DHS-2 CAC. Annualized change in atherosclerosis in relation to cognitive performance (CAC change divided

by the number of years between DHS-1 and DHS-2) was also calculated. In the DHBAS sample, CAC change was also examined using CAC tertiles to examine the very high and low change groups.

Cognitive Measures

The Montreal Cognitive Assessment (MoCA) was administered at DHS-2 and DHBAS-1. During DHBAS visit 1, neuropsychological measures from the following domains were also administered (see Appendix A for test descriptions):

a) Global cognition: Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975)
b) Memory: Wechsler Memory Scale-Revised- Logical Memory Story A Delayed Recall, and Visual Reproduction Delayed Recall (Wechsler, 1987) California Verbal Learning Test- Total Learning and Delayed Recall (Delis, Kramer, Kaplan, & Ober, 1987)
c) Language: 30-item Boston Naming Test (Kaplan, 1983, 1989), Controlled Oral Word Association Test, Animal fluency (Benton, Hamsher, & Sirvan, 1994)
d) Attention/processing speed: Wechsler Memory Scale-Revised- Digit Symbol Coding, Digit Span (Wechsler, 1987), Trail Making Test- Part A (Reitan, 1979)
e) Executive functioning: Wechsler Adult Intelligence Scale-Revised- Block Design (Wechsler, 1981), Trail Making Test- Part B (Reitan, 1979), Wisconsin Card Sorting Test Perseverative Errors (Heaton, Chelune, Talley, Kay, & Curtiss, 1993).

Traditional Risk Factors

Hypertension (HTN) was defined as average systolic blood pressure ≥ 140 mm Hg and /or diastolic blood pressure ≥ 90 mm Hg, or the use of antihypertensive medication. Diabetes mellitus (DM) was defined as fasting glucose level ≥ 126 mg/dl or use of hypoglycemic medication. Hypercholesterolemia (CHOL) was defined as low-density lipoprotein cholesterol ≥ 160 mg/dl, total cholesterol ≥ 240 mg/dl, or the use of statin medication. Waist circumference was defined as the horizontal plane 1 cm above the iliac crest measured in centimeters. Hip circumference was measured as the horizontal plane at the widest point of the hips in centimeters.

Statistical Analysis

Descriptive statistics were calculated for all variables, including means and standard deviations for normally distributed, continuous variables and medians and range for non-normally distributed, continuous variables. Frequencies and percentages were calculated for categorical variables. Graphs, frequency and bivariate plots were generated for qualitative examination of data distributions. Continuous change in atherosclerosis was calculated, and classification of the CAC progression groups (None, Incidence, Non-Progressors and Non-Progressors) were completed using DHS parameters mentioned previously. With regard to cognitive measures, demographically-corrected standardized-scores were utilized when possible. T-scores were calculated for all measures except for global indices. A Global Composite Score was calculated for each participant by averaging the T scores in each domain and calculating the mean of the 4 domains.

Statistical assumptions were examined and appropriate transformations were applied if warranted. The level of significance was set at $p<0.05$ unless otherwise stated. Effect size was calculated utilizing Cohen's D for T-test, as well as eta^2 for ANOVA and linear multiple regression. For multiple regression analyses, variables were entered using a forward stepwise procedure to determine which variables contribute significantly in the prediction of the variance in target variable. The threshold for variables included in the model will be $p \leq 0.15$. Post-hoc analyses will be used when omnibus test results are significant. Statistical analyses were completed using IBM© SPSS© Version 20.0 (SPSS, Inc., Chicago, IL). Sociodemographic variables include age, gender, ethnicity, and education. Traditional risk factors include hypertension (HTN), diabetes mellitus (DM), hypercholesterolemia (CHOL), and waist to hip ratio (WHR), which was calculated by dividing the circumference of the waist in cm by the circumference of the widest part of the hips in cm.

Aim 1

Hypothesis 1: Atherosclerotic progression, as measured by CAC difference between Dallas Heart Study phase 1 (DHS-1) and phase 2 (DHS-2) will have an inverse relationship with scores on a cognitive screening tool (Montreal Cognitive Assessment administered in DHS-2) and the effect size will be small. However, the relationship will be attenuated by sociodemographic variables and cardiovascular risk factors.

Analyses: Pearson product-moment correlations were used to explore the relationship between change in CAC and MoCA total score. ANCOVA was used to compare the means of MoCA total score based on CAC group (None, Incidence, Progressors, and Non-Progressors), controlling for sociodemographic variables, traditional risk factors, and baseline CAC. Linear

multiple regression was used to examine the relationship between change in CAC (independent variable) and MoCA total score (dependent variable), and sociodemographic variables, traditional risk factors, and baseline CAC were included in the analysis to control for their effect.

Aim 2

Hypothesis 2: There will be a stronger relationship between CAC change and performance on tests of attention/processing speed (Digit Span, Digit Symbol Coding, Trail Making, Part A) and executive functioning (WCST, Block Design, Trail Making, Part B) compared to other cognitive domains (e.g. language).

Analyses: MANOVA was used to compare domains (attention/processing speed, executive functioning, memory, and language) between CAC progression groups (None, Incidence, Non-Progressor, and Non-Progressor) and 1st and 3rd tertile groups for each domain score with a subsequent MANCOVA to control for baseline CAC, sociodemographic variables, and traditional risk factors. Additionally, MANOVA was used to compare performance on each subtest (Visual Reproduction II, Logical Memory II Story A, CVLT Total Recall, CVLT Long Delay, Boston Naming Test, COWAT, Animal Fluency, Digit Symbol Coding, Trail Making Test A and B, Digit Span Forward, Digit Span Backward, Block Design, Wisconsin Card Sorting Test Perseverative Errors) between CAC progression groups (None, Incidence, Non-Progressor, and Non-Progressor) and 1st and 3rd tertile groups. MANCOVA was used to control for baseline CAC, sociodemographic variables, and traditional risk factors.

Hypothesis 3: There will be a significant inverse relationship between CAC change (DHS-1 to DHS-2) and a Global Composite Score (GCS) derived from the comprehensive

neuropsychological battery, and the effect size will be greater than the observed relationship between atherosclerotic change and the cognitive screening tool (MoCA).

Analyses: Pearson product-moment correlation was used to examine the relationship between CAC change and a GCS, as well as the relationship between CAC change and DHBAS MoCA, and the effect size for each relationship was compared. ANOVA was used to compare GCS scores between CAC progression groups and tertiles.

Aim 3

Hypothesis 4: There will be a significant inverse relationship between CAC levels at DHS-2 and subsequent change in MoCA scores (DHS-2 to DHBAS-1), and CAC Progressors will demonstrate significantly greater change in MoCA than Non-Progressors. There will also be a significant inverse relationship between CAC change (DHS-1 to DHS-2) and subsequent change in MoCA scores (DHS-2 to DHBAS-1).

Analyses: Pearson product-moment correlation was used to examine the relationship between CAC change and change in MoCA total score. Linear multiple regression was conducted in order to determine whether CAC change predicted subsequent change in MoCA total score, and the model also included sociodemographic variables, traditional risk factors, baseline CAC, and baseline MoCA scores. ANOVA was used to compare the change in MoCA total scores by CAC progression groups (None, Incidence, Non-Progressor, and Progressor). In order to determine whether CAC levels at one time point were associated with cognitive change over time, these analyses were repeated using DHS-2 CAC levels and change in MoCA total score (DHS-2 to DHBAS-1)

Exploratory Aim 1

Hypothesis 5: CAC Progressors will be more likely to be diagnosed with cognitive impairment than Non-Progressors.

Analyses: The DHBAS sample was dichotomized based on consensus diagnosis into a normal control group (n=46) and a cognitively impaired group (n=55), which was comprised of participants with MCI (n=48), Alzheimer's disease (n=3), or other dementia (n=4). Chi squared was used to examine the proportion of normal and cognitively impaired DHBAS participants among CAC groups. ANOVA was used to compare the means of CAC change between normal controls and cognitively impaired individuals.

Exploratory Aim 2

Hypothesis 6: The relationship between CAC progression and cognitive functioning will be attenuated by sociodemographic variables and traditional risk factors.

Analyses: Sociodemographic variables (race, age, sex, education) and traditional risk factors (HTN, DM, WHR, CHOL) were incorporated in the above models to control for and examine their effects. Linear multiple regression, ANCOVA, and MANCOVA analyses were used. To further examine the effect of sociodemographic variables on the relationship between CAC change and cognitive performance, DHBAS participants were stratified into dichotomous groups (Blacks and Whites; 65 years and older and younger than 65; males and females; 12 years of education or less and more than 12 years of education) and ANCOVA was used to examine the effects between demographic group membership and CAC change. For results and discussion of this hypothesis, please see Appendix C

CHAPTER FOUR

Results

DHS Demographic Characteristics

Of the 3,401 participants who participated in DHS-1 and 2, 1,386 participants had CAC data at both time points as well as the DHS-2 MoCA (see Table 1). Whites had significantly higher levels of education than Blacks and Hispanics, and Blacks had higher levels of education than Hispanics ($F(2,1370)=168.169$, $p<0.001$, partial $eta^2=0.197$). Whites obtained higher MoCA scores than Blacks and Hispanics ($F(2,1383)=170.449$, $p<0.001$, partial $eta^2=0.198$). Hispanics were significantly younger Blacks and Whites ($F(2,1383)=16.287$, $p<0.001$, partial $eta^2=0.023$). There were no significant sex differences in MoCA scores, age, or education ($p\geq0.125$).

A higher proportion of women were hypertensive ($x^2(1)=7.42$, n=1386, $p=0.006$) and a higher proportion of men had DM ($x^2(1)=4.85$, n=1386, $p=0.028$). African Americans had higher rates of HTN ($x^2(1)=102.24$, n=1386, $p<0.001$) and DM ($x^2(1)=16.26$, n=1386, $p<0.001$) compared to other races. Hispanics had significantly higher WHRs than African Americans though the effect was small ($F(2,1381)=3.921$, $p=0.02$, partial $eta^2=0.006$).

DHBAS Demographic Characteristics

Of the 185 DHBAS participants, 126 completed a valid DHS-2 MoCA and valid CAC scans at DHS-1 and DHS-2. Of the 126 participants, 14 (11 females; 9 Blacks and 5 Whites; mean age=67, SD=4.8) did not complete 1 or more neuropsychological tests and were excluded from subsequent analysis. The number of participants missing data by subtest was: California

Verbal Learning Test Total Learning (5), California Verbal Learning Test Delayed Recall (5), Wisconsin Card Sorting Test Perseverative Errors (4), Trail Making Test Part B (3), Visual Reproduction Delayed Recall (2), and Digits Backward (1). Of the 14 participants, 6 were missing 1 test and 8 were missing 2 tests.

