SUBCLINICAL ATHEROSCLEROSIS AND COGNITIVE FUNCTIONING

IN A POPULATION-BASED SAMPLE

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SUBCLINICAL ATHEROSCLEROSIS AND COGNITIVE FUNCTIONING IN A POPULATION-BASED SAMPLE

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Clinical risk factors for and signs of atherosclerosis have been linked to Alzheimer disease and milder forms of cognitive impairment. This study examines the relationship between subclinical atherosclerosis and cognition in a sample from the Dallas Heart Study (DHS), a population-based study of cardiovascular disease, who were followed 8 years later (DHS-II); N = 1904, mean age = 42.9, SD = 10.5, range 8-65. We analyzed atherosclerosis data from DHS-I participants who had completed the Montreal Cognitive Assessment (MoCA) in DHS-II. The relationship between MoCA scores, coronary artery

calcium (CAC), abdominal aortic plaque, and abdominal aortic wall thickness (AWT) was examined in the group as a whole, and in relation to age and ApoE4 allele status. Indirect measures of atherosclerosis (diabetes, hypertension, hypercholesterolemia, abdominal obesity) were also examined. Logistic regression was used to examine the association between direct and indirect measures of subclinical atherosclerosis and cognitive function, adjusting for other correlates of cognition. CAC (N = 1414, rho = -.06), abdominal AWT (N = 1284, rho = -.04), and abdominal aortic plaque (N = 1286, rho = -.06) did not correlate with MoCA Total Score ($p \geq .048$). Though MoCA scores were successively lower with increasing numbers of both direct atherosclerotic indicators [$F(2, 633) = 1.40$)] and indirect atherosclerotic indicators [$F(2, 1048) = 1.09$], the differences were not significant ($p \geq .248$). The factors that most related to lower MoCA performance were race, gender, and education. There was no difference in MoCA Total Scores or measures of atherosclerosis between participants with an E4 allele and those without the E4 allele. There was no significant relationship between positive CAC, elevated abdominal AWT, and abdominal aortic plaque to MoCA scores obtained 7-8 years later. This relationship did not significantly increase with age and was not influenced by the presence of one or more apolipoprotein E4 alleles. This study does not support an association between direct or indirect measures of atherosclerosis in middle age and global cognition assessed 8 years later in this ethnically diverse population-based sample.

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AD	Alzheimer's Disease
APOE	Apolipoprotein E
AWT	Aortic Wall Thickness
BMI	Body Mass Index
CAC	Coronary Artery Calcium
cIMT	Carotid Artery Intima-Media Thickness
CI	Confidence Interval
CVD	Cardiovascular Disease
DHS	Dallas Heart Study
EBCT	Electron Beam Computed Tomography
ECG	Electrocardiogram
MoCA	Montreal Cognitive Assessment
MCI	Mild Cognitive Impairment
MMSE	Mini Mental State Examination
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association

SECTION ONE

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Introduction

It is often held that vascular factors contribute to the onset and progression of cognitive impairment in neurodegenerative diseases such as Alzheimer disease (Chui, et al., 2006; Hofman, et al., 1997; Viswanathan, Rocca, & Tzourio, 2009), but it is difficult to dissect the vascular impact from the neurodegenerative component in these cases. Given the long latency between onset of vascular risk factors and disease processes such as Alzheimer disease, vascular factors may exert an effect on cognition years before disease expression. The population-based Dallas