Of the remaining 112 participants, 11 (3 females, 6 Blacks and 5 Whites; mean age= 65, SD= 4.6) obtained negative CAC change scores, meaning the DHS-2 CAC scores were less than the DH-1 CAC scores. These participants were excluded because CAC scores were quite low for DHS-1 and DHS-2 (below 5.35), making it unclear as to whether these participants were truly Non-Progressors or better characterized as part of the None group.

After these exclusions, 101 DHBAS subjects were available for analyses. Compared to the DHS sample, the DHBAS sample had higher levels of education ($t(1371)= -3.825$, $p<0.001$). Individuals who returned for DHBAS had significantly higher MoCA scores at DHS-2 than the remainder of the DHS sample ($t(152)=-5.304$, $p<0.001$). There were no differences in the frequency of males and females who returned for DHBAS ($p=0.788$), but fewer Hispanics returned ($x^2(1)17.43$, n=101, $p<0.001$). In the DHBAS sample, there were no significant sex differences in CAC change, age, or education ($p\geq0.080$). With regard to race, there were no significant differences in CAC change or age ($p\geq0.645$) but Caucasians had significantly higher levels of education ($p<0.001$). Significantly more African Americans were hypertensive and there was an association between African American race and HTN ($x^2(1)=8.04$, n=101, $p=0.005$, phi=0.282). There were no differences in rates of DM, HTN, or hypercholesterolemia by gender ($p\geq0.174$).

CAC Progression

The average time between DHS-1 and DHS-2 CAC scans was 7.32 (SD=0.77) years. Average CAC change was 2.36 (SD=5.33) Agatston units. The average rate of annualized CAC change was 0.32 (SD=0.74) Agatston units. Males had significantly higher levels of CAC change than females ($t(1016)=4.348$, $p<0.001$). CAC change was similar across racial groups ($F(2,1383)=0.292$, $p=0.747$). Education ($r(1371)= -0.070$, $p=0.009$) and age ($r(1384)=0.343$, $p<0.001$) were significantly correlated with CAC change.

Participants were stratified into the 4 CAC progression groups (see Table 3). The majority fell in the None group (n=593, 43%), meaning 0 levels of CAC at both DHS-1 and DHS-2. Age was significantly different across progression groups ($F(3,1386)=108.45$, $p<0.001$, partial $eta^2= 0.191$), as the None group was the youngest, followed by the Non-Progressor group, then the Incidence group, and finally the Progressor group. Education did not differ significantly across groups ($F(3,1373)=1.069$, $p=0.361$). Regarding sex, frequency differences were observed in CAC progression groups ($x^2=55.600$, $p<0.001$), as males were more likely to be members of the Non-Progressor and Progressor groups, and less likely to be in the None group. Women were significantly more likely to be in the None group, and less likely to be in the Progressor group. There were significant differences in racial frequency in the CAC progression groups ($x^2=28.634$, $p<0.001$), as Blacks were significantly more likely to be in the Non-Progressor group, while Whites were significantly less likely to be members of the Non-Progressor group and more likely to be members of the Incidence group. For individuals who were 50 years old or less, average CAC change was 0.71 (3.2).

Of the DHS participants, 34 had a history of stroke. Of these 34, 22 were in the Progressor group, 8 were in the Non-Progressor group, 2 were in the Incidence group, and 2 were in the None group. The mean age for participants with history of stroke was 60 (8.9), mean education was 11.6 (2.6). Of the participants with stroke 19 were female, 23 were Black, and 4 were Hispanic. The average MoCA scores for participants with stroke was 19.8 (4.6).

The average time between DHS-2 and DHBAS was 4.7 years. In the DHBAS sample, the average time between DHS-1 and DHS-2 CAC scans was 7.1 years (SD=0.76) which is comparable to the larger DHS sample. The average rate of CAC change in the DHBAS was 4.64 (SD=4.9) Agatston units. DHBAS participants had significantly higher levels of CAC change (t(134.773)=-3.798, p<0.001) compared to those who did not return for follow-up in DHBAS. Of the DHBAS participants, 52.5% were in the Progressor group (n=53), 27.7% were in the None group (n=28), 14.9% were in the Incidence group (n=15), and 4.9% were in the Non-Progressor group (n=5). There were no significant differences in age, race, or sex ($p \geq 0.23$) across CAC progression groups in the DHBAS (see Table 4). Given the unequal cell size across CAC groups in the smaller DHBAS sample, CAC was also examined based on 1st or 3rd CAC tertile. The 3rd tertile was significantly older than the 1st tertile (t(60,65)= -2.160, p=0.035). In the 1st tertile, CAC change ranged from 0.0-0.7 AU and in the 3rd tertile CAC change ranged from 6.6-24.3 AU. No DHBAS participants had a history of stroke.

Hypothesis 1: CAC Progression and MoCA Performance

There was a modest but significant inverse relationship between continuous CAC change and DHS-2 MoCA score (r(1384)= -.129, p<0.001), though the effect size was very small (r^2= 0.01). When participants who reported a history of stroke were excluded, the relationship

between CAC and DHS-2 MoCA scores was similar (r= -0.11, p<0.001). Continuous CAC, baseline CAC, demographic and traditional risk factors were added to a multiple regression model in a forward entered fashion (see Table 5) and CAC was no longer a significant predictor. The final model included Hispanic race (β= -0.147, p<0.001), Black race (β= -0.395, p<0.001), age (β= -0.165, p<0.001), and education (β= 0.386, p<0.001) and accounted for 35 % of variance (F(4,1372)= 184.540, p<0.001). When participants with a history of stroke were excluded and this multiple regression model was repeated, the final model was similar.

When DHS-2 MoCA performance was compared by CAC groups (None, Incidence, Non-Progressors, and Progressors), Progressors had significantly lower MoCA scores (see Figure 1) than all other groups (F(3,1382)= 3.706, p=0.011, partial eta^2= 0.008). Using Bonferroni adjusted alpha levels of 0.0125, pairwise comparisons revealed that Progressors had significantly lower MoCA scores (M=22.4, SD=4.5) than the None group (M=23.8, SD=3.9), and the Non-Progressor group (M= 23.4, SD=4.0), but not the Incidence group (M= 23.7, SD=3.5) which was significant at p=0.028. Results were similar when participants with a reported history of stroke were excluded from the analyses. After controlling for baseline CAC, sociodemographic variables and traditional risk factors, there were no longer significant differences in MoCA score based on CAC progression group membership (F(3,1358)=1.370, p=0.250).

A multiple regression model using CAC groups (i.e., Incidence, Non-Progressors, Progressors) to predict MoCA scores showed that membership in the Progressor group (r= -0.138, p<0.001) and baseline CAC (r= -0.122, p<0.001) were significantly associated with MoCA scores, though the Progressor group was the only significant predictor of MoCA scores in

the model ($F(4,1385)=8.004$, $p<0.001$, $\beta= -0.119$, $p=0.001$). The amount of variance accounted for by Progressor group membership was, again, small ($r^2=0.023$). A multiple regression model using CAC groups and baseline CAC to predict MoCA scores was repeated with the exclusion of stroke participants, and the final model included both baseline CAC ($\beta= -0.68$, $p=0.043$) and Progressor group membership ($\beta= -0.068$, $p=0.043$). The CAC groups, baseline CAC, and demographic and traditional risk factors were then added to a model in a forward entered fashion (see Table 6). The final model included Progressor group membership ($\beta= -0.54$, $p=0.025$), Hispanic ethnicity ($\beta= -0.145$, $p<0.001$), African American race ($\beta= -0.389$, $p<0.001$), age ($\beta= -0.142$, $p<0.001$), and education ($\beta=0.386$, $p<0.001$), and accounted for 35% of the variance in MoCA scores ($F(5,1357)=145.895$, $p<0.001$). However, when stroke participants were excluded from the sample and this multiple regression model was repeated, Progressor group membership was no longer included in the model.

Hypothesis 2: CAC Change and Later Cognitive Performance by Domain

Most of the scores on the neuropsychological battery were low average or higher (see Table 7). There were no differences in performance by domain between sexes, though differences were seen at the subtest level as males had significantly higher scores on Block Design ($p=0.004$) and Boston Naming Test ($p=0.006$). Caucasians earned significantly higher scores in each domain, including executive functioning ($p<0.001$), attention and processing speed ($p<0.001$), language ($p=0.003$), and memory ($p=0.004$).

There were no significant differences in the domains of attention/processing speed, executive functioning, memory, and language among the 4 CAC progression groups (Wilks' Lambda=0.956, $F(12, 249)=0.358$, $p=0.977$). There were also no significant differences in

cognitive performance by CAC tertile (Wilks' Lambda=0.927, $F(4,60)=1.175$, $p=0.331$). Cognitive performance was further analyzed by subtest (see Table 9) and there were no significant differences in cognitive performance by CAC progression group (Wilks' Lambda=0.612, $F(42,250)=1.070$, $p=0.366$) or CAC tertile (Wilks' Lambda=0.667, $F(14,50)=1.785$, $p=0.068$).

Hypothesis 3: CAC Change and Later Global Cognitive Performance

The Global Composite Score was comprised of scores that were corrected for age and education. The mean T-score was in the average range [mean=48.7(5.7)] for the DHSBAS sample as a whole, and ranged from 33 to 62 (see Table 7). The average DHBAS MoCA was 24.1(3.7)(see Table 2). Males and females earned similar DHBAS MoCA scores ($p=0.491$). Caucasians earned significantly higher scores on DHBAS MoCA than Blacks ($p\leq0.034$). DHBAS MoCA scores were significantly correlated with age ($p=0.009$) and education ($p<0.001$).

The relationship between continuous CAC change and GCS was not significant ($p=0.534$), nor was the relationship between continuous CAC change and DHBAS MoCA ($p=0.862$). There was a very small but significant positive relationship between baseline CAC scores and the Global Composite Score ($r=0.176$, $p=0.047$), though not in the expected direction. Multiple regression using continuous CAC change, as well as baseline CAC, sociodemographic variable, and traditional risk factors entered in a forward fashion to predict the Global Composite Score resulted in a model that included only Black race ($\beta= -0.507$, $p<0.001$), which accounted for 26% of the variance in Global Composite Scores ($F(1,90)=31.069$, $p<0.001$).

The Global Composite Score was similar across all 4 CAC groups (None, Incidence, Non-Progressors, and Progressors) using both ANOVA (p=0.625) and the Kruskal-Wallis Test (p=0.537). The GCS was also compared by CAC 1st and 3rd tertile using a student's T-test, and there was not a significant difference in GCS between tertiles (p=0.353).

There were no significant differences in DHBAS MoCA performance among None, Incidence, Non-Progressors, and Progressors (p=0.966) or by CAC tertile (p=0.997). There was also no significant relationship between DHBAS MoCA and membership in the Incidence (p=0.455), Non-Progressor (p=0.332), or Progressor (p=0.378) groups. In the DHBAS sample, 57 of the 101 scored below the suggested cutoff of 26 for impairment on the MoCA. Of these 57 participants, 10 were classified by consensus diagnosis as normal controls.

Hypothesis 4: CAC and Subsequent MoCA Change (DHS-2 to DHBAS)

From DHS-2 to DHBAS, an average of 4.7 (SD=0.83) years later, the mean MoCA change score was -0.62 (SD=2.5) and ranged from 5 to -7 points. Change in MoCA Total Score was not significantly associated with sex, race, or education, but age showed a significant, inverse relationship with change in MoCA Total Score (r(99)=-0.334, p=0.004). There was no significant relationship between CAC at DHS-2 and MoCA change scores from DHS-2 and DHBAS (p=0.807). Similarly, there was no significant correlation between CAC change and MoCA change (p=0.264). The change in MoCA score was compared by CAC groups (None, Incident, Non-Progressors, and Progressors) using ANOVA and the scores were similar across all 4 groups (p=0.973) and by CAC tertile (p=0.629). The linear multiple regression model predicting MoCA change scores by continuous CAC change highlighted only age as a significant predictor (see Table 10).

Hypothesis 5: CAC Progression and Later Diagnosis of Cognitive Impairment

There were similar proportions of normal and cognitively impaired individuals in the CAC progression groups (p=0.592; see Figure 4). Similarly, there were no significant differences in consensus diagnosis between CAC tertiles (p=0.256). When frequency of clinical diagnosis was examined between the None group and the Progressor group, there were also similar proportions of normal and cognitively impaired individuals (p=0.230). The average CAC change was similar between controls and cognitively impaired (p=0.486), as was annualized CAC change (p=0.618)

CHAPTER FIVE

Discussion

In the current investigation, an increase in coronary artery calcification over a period of 7 years was minimally associated with poorer performance on a global cognitive measure. The association between continuous CAC change and MoCA scores was attenuated after accounting for sociodemographic variables. The relationship between Progressor status and lower MoCA scores remained significant after controlling for demographic variables and traditional risk factors when individuals with stroke were included. When individuals with stroke were excluded, Progressor status was no longer a predictor. The difference between the Progressor group and the other CAC groups was small, about one point lower in MoCA total score. When the wide age range of the sample is considered, it is possible that healthier younger people diluted the effect of the relationship between continuous CAC progression and MoCA scores, and sorting by CAC groups allowed the effect to become more apparent. Additionally, it may require a clinical event, such as stroke, for change in CAC to be related to global cognitive performance. While few studies have investigated CAC progression and cognition, this finding is in line with other studies that found an association between higher atherosclerosis levels and poorer global cognitive performance (Auperin et al., 1996; Komulainen et al., 2007; Zhong et al., 2011). These results suggest that progression of coronary atherosclerosis has a very subtle, inverse association with global cognitive performance.

The carotid artery is most commonly used when examining the relationship between atherosclerosis and cognitive functioning in part because imaging tools used to capture carotid

atherosclerosis are cheaper and less cumbersome than computed tomography. However, atherosclerosis develops extracranially prior to developing intracranially (D'Armiento et al., 2004) and this study supports the notion that higher levels of atherosclerosis in vessel beds more distal to the brain, in this case the coronary arteries, can be associated with poorer cognitive performance. This association has been supported in the few previous studies using CAC. In a large sample of older adults, high levels of CAC were associated with poorer cognitive status (Rosano et al., 2005), and higher volumes of CAC were also associated with poorer cognitive performance in an older, primarily White sample (Bos et al., 2012). Additionally, in a large biracial population-based sample that was similar in age and size to DHS, higher levels of CAC and abdominal aortic plaques were associated with poorer cognitive performance after adjusting for demographic and vascular risk factors (Reis et al., 2013). It appears that atherosclerosis development in areas where it accumulates relatively early in the progression process is related to cognitive outcomes.

In a previous DHS study, there was a subtle relationship between atherosclerosis levels and the MoCA in a population-based sample with a wide age range, which was attenuated once sociodemographic variables were considered (Rossetti et al., in preparation). This raised the question of whether a global cognitive screening tool is sensitive enough to detect subtle cognitive changes related to atherosclerosis in a generally healthy sample. In an effort to address this question, the current investigation examined both a commonly used global cognitive screening test and a Global Composite Score representative of more detailed neuropsychological testing. In the current study, there was no relationship between CAC progression and subsequent scores on either the MoCA or Global Composite Scores, suggesting that there little association

between CAC change and subsequent cognitive performance. In fact, neuropsychology scores were similar across CAC progression groups and tertiles in the DHBAS cohort. It is possible that the relative utility of the MoCA and a comprehensive neuropsychological battery would vary in different samples, such as older groups or those with more advanced cognitive impairment or atherosclerosis.

In contrast to prior investigations that have found associations between baseline atherosclerosis, atherosclerosis progression, and later cognitive performance (Zhong et al., 2012; Komulainen et al., 2007; Arntzen et al., 2012), the current study found no association between CAC progression and cognitive performance at follow-up 5 years later, either globally or by cognitive domain. There are a few possible explanations for these discrepant results. The current study focused on CAC change in relation to cognitive functioning. A change variable likely represents a more nuanced process than baseline or concurrent variables and does not directly account for the amount of atherosclerosis at any one time point; therefore, subclinical change as an indicator may not be robust enough to detect differences in cognitive domains. A separate consideration is the difference in the atherosclerotic variable of interest. Coronary atherosclerosis may reflect or suggest underlying pathology such as changes in vessel permeability that could affect the brain over time. Most studies examine carotid atherosclerosis which is proximal to the brain while the current investigation utilized coronary atherosclerosis, a distal region in which atherosclerosis accumulates early and presumably may have a more subtle, generalized effect on the brain and cognition that is not necessarily localized to any particular region or domain. Finally, the degree of CAC progression in this sample was minimal (average change of 2.3 Agatston units over 7 years) particularly when considered in relationship to prior

work showing that CAC did not exert an effect on cognition until reaching a threshold of at least 333 Agatston units (Rosano et al., 2005). There is evidence to suggest if community dwellers with atherosclerosis are followed longitudinally, an eventual decline in cognitive performance can be observed in participants with higher levels of atherosclerosis (Wendell et al., 2009). It is possible that CAC change was too subtle to predict future cognitive performance in a relatively healthy sample; however, minor changes in cognitive performance may become apparent if the sample is followed over time. Another consideration is that there is not a relationship between change in CAC and cognitive performance. However, the current study is the first to examine this relationship and is not sufficient to rule out the association between CAC change and detailed neuropsychological testing. There was a 5-year delay between the measure of CAC change and testing, and it is possible that participants demonstrated various degrees of CAC change in those 5 years making the classification of change from DHS-1 to DHS-2 no longer applicable. As mentioned before, CAC change may be a nuanced indicator of atherosclerotic burden; therefore, detecting the relationship between CAC change and cognitive performance on a comprehensive neuropsychological battery may necessitate that neuropsychological testing and the second measure of CAC are completed concurrently.

In the DHBAS subset, CAC progression was unrelated to clinical diagnosis. The frequency of dementia has been positively and significantly associated with degree of atherosclerosis (Hofman et al., 1997), and higher levels of atherosclerosis have been linked to an increased chance of developing dementia (van Oijen et al., 2007). However, these associations are typically observed in samples that are significantly older than the DHBAS sample and include subjects with dementia. The lack of a relationship between CAC progression and

cognitive impairment may be attributable to the relatively young age of the DHBAS sample, as well as the small number of participants with dementia.

Participants who decided to return for follow-up in the DHBAS were older, had higher levels of education, higher MoCA scores at baseline, as well as higher levels of CAC. It is possible that the returning individuals were more concerned about their cognitive functioning and were more aware of risks associated with cardiovascular health and concerned about their own health. These factors may have created an educated self-selected sample. Although the DHBAS sample had higher levels of CAC compared to the remaining DHS sample, which may increase the risk for poorer cognitive performance related to cardiovascular risk factors, protective factors such as higher levels of education may have masked subtle changes in cognitive abilities related to the effects of subclinical atherosclerosis. This may have affected the neuropsychological outcomes because higher levels of education tend to be protective against cognitive decline because of compensatory strategies (Christensen et al., 1997; Stern, 2009). It is likely that subclinical levels of CAC would need to progress more substantially in order to see more overt changes in cognitive performance.

In summary, the results of this study suggest there is a minimal relationship between CAC progression and global cognitive performance in an ethnically diverse, community-based sample. Although the association between CAC and cognitive performance was very small, with essentially a 1-point difference in MoCA total score, large effects were not anticipated given that this study utilized a gross cognitive screening measure in a relatively young and healthy sample. Furthermore, the effects of atherosclerosis would not necessarily be expected to account for substantial variance in cognition scores given that atherosclerosis likely exerts a subtle, indirect

effect on cognitive performance. It is also possible that a clinical event, such as stroke, is needed to see a relationship. In the sample that returned for further testing, the relationship between CAC change and cognitive performance did not differ based on method of assessment (screening measure vs. comprehensive battery). This may be due to the fact that CAC change may not predict future cognitive performance, or that CAC levels were subclinical for all DHBAS participants.

Limitations

As with many community-based studies, a limitation is that participants were not screened for psychiatric or neurologic disorders that may influence cognitive performance. Additionally, there was no baseline measure of cognitive performance for DHS participants, so assessment of cognitive change over time was limited to the smaller DHBAS sample. In the DHBAS subset, education levels were different between races and this may have influenced performance on neuropsychological testing. Of the DHS participants, a larger number of Progressors returned for DHBAS and CAC progression groups differed in size, which may have limited the power of these analyses. To address small cell sizes of CAC progression groups the DHBAS sample was divided into tertiles, and inclusion of members from differing CAC groups in each tertile may mask any effect of CAC change on cognitive performance. A global composite score was derived in an attempt to leverage the multiple available data-points from several cognitive tests; however, this approach combined subtest scores into domains based on clinical convention, and these domain scores were used to calculate a composite score. Although there were no differences in performance at the subtest level, this approach could mask isolated areas of weakness or impairment that may be associated with CAC progression. In the DHBAS

sample, few participants were diagnosed with dementia, which may have contributed to the negative finding regarding the relationship between atherosclerosis progression and the diagnosis of cognitive impairment due to reduced power. The few statistically significant findings had very small effect sizes, especially when sociodemographic variables were considered. These factors, including age and education, had a significantly greater influence on cognition than atherosclerosis, which left less variance to be accounted for atherosclerotic progression. An additional limitation is the multiple ways in which the sample was divided and the multiple analyses which were conducted to examine the relationship between CAC and cognitive performance. Group categorization and repeated analyses may have inflated alpha and increased the chance of committing a type I error.

Strengths

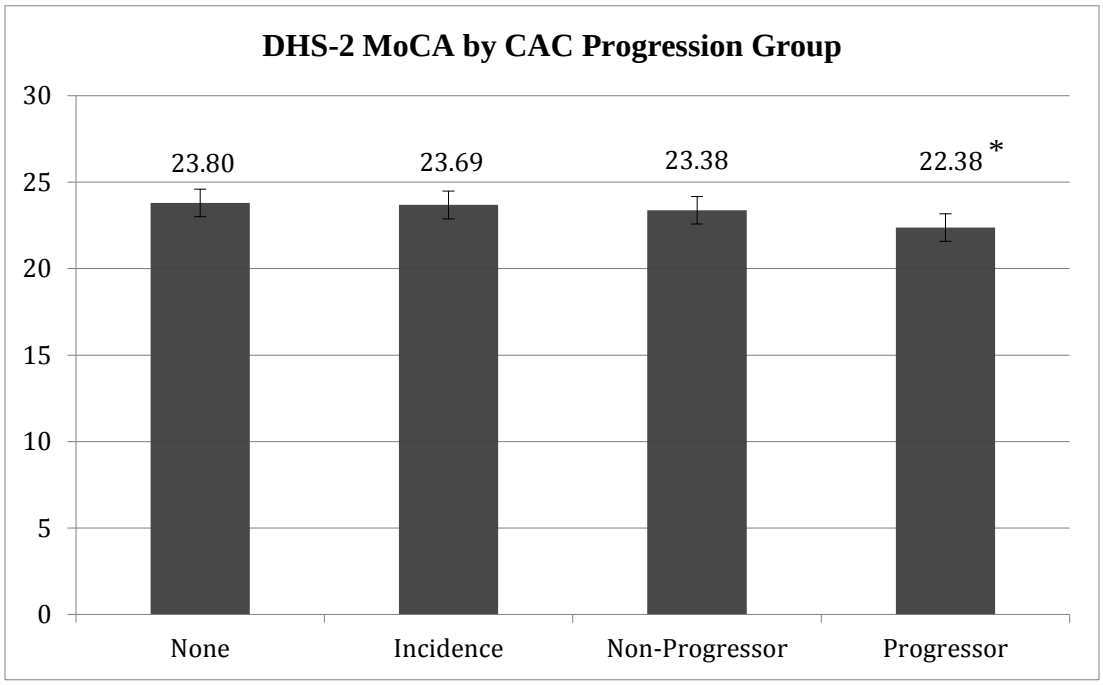
This study is the first to examine the relationship between CAC change and cognitive performance in a large, multiracial, community-based sample. This study used imaging to characterize and quantify CAC. While much of the prior literature on this topic has relied on a single cognitive screening measure, a strength of this study was the inclusion of a longitudinal component in which a subset of participants completed a comprehensive neuropsychological battery that examined several cognitive domains. This component allowed for monitoring of cognitive performance over time.

Future Directions

Given the literature connecting atherosclerosis and cognitive performance, it would be worthwhile to follow these participants over time to determine if CAC as an indicator of progression is related to poorer cognitive performance, or if CAC needs to manifest clinically to

affect cognitive functioning. This is the first study to examine the relationship of CAC change to cognitive performance, compared to other studies examining atherosclerosis and cognition the samples which have utilized other atherosclerosis indicators and exhibited higher levels of atherosclerotic burden. Future directions include longitudinal study of this relatively young DHS sample to monitor cognitive performance. Individuals from all of the CAC progression groups, particularly individuals who demonstrate more progression and may have greater risk for cognitive change, should be recruited and followed over time. Evidence suggests atherosclerosis levels in various vessel beds may have differential effects on cognition. The same may be true for atherosclerosis progression and future endeavors should include examining other indicators of atherosclerosis progression, such as change in abdominal aortic plaques and abdominal aortic wall thickness. It may be that intervention before atherosclerosis is allowed to develop to a clinical level may prevent the negative effects of atherosclerosis on cognition. A better understanding of the association between atherosclerosis progression and cognitive function could have important implications for treatment of associated modifiable risk factors in order to mitigate or postpone cognitive decline.

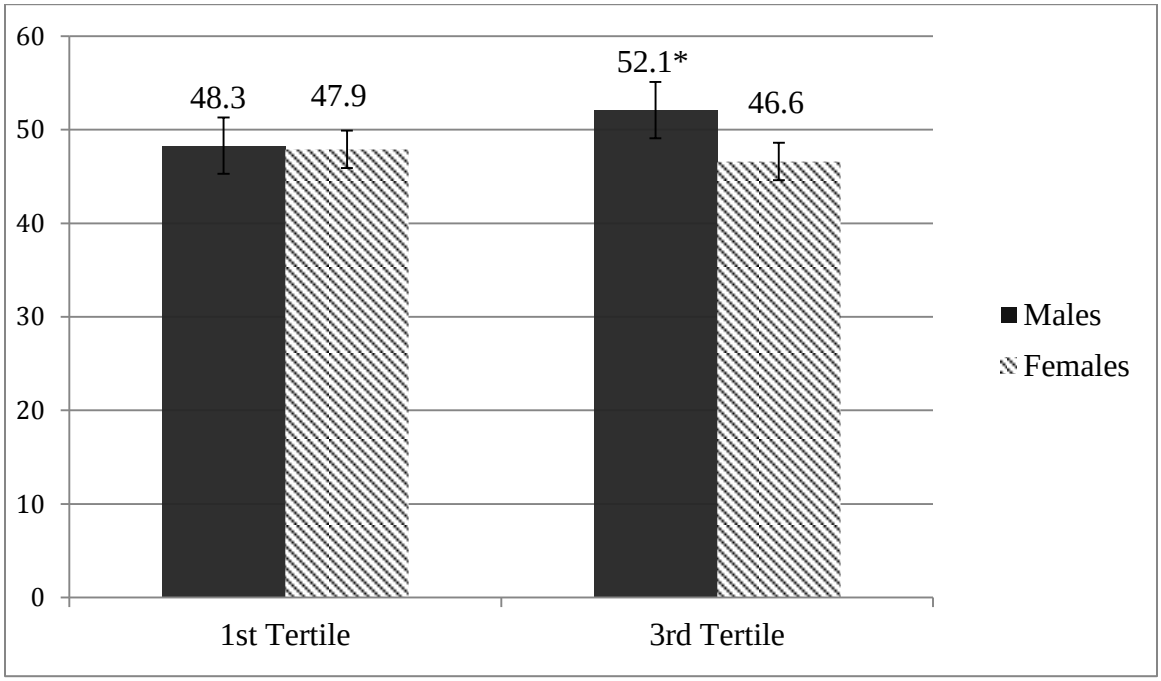
Figure 1. *DHS-2 MoCA Total Score by CAC Progression Group Membership*



Note: MoCA=Montreal Cognitive Assessment; CAC=Coronary artery calcification

*Significantly lower MoCA scores than all other groups (p=0.011).

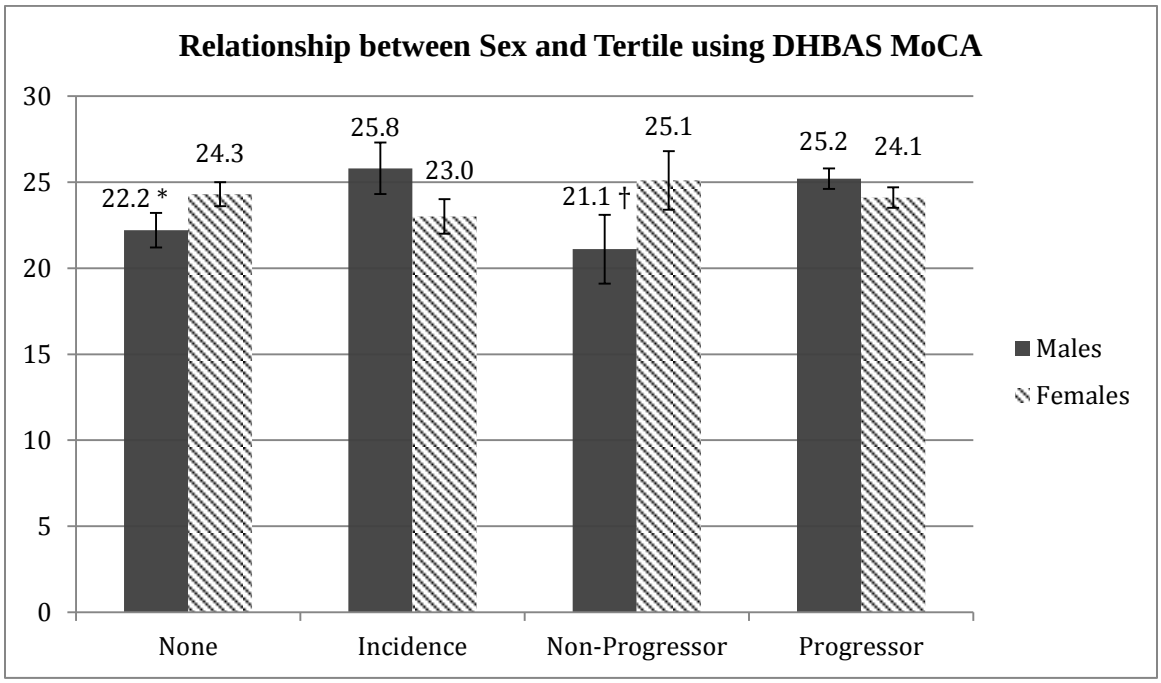
Figure 2: Relationship between Sex and CAC Tertile using Global Composite Score



Note: CAC=Coronary artery calcification, Covariates appearing in the model are DM, race, and age.

* Significantly higher GCS scores than 3rd tertile females after controlling for sociodemographic variables and traditional risk factors.

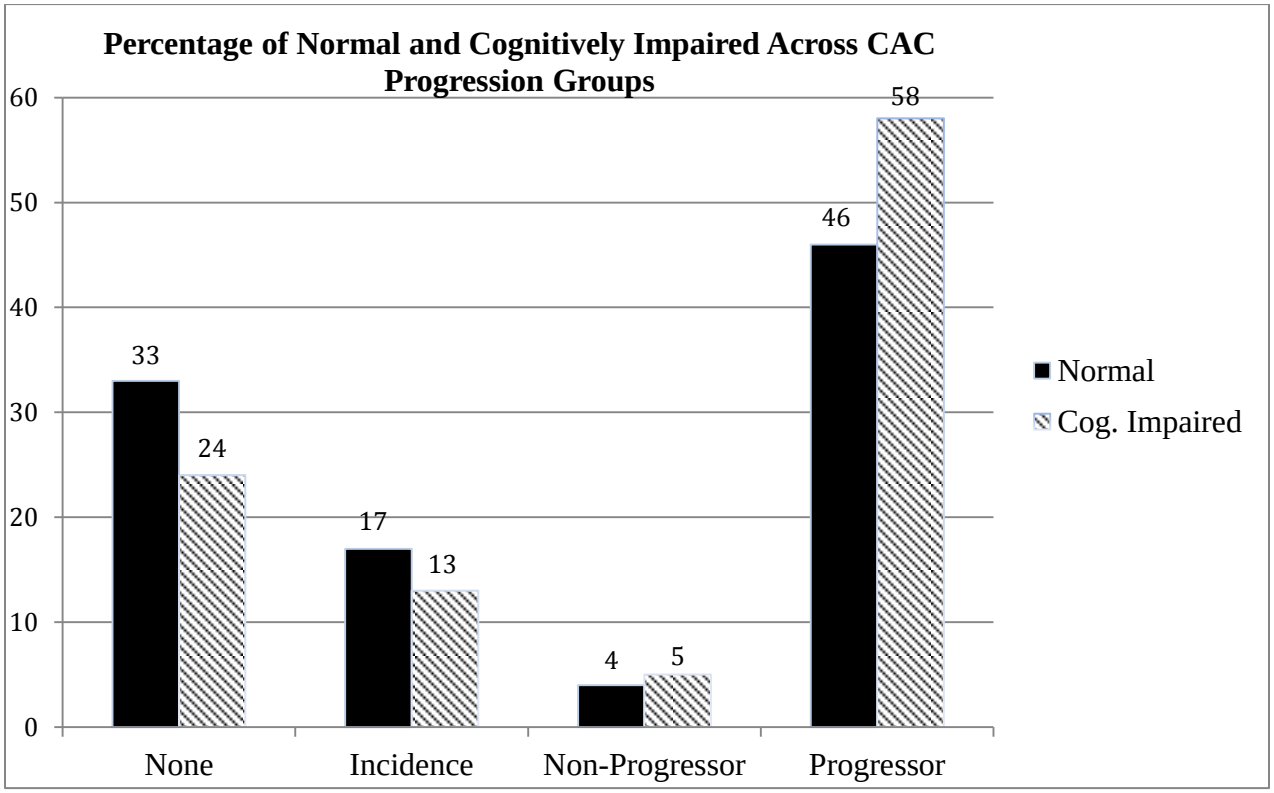
Figure 3: Relationship between Sex and CAC Progression Group Membership using DHBAS MoCA



Note: MoCA= Montreal Cognitive Assessment

† Significantly lower MoCA scores than females in the Incidence and Progressor groups.
* Significantly lower MoCA scores than females in the None and Non-Progressor groups, as well as males in the Incidence and Progressor groups, after controlling for sociodemographic variables and traditional risk factors (p=0.035).

Figure 4: DHBAS Percentage (%) of Normal and Cognitively Impaired Participants across CAC Progression Groups



Note: CAC= Coronary artery calcification, Cog. Impaired= Cognitively Impaired; consensus diagnosis of MCI or dementia

No significant differences in frequency of normal and cognitively impaired diagnoses between groups.

Table 1.

Demographic Characteristics of DHS Sample

		Males (n=602)	Females (n=784)	Blacks (n=662)	Whites (n=505)	Hispanics (n=219)	Overall (n=1386)
CACΔ	M (SD)	3.1 (6.3)	1.8 (4.4)	2.5 (0.2)	2.2 (0.2)	2.3 (0.4)	2.4 (5.3)
MoCA	M (SD)	23.4 (3.9)	23.3 (4.2)	21.8 (4.1)	[b]25.7 (2.8)**	22.3 (4.1)	23.3 (4.1)
Edu	M (SD)	12.8 (2.4)	12.6 (2.2)	[a]12.6 (1.5)**	[a]13.6 (1.7)**	10.5 (3.6)	12.7 (2.3)
Age	M (SD)	51.8 (8.7)	52.2 (9.2)	52.5 (9.0)	52.9 (9.0)	[c]48.9 (8.7)**	52.1 (9.0)
HTN	n (%)	285 (40)	429 (60)	435 (61)	200 (28)	79 (11)	714 (52)
DM	n (%)	103 (50)	101 (50)	124 (60)	40 (20)	40 (20)	204 (15)
CHOL	n (%)	75 (46)	87 (54)	76 (47)	67 (41)	19 (12)	162 (12)
WHR	M (SD)	0.94 (0.1)	0.86 (0.1)	0.89 (0.1)	0.90 (0.1)	0.90 (0.1)	0.89 (0.1)

Note: M=Mean, CACΔ=CAC Change in Agatston units [√(DHS-2)-√(DHS-1)], Edu= Education, HTN= Hypertension, DM= Diabetes Mellitus, CHOL=Hypercholesterolemia, WHR=Waist to Hip Ratio in cm

**$p<0.01$

[a]Whites had significantly higher levels of education than Blacks and Hispanics; Blacks had higher education than Hispanics.

[b]Whites obtained higher MoCA scores than Blacks and Hispanics.

[c]Hispanics were significantly younger Blacks and Whites.

Table 2.

Demographic Characteristics of the DHBAS Cohort

		Males (n=42)	Females (n=59)	Blacks (n=38)	Whites (n=54)	Overall (n=101)
CAC Δ	M (SD)	4.9 (4.6)	4.4 (5.1)	5.2 (4.9)	4.4 (5.2)	4.6 (4.9)
GCS	M (SD)	49.5 (4.7)	48.1 (6.2)	45.5 (5.2)	51.4 (4.8)	48.7 (5.7)
DHBAS MoCA	M (SD)	24.2 (3.6)	24.1 (4.0)	21.6 (4.0)	25.9 (2.5)	24.1 (3.7)
Education	M (SD)	14.4 (3.4)	14.6 (2.8)	13.0 (2.6)	[a]15.7 (2.9)**	14.5 (2.8)
Age	M (SD)	67.5 (4.9)	65.7 (5.2)	66.3 (4.6)	66.5 (5.5)	66.4 (5.1)
HTN	n (%)	26 (44)	33 (56)	[b]29 (49)**	27 (46)	59 (58)
DM	n (%)	6 (60)	4 (40)	4 (40)	4 (40)	10 (10)
CHOL	n (%)	6 (29)	15 (71)	6 (29)	14 (67)	21 (21)
WHR	M (SD)	0.94 (0.1)	0.86 (0.1)	0.87 (0.1)	0.90 (0.1)	0.89 (0.1)

Note: M= Mean, CAC Δ=CAC Change in Agatston units [√(DHS-2)-√(DHS-1)], GCS= Global Composite Score, HTN= Hypertension, DM= Diabetes Mellitus, CHOL=Hypercholesterolemia, WHR=Waist to Hip Ratio in cm

** $p<0.01$

[a] Whites had higher levels of education than Blacks ($p<0.001$) .

[b] Higher proportion of Blacks were hypertensive ($p=0.005$).

Table 3.

Characteristics of the DHS CAC Progression Groups

	None (n=593)	Incidence (n=99)	Non-Progressor (n=319)	Progressor (n=375)
[a]Males n (%)	190 (32)	49 (49)	162 (51)**	201 (54)**
[b]Females n (%)	403 (68)**	50 (51)	157 (49)	174 (46)
[c]Black n (%)	262 (44)	34 (34)	179 (56)**	187 (50)
[d]White n (%)	224 (38)**	54 (55)	92 (29)	135 (36)
Hispanic n (%)	107 (18)	11 (11)	48 (15)	53 (14)
[c]Age M(SD) Range	48.8 (8.0)** 35-71	53.8 (8.5)** 37-71	50.5 (8.2)** 35-74	58.2 (8.2)** 37-74
Education M(SD) Range	15.3 (3.3) 0-16	14.6 (2.8) 1-16	14.3 (2.4) 2-16	14.3 (2.9) 0-16
MoCA M(SD) Range	23.8 (3.9) 10-30	23.7 (3.5) 12-30	23.4 (4.0) 7-30	22.4 (4.5) 7-30
WHR M(SD)	0.86 (0.07)	0.90 (0.06)	0.91 (0.07)	0.92 (0.09)
HTN n (%) Total N= 714	225 (32)	52 (7)	176 (25)	261 (37)
DM n (%) Total N= 204	46 (23)	18 (8)	55 (27)	85 (42)
CHOL n (%) Total N= 162	42 (26)	15 (9)	27 (17)	78 (48)

Note: HTN=Hypertension, DM=Diabetes Mellitus, CHOL= Hypercholesterolemia, WHR=Waist to Hip Ratio in cm, M=Mean

**$p<0.001$

[a]Males more likely to be in Non-Progressor and Progressor groups; less likely to be in the None group.

[b]Females more likely to be in the None group and less likely to be in the Progressor group.

[c]Blacks more likely to be in the Non-Progressor group.

[d]Whites more likely to be in the None group

[e]Significant differences in age between all 4 CAC progression groups.

Table 4.

DHBAS Demographic Characteristics for CAC Progression Groups

		None (n=28)	Incidence (n=15)	Non-Progressor (n=5)	Progressor (n=53)
Males	n (%)	9 (21)	5 (12)	2 (5)	26 (62)
Females	n (%)	19 (32)	10 (17)	3 (5)	27 (46)
Blacks	n (%)	11 (29)	5 (13)	2 (5)	20 (53)
Whites	n (%)	15 (28)	8 (15)	3 (6)	28 (52)
GCS	M (SD)	48.4 (4.7)	47.7 (7.0)	51.4 (4.8)	48.9 (5.9)
Age	M (SD)	65.0 (4.6)	65.2 (4.6)	64.4 (5.0)	67.7 (5.3)
Edu	M (SD)	15.3 (3.4)	14.6 (2.8)	12.6 (2.1)	14.3 (2.9)
HTN	n (%)	13 (22)	7 (12)	4 (7)	35 (59)
DM	n (%)	1 (10)	2 (20)	1 (10)	6 (60)
CHOL	n (%)	2 (10)	6 (29)	0 (0)	13 (61)
WHR	n (%)	0.88 (0.07)	0.88 (0.06)	0.97 (0.12)	0.90 (0.09)

Note: M=Mean, GCS=Global Composite Score, HTN=Hypertension, DM=Diabetes Mellitus, CHOL=Hypercholesterolemia, WHR= Waist to Hip Ratio

Table 5.

DHBAS Demographic Characteristics for Tertiles Based on CAC Change

		1st Tertile (n=33)	3rd Tertile (n=32)
Males	n (%)	11 (48)	12 (52)
Females	n (%)	22 (52)	20 (48)
Blacks	n (%)	13 (45)	16 (55)
Whites	n (%)	18 (55)	15 (45)
GCS	M (SD)	48.4 (4.7)	47.5 (6.3)
Age	M (SD)	64.9 (4.6)	[a]**67.6 (5.6)***
Education	M (SD)	14.9 (3.3)	14.5 (2.8)
HTN	n (%)	17 (39)	27 (61)
DM	n (%)	2 (29)	5 (71)
CHOL	n (%)	2 (14)	12 (86)
WHR	M (SD)	0.89 (0.09)	0.90 (0.08)

GCS=Global Composite Score, HTN=Hypertension, DM=Diabetes Mellitus, CHOL=Hypercholesterolemia, WHR= Waist to Hip Ratio

* $p<0.05$

[a] 3rd tertile significantly older than the 1st tertile ($p=0.035$).

Table 6.

Multiple Regression Predicting DHS MoCA Total Score by Continuous CAC Change

		Standardized Coefficients			95.0% C.I.	
		Beta	t	Sig.	Lower Bound	Upper Bound
Full Model[1]	(Constant)		23.41	<.001	18.28	21.63
	CACΔ	-0.29	-1.01	0.313	-0.07	0.02
	Baseline CAC	-0.01	-0.41	0.679	-0.05	0.03
	Black	-0.40	-15.52	<.001	-3.66	-2.84
	Hispanic	-0.15	-5.39	<.001	-2.24	-1.05
	Age	-0.15	-6.03	<.001	-0.09	-0.05
	Sex	0.04	1.78	0.076	-0.03	0.69
	Education	0.39	15.71	<.001	0.60	0.77
	HTN	-0.00	-0.08	0.934	-0.41	0.38
	DM	-0.00	-0.10	0.923	-0.55	0.50
	WHR	-0.01	-0.64	0.525	-0.00	0.00
	CHOL	0.01	0.35	0.724	-0.00	0.00
Reduced Model[2]	(Constant)		24.47	<.001	18.72	21.99
	Hispanic	-0.15	-5.44	<.001	-2.24	-1.06
	Black	-0.40	-16.11	<.001	-3.63	-2.84
	Age	-0.17	-7.48	<.001	-0.09	-0.06
	Education	0.39	15.84	<.001	0.60	0.77

Dependent Variable: DHS-2 MoCA

[1]R^2=0.35

[2]R^2=0.35

Note: CACΔ=CAC Change in Agatston units [√(DHS-2 CAC)-√(DHS-1CAC)], Baseline CAC=√(DHS-1 CAC), HTN= Hypertension, DM= Diabetes Mellitus, CHOL=Hypercholesterolemia, WHR=Waist to Hip Ratio in cm

Table 7.

Multiple Regression Predicting DHS MoCA Total Score by CAC Group Membership

		Standardized Coefficients			95.0% C.I.	
		Beta	t	Sig.	Lower Bound	Upper Bound
Full Model[1]	(Constant)		23.05	<.001	18.12	21.49
	Incidence	-0.01	-0.45	0.655	-0.89	0.56
	Non-Progressor	0.02	0.91	0.363	-0.25	0.69
	Progressor	-0.03	-1.08	0.280	-0.88	0.25
	Baseline CAC	-0.01	-0.40	0.686	-0.05	0.03
	Black	-0.40	-15.53	<.001	-3.68	-2.85
	Hispanic	-0.15	-5.41	<.001	-2.26	-1.06
	Age	-0.14	-5.57	<.001	-0.09	-0.04
	Sex	0.04	1.78	0.075	-0.03	0.70
	Education	0.39	15.70	<.001	0.60	0.77
	HTN	-0.00	-0.12	0.907	-0.42	0.38
	DM	-0.01	-0.24	0.814	-0.58	0.46
	WHR	-0.02	-0.70	0.486	-0.00	0.00
	CHOL	0.01	0.39	0.699	-0.00	0.00
Reduced Model[2]	(Constant)		23.65	<.001	18.35	21.67
	Progressor	0.39	15.78	0.030	-0.91	-0.46
	Hispanic	-0.15	-5.39	<.001	-2.23	-1.04
	Black	-0.39	-16.08	<.001	-3.63	-2.84
	Age	-0.14	-5.93	<.001	-0.09	-0.04
	Education	0.38	15.78	<.001	0.60	0.77

Dependent Variable: DHS-2 MoCA

[1]R^2=0.36

[2]R^2=0.35

Note: Baseline CAC=√(DHS-1), HTN= Hypertension, DM= Diabetes Mellitus, CHOL=Hypercholesterolemia, WHR=Waist to Hip Ratio in cm

Table 8.

DHBAS Neuropsychology Measures (Mean T-scores)

	Overall (n=101) Mean (SD)	Range
Global Composite Score	48.7 (5.7)	33-62
Attention/Processing Speed	50.5 (6.8)	36-69
Trail Making Test Part A	53.0 (10.6)	25-82
Digit Symbol Coding	49.0 (7.8)	26-70
Digits Forward	50.9 (9.2)	29-73
Digits Backward	49.3 (10.1)	27-73
Memory Domain	48.2 (6.0)	33-67
WMS-R- LMII	43.7 (4.9)	34-54
WMS-R- VRII	51.0 (9.8)	29-73
CVLT Total	48.7 (9.3)	27-79
CVLT Long Delay	49.4 (9.9)	14-81
Executive Functioning	47.3 (9.9)	19-69
Trail Making Test Part B	49.4 (9.8)	22-79
Block Design	46.7 (9.6)	23-76
WCST Errors	45.8 (16.7)	5-90
Language	48.7 (7.1)	31-73
Boston Naming Test	47.9 (11.3)	26-91
Animals	50.7 (10.1)	24-79
FAS	47.7 (9.1)	18-78

WMS-R: Wechsler Memory Scale-Revised; LM: Logical memory, Story A, VR: Visual Reproduction; CVLT: California Verbal Learning Test; WCST: Wisconsin Card Sorting Test

Table 9.

DHBAS Neuropsychology Measures (Mean T-scores) by Demographic Groups

	[a]Male (n=42)	Female (n=59)	Black (n=38)	[b]White (n=54)
Global Composite Score	49.5	48.1	**45.5****	**51.4****
Attention/Processing Speed	51.0	50.2	47.1	**53.4****
Trail Making Test Part A	52.5	53.4	50.6	55.2
Digit Symbol Coding	50.7	47.7	44.6	51.8
Digits Forward	51.0	50.7	50.0	52.6
Digits Backward	49.7	49.0	46.0	52.5
Memory Domain	48.2	48.2	46.3	**49.9****
WMS-R- LMII	43.1	44.2	41.9	44.9
WMS-R- VRII	52.1	50.1	47.8	52.9
CVLT Total	47.3	49.7	49.0	48.6
CVLT Long Delay	50.2	48.9	48.8	50.1
Executive Functioning	48.6	46.4	42.2	**51.4****
Trail Making Test Part B	51.2	48.1	48.5	50.4
Block Design	49.9*	44.4*	39.6	50.9
WCST Errors	44.7	46.7	38.6	50.7
Language	50.3	47.6	46.4	**50.8****
Boston Naming Test	51.5*	45.3*	44.0	50.6
Animals	51.9	49.8	49.8	51.7
FAS	47.5	47.9	48.0	47.8

WMS-R: Wechsler Memory Scale-Revised; LM: Logical Memory Story A, VR: Visual Reproduction; CVLT: California Verbal Learning Test; WCST: Wisconsin Card Sorting Test

**p<0.01.

[a] Males earned higher scores on Block Design (p=0.004) and Boston Naming Test (p=0.006).

[b] Caucasians had higher Global Composite Scores (p<0.001) and higher domain scores, including executive functioning (p<0.001), attention and processing speed (p<0.001), language (p=0.003), and memory (p=0.004).

Table 10.

DHBAS CAC Progression Groups: Neuropsychology Data (Mean T-Scores)

	None	Incidence	Non-Progressor	Progressor
	Mean(SD)	Mean (SD)	Mean (SD)	Mean (SD)
Global Composite Score	48.4 (4.7)	47.7 (7.0)	51.4 (4.8)	48.9 (5.9)
Attention/Processing Speed	50.4 (6.4)	49.2 (7.2)	52.3 (9.3)	50.8 (6.8)
Trail Making Test Part A	51.8 (11.0)	52.1 (12.0)	56.4 (14.2)	53.6 (9.7)
Digit Symbol Coding	47.5 (7.4)	49.7 (8.8)	49.0 (6.8)	49.5 (7.9)
Digits Forward	50.8 (9.4)	46.9 (7.4)	49.6 (11.0)	52.1 (9.4)
Digits Backward	51.6 (10.7)	47.9 (10.1)	54.2 (12.0)	48.0 (9.5)
Memory Domain	47.5 (5.9)	47.6 (5.1)	50.9 (1.5)	48.5 (6.5)
WMS-R- LMII	42.9 (5.1)	43.5 (4.5)	42.4 (3.8)	44.4 (4.9)
WMS-R- VRII	50.7 (9.1)	50.2 (9.3)	55.8 (7.3)	50.8 (10.5)
CVLT Total	48.4 (10.0)	47.7 (8.2)	50.8 (3.3)	48.9 (9.7)
CVLT Long Delay	48.0 (11.3)	49.0 (9.1)	54.4 (5.5)	49.8 (9.6)
Executive Functioning	47.3 (9.3)	46.8 (11.7)	52.3 (5.6)	47.0 (10.0)
Trail Making Test Part B	47.6 (9.1)	47.9 (12.9)	57.6 (3.2)	50.0 (9.3)
Block Design	45.6 (9.5)	46.8 (11.0)	49.8 (9.5)	46.9 (9.5)
WCST Errors	48.8 (15.0)	45.9 (15.8)	49.4 (8.4)	43.9 (18.0)
Language	48.3 (7.0)	47.1 (8.9)	50.3 (6.2)	49.3 (6.7)
Boston Naming Test	47.4 (8.8)	44.7 (10.4)	51.4 (12.5)	48.7 (12.6)
Animals	50.4 (10.6)	49.2 (13.0)	53.2 (9.3)	51.0 (9.3)
FAS	47.1 (8.1)	47.4 (11.4)	46.2 (5.1)	48.2 (9.4)

Note: WMS-R: Wechsler Memory Scale Revised; LM: Logical Memory Story A, VR: Visual Reproduction; CVLT: California Verbal Learning Test; WCST: Wisconsin Card Sorting Test

Table 11.

DHBAS Mean T-scores for Tertiles based on CAC Change

	1st Tertile (n=33)	3rd Tertile (n=32)
	Mean(SD)	Mean (SD)
Global Composite Score	48.8 (4.7)	47.5 (6.3)
Attention/Processing Speed	50.7 (6.8)	50.4 (7.9)
Trail Making Test Part A	52.5 (11.4)	53.2 (11.1)
Digit Symbol Coding	47.7 (7.2)	48.3 (9.2)
Digits Forward	50.6 (9.5)	51.1 (10.0)
Digits Backward	52.0 (10.7)	48.9 (9.0)
Memory Domain	48.0 (5.6)	48.3 (6.8)
WMS-III- LM II	42.8 (4.9)	44.4 (5.1)
WMS-III- VR II	51.5 (9.0)	49.5 (9.6)
CVLT Total	48.7 (9.3)	49.5 (11.1)
CVLT Long Delay	49.0 (10.8)	49.5 (9.6)
Executive Functioning	48.1 (9.0)	44.1 (9.4)
Trail Making Test Part B	49.2 (9.1)	49.4 (10.4)
Block Design	46.2 (9.5)	43.4 (9.7)
WCST Errors	48.9 (14.7)	39.3 (14.2)
Language	48.6 (6.8)	47.5 (7.5)
Boston Naming Test	48.0 (9.3)	45.3 (13.8)
Animals	50.8 (10.3)	48.9 (9.1)
FAS	47.0 (7.6)	48.3 (9.8)

Note: WMS: Wechsler Memory Scale-Revised; LM: Logical Memory Story A, VR: Visual Reproduction; CVLT: California Verbal Learning Test; WCST: Wisconsin Card Sorting Test

Table 12.

Multiple Regression Predicting MoCA Change (DHS-2 to DHBAS) using Continuous CAC Change

		Standardized Coefficients			95.0% C.I.	
		Beta	t	Sig.	Lower Bound	Upper Bound
Full Model[1]	(Constant)		2.94	.004	6.26	32.51
	CACΔ	0.28	2.08	.041	0.01	0.28
	Baseline CAC	-0.10	-0.85	.400	-0.12	0.05
	DHS-2 MoCA	-0.29	-2.18	.032	-0.46	-0.02
	Black	-0.31	-2.16	.034	-3.06	-0.13
	Age	-0.43	-3.81	<.001	-0.32	-0.10
	Sex	-0.03	-0.25	.801	-1.44	1.12
	Education	0.01	0.11	.915	-0.20	0.23
	HTN	0.01	0.09	.931	-1.13	1.23
	DM	-0.17	-1.50	.137	-3.42	0.48
	WHR	0.01	0.06	.954	-8.13	8.62
	CHOL	-0.16	-1.30	.196	-2.44	0.51
Reduced Model[2]	(Constant)		3.16	.002	3.82	16.77
	Age	-0.33	-3.32	.001	-0.26	-0.07

a. Dependent Variable: MoCA Change (DHS-2 to DHBAS)

[1]R^2=0.19

[2]R^2=0.11

Note: CACΔ=Coronary Artery Calcification Change in Agatston units [√(DHS-2)- √DHS-1)],Baseline CAC=√(DHS-1 CAC), HTN= Hypertension, DM= Diabetes Mellitus, CHOL=Hypercholesterolemia, WHR=Waist to Hip Ratio in cm

APPENDIX A
Description of Cognitive Measures

Montreal Cognitive Assessment (MoCA)

The MoCA is a brief, 30-item screening measure of global cognitive function. It consists of tasks that assess short-term memory, visuospatial skills, aspects of executive functioning, language fluency, verbal abstraction, simple and sustained attention, as well as naming. The range of scores for each area varies by domain: visuospatial/executive abilities (5 points), naming (3 points), attention (6 points), language (3 points), abstraction (2 points), orientation (6 points), and verbal memory (5 points). Higher scores indicate more intact cognitive function. MoCA total scores were calculated without the 1-point education correction. MoCA scores were collected during DHS-2, and during the DHBAS. MoCA total score was used in analyses. The MoCA can distinguish between no impairment, mild cognitive impairment, and AD more reliably than other commonly used cognitive screening tools. Also, the MoCA is useful in populations with cardiovascular and metabolic symptoms. In a sample of individuals who experienced congestive heart failure (Cameron, Worrall-Carter, Page, Stewart & Ski, 2013) and in a sample with diabetes (Alagiakrishnan, Zhao, Mereu, Senior & Senthilselvan, 2013) the MoCA identified cognitive decline more frequently than the MMSE. Another benefit of the MoCA over other cognitive screens is the availability of normative data in a diverse sample (Rossetti, Lacritz, Cullum & Weiner, 2011).

Mini Mental State Examination

The MMSE is a brief cognitive screening measure that assesses orientation, simple attention, confrontation naming, repetition, memory and ability to follow a complex demand. The MMSE is comprised of 30-items and is commonly used to assess cognitive functioning in a medical setting (Folstein, Folstein & McHugh, 1975), although there are other measures that are more sensitive to change in cognitive decline (Nasreddine et. al., 2005). MMSE scores were collected during DHBAS, and MMSE total scores were used to examine excluded participants. In a community-based sample with adults age 21-84, there was a significant inverse relationship between cIMT and MMSE total score even after controlling for age, education, and income (Zhong et. al., 2011).

Logical Memory

The Logical Memory subtest of the Wechsler Memory Scale-Revised assesses memory for verbal contextual information. This test involves verbal presentation of a short story, which is recalled immediately and after a 20-30 minute delay (Wechsler, 1987). Logical Memory Story A was administered during the DHBAS, and raw scores for Story A delayed recall were converted to T-scores for analyses. When Logical Memory immediate and delayed recall scores of normotensive and hypertensive patients were compared, normotensive patients performed better (Franceschi, Tancredi, Smirne, Mercinelli and Canal, 1982). However, in another study no relationship between Logical Memory immediate and delayed recall scores and CAC, or cIMT was observed (Gatto et. al., 2008).

Digit Span

Digit Span is a task of simple attention. It involves verbal presentation and recall of a string of numbers that increase in length with each trial. Test-takers recite numbers in forward and backward order (Wechsler, 1987). Digit Span was administered during DHBAS and performance was reflected in scaled scores. Scaled scores for Digit Span were converted to T scores for analyses. In a group of elderly individuals with history of cardiovascular disease, WAIS-III Digit Span scores were significantly and inversely related to cIMT (Cohen et. al., 2008).

Verbal Fluency

Participants are asked to list as many words as possible that begin with a certain letter (F, A, and S; Benton, Hamsher & Sivan, 1994) or belong in a specified category (animal and vegetable; Goodglass & Kaplan, 1972) in 60 seconds. Participants are asked not to repeat words during each condition, and responses that do not begin with the appropriate letter or are not members of the specified category are losses of set. Scores were collected for phonemic (F, A, and S) and semantic (animals and vegetables) fluency, and raw scores were converted to T scores for analyses. In a group of elderly individuals with history of cardiovascular disease, COWAT scores were significantly, inversely related to cIMT (Cohen et. al., 2008); however, this has not been replicated and Gatto et al. (2008) found no relationship between verbal fluency scores and CAC or cIMT.

Trail Making Test A & B

The Trail Making Test is a two-part timed test that assesses visuoscanning and executive functioning. Before the initiation of each part, test-takers are allowed to complete sample

trials. The first part, Trails A, involves drawing a line to the appropriate numeric circles, in order. The second part, Trails B, is a more complex version of the first that involves alphanumeric alteration (Reitan, 1979). Trails A and Trails B performance is captured in T-scores, which were used for analyses. In a group of elderly individuals with history of cardiovascular disease, Trail Making Test B, but not A, scores were significantly and inversely related to cIMT (Cohen et. al., 2008) and there was a significant inverse relationship between CIMT at baseline and time to complete TMT-B 10 years later (Zhong et. al., 2012). However, a relationship does not always exist between TMT-A and B scores and CAC or cIMT (Gatto et. al., 2008).

Digit Symbol Coding

Coding is a paper and pencil graphomotor copy task of processing speed that involves visuoscanning. Test-takers are asked to match nonsensical symbols with the appropriate digit. The test is timed and participants are stopped after 120 seconds (Wechsler, 1981). Coding scaled scores were converted to T scores for analyses. In a group of elderly individuals with history of cardiovascular disease, WAIS-III Digit Symbol Coding scores were significantly and inversely related to cIMT (Cohen et. al., 2008).

Boston Naming Test

The Odd numbered Boston Naming Test is an abbreviated 30-item confrontation-naming task. Test takers are shown line drawings of common items, presented in increasing difficulty, and asked to name them. Items are administered in consecutive order (Kaplan, 1983, 1989). Total scores were converted to T scores and used for analyses. In a group of elderly individuals with history of cardiovascular disease, abbreviated BNT scores did

not have a significant relationship with cIMT (Cohen et. al., 2008; Gatto et. al., 2008) or CAC (Gatto et. al., 2008).

Visual Reproduction

The Visual Reproduction subtest of the Wechsler Memory Scale-Revised assesses visual memory. It involves presentation of 7 simple to complex visual stimuli for ten seconds, which are immediately reproduced using pencil and paper. Test takers are instructed to remember the visual stimuli and asked to recall each figure using paper and pencil after a 20 to 30 minute delay (Wechsler, 1987). This test was not administered if the MMSE score was $\leq$ 20. These scores were collected as part of the DHBAS. Delayed recall standard scores were converted to T-scores and used for analyses. When Visual Reproduction immediate and delayed recall scores of normotensive and hypertensive patients were compared, normotensive patients performed better (Franceschi, Tancredi, Smirne, Mercinelli and Canal, 1982).

California Verbal Learning Test

The California Verbal Learning Test (CVLT) is a verbal list-learning task that provides 5 trials, during which the examiner reads the list of 16 words and the participants recall them. After a 20-minute delay, participants are asked to freely recall the 16 words then to recall words based on category cues (Delis, Kramer, Kaplan, & Ober, 1987). The CVLT was administered during DHBAS. Total recall and delayed recall were reported as T scores and used for analyses. Verbal learning on the CVLT was weakly, though negatively correlated with cIMT (Gatto et. al., 2008). In a group of elderly individuals

with history of cardiovascular disease, CVLT did not demonstrate a significant relationship with cIMT (Cohen et. al., 2008).

Wisconsin Card Sorting Test

The Wisconsin Card Sorting Test (WCST) is an untimed test of abstraction and problem-solving. Test-takers are instructed to match cards to four key cards with minimal feedback from the examiner (Heaton, Chelune, Talley, Kay & Curtiss, 1993). Error T-scores were used for analyses. The WCST was not administered if Trails B was discontinued. For perseverative errors, severity of peripheral vascular disease accounted for 15% of variance in performance and disease severity was predictive of poorer scores (n=88; Phillips & Mate-Kole, 1997).

Block Design

Block Design is a timed visuospatial task that involves the manipulation of bi-colored blocks. Test takers are asked to assemble blocks to look similar to block construction completed by the examiner, and then a visual stimulus that is presented during testing (Wechsler, 1981). Block design scaled scores were converted to T scores for analyses. In a group of elderly individuals with history of cardiovascular disease, WAIS-III Block Design scores were significantly and inversely related to cIMT (Cohen et. al., 2008).

APPENDIX B
Additional Methods

Magnetic resonance imaging was utilized to collect 6 transverse slices of the infrarenal abdominal aorta. A 1.5 Tesla whole body system was used, with additional parameters that included repetition after 3 heartbeats, 45 msec echo time, turbo spin-echo factor of 14, a 264 x 330 mm field of view, and matrix size of 256 x 512mm. Images were processed and aortic plaque and wall thickness were quantified. Abdominal aortic plaque was calculated by dividing the total aortic plaque area by the total adventitial aortic area, and multiplying the ratio by 100. Mean aortic wall thickness was calculated by averaging the distance between the adventitial and luminal contours (Victor et al., 2004; Maroules et al., 2013; Paixao et al., in preparation).

APPENDIX C
Additional Analyses

Hypothesis 6: CAC Progression, Cognitive Performance, Sociodemographic Variables, and Traditional Risk Factors

There was a modest but significant inverse relationship between continuous CAC change and DHS-2 MoCA score; however, when baseline CAC, demographic and traditional risk factors were then added to the model in a forward entered fashion (see Table 5) and CAC was no longer a significant predictor. The final model included Hispanic race (β= -0.147, p<0.001), Black race (β= -0.395, p<0.001), age (β= -0.165, p<0.001), and education (β= 0.386, p<0.001) and accounted for 35 % of variance *(*F(4,1372)= 184.540, p<0.001).

When DHS-2 MoCA performance was compared by CAC groups (None, Incidence, Non-Progressors, and Progressors), Progressors had significantly lower MoCA scores (see Figure 1) than all other groups, though after controlling for baseline CAC, sociodemographic variables and traditional risk factors, there were no longer significant differences in MoCA score based on CAC progression group membership (F(3,1358)=1.370, p=0.250).

When a multiple regression model using CAC groups, baseline CAC, demographic factors, and traditional risk factors were added in a forward entered fashion to predict DHS-2 MoCA, the final model included Progressor group membership (β= -0.54, p=0.025), Hispanic ethnicity (β= -0.145, p<0.001), African American race (β= -0.389, p<0.001), age (β= -0.142, p<0.001), and education (β=0.386, p<0.001), and accounted for 35% of the variance in MoCA

scores ($F(5,1357)=145.895$, $p<0.001$). When individuals with stroke were excluded from the sample, Progressor group membership was no longer in the model.

Multiple regression using the variables continuous CAC change, as well as baseline CAC, sociodemographic variable, and traditional risk factors entered in a forward fashion to predict the Global Composite Score resulted in a model that included only Black race (β= -0.507, $p<0.001$), which accounted for 26% of the variance in Global Composite Scores ($F(1,90)=31.069$, $p<0.001$).

The linear multiple regression model predicting MoCA change scores by continuous CAC change highlighted only age as a significant predictor when baseline MoCA, baseline CAC, sociodemographic variables and traditional risk factors were included (see Table 10). The relationship between CAC progression and later cognitive performance on a comprehensive battery was also examined by stratifying DHBAS participants by race (Blacks and Whites), age (65 years and older and younger than 65), education (12 years of education or less and more than 12 years of education), and sex (males and females). There was a significant interaction between the factors CAC progression group membership and age ($F(3,101)=3.096$, $p=0.031$, partial $eta^2=0.091$), as younger individuals in the Incidence group earned significantly lower scores on the Global Composite Score than older individuals. In contrast, younger individuals in the Non-Progressor group earned significantly higher scores than the older group. After controlling for sociodemographic variables and traditional risk factors, the interaction was no longer significant ($p=0.125$). There were no significant interactions between CAC progression groups and race ($p=0.727$), education ($p=0.873$), and sex ($p=0.124$).

There was a significant interaction between CAC tertile and sex ($F(1,65)=4.827$, $p=0.032$, partial $eta^2=0.073$), as males in the 3rd tertile had significantly higher GCS scores than females in the 3rd tertile (see Figure 2). This interaction remained significant after controlling for sociodemographic variables and traditional risk factors ($F(1,62)=4.084$, $p=0.048$, partial $eta^2=0.069$). There was no a significant interaction between tertiles and Blacks and Whites ($p=0.533$), education groups ($p=0.595$), or age groups ($p=0.307$) for GCS.

The relationship between CAC change, sociodemographic groups, and performance on the DHBAS MoCA was also examined. There was a significant interaction between sex and CAC progression group with regard to MoCA scores ($F(3,99)=2.845$, $p=0.042$, partial $eta^2=0.086$). Males in the Non-Progressor group had significantly lower MoCA scores than females in the Incidence and Progressor groups. Additionally, males in the None group had significantly lower MoCA scores than females in the None group, females in the Non-Progressor group, males in the Incidence group, and males in the Progressor group. This interaction remained significant after controlling for sociodemographic variables and traditional risk factors ($F(3,90)=3.023$, $p=0.035$, partial $eta^2=0.103$)(see Figure 3). When the interaction between age groups and CAC progression group membership was examined, it was significant ($F(3,99)=4.821$, $p=0.004$, partial $eta^2=0.137$), as individuals 65 years and older in the Non-Progressor group had significantly lower mean MoCA scores (M=17.5) than all other groups. Younger individuals in the Non-Progressor group earned significantly higher MoCA scores than older individuals in the None group and younger individuals in the Incidence group. After controlling for sociodemographic variables and traditional risk factors, the interaction between the factors age group and CAC group membership was no longer significant ($p=0.104$). There

were no significant factors among CAC group membership, MoCA scores, and race (p=0.298) or education group (p=0.673).

Hypothesis 6 Discussion

Overall, sociodemographic variables accounted for more variance in cognitive scores than CAC and traditional risk factors, which is not unexpected in this sample with relatively low levels of CAC. In several of the analyses, race, age, and education were significant predictors of cognitive scores. Although several of the measures accounted for age, race, and education levels, differences seen in neuropsychological scores between racial groups most likely reflect differences in education level and/or quality.

This study also examined the relationship between atherosclerosis and cognitive performance by certain sociodemographic grouping. In the current study, men demonstrated more CAC progression than females but this did not appear to negatively impact cognitive performance. In contrast, males with incident CAC or CAC progression from DHS-1 to DHS-2 scored higher on the MoCA administered at DHBAS follow-up compared to males who had no CAC progression. This effect was observed after controlling for sociodemographic variables and traditional risk factors. It is important to note that the size of CAC progression groups at DHBAS, particularly when divided based on demographics, was quite small and likely limits the clinical significance of this finding. When the interaction between sex and CAC tertile was examined, males in the 3rd tertile earned higher Global Composite Scores than females in the 3rd tertile. This is inconsistent with prior findings that have increased atherosclerosis in males negatively affecting cognitive performance (van Exel et al., 2001). For example, in a community-based sample similar in age to the DHBAS sample, atherosclerosis severity was

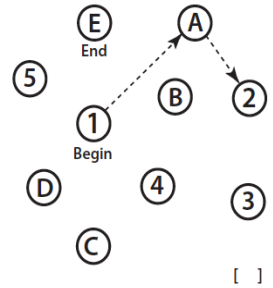
equal between the sexes but only males demonstrated poorer cognitive performance (Auperin et al., 1996). This study also did not show an interaction between Black race, lower levels of education, or older age and CAC group with regard to cognitive performance. Even though there is evidence to suggest these groups may develop atherosclerosis at higher rates than their counterparts, CAC change did not differentially affect cognitive performance in these groups. It is possible that even though these populations are vulnerable to atherosclerosis, the amount of CAC progression in this relatively healthy sample was not sufficient to affect cognitive performance.

APPENDIX D
Montreal Cognitive Assessment Protocol

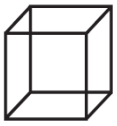
MONTREAL COGNITIVE ASSESSMENT (MOCA)

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

VISUOSPATIAL / EXECUTIVE — POINTS



Copy cube



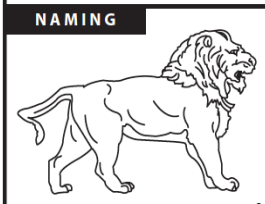
[ ] [ ]

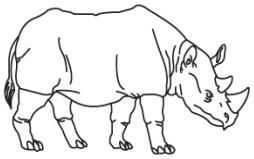
Draw CLOCK (Ten past eleven) (3 points)

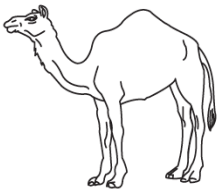
[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING







[ ] [ ] [ ]

__/3

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

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

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

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

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

__/2

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

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

__/1

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

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

__/3

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

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

__/2

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

__/1

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

__/2

DELAYED RECALL

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

__/5

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

__/6

© Z.Nasreddine MD Version 7.1 **www.mocatest.org** Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

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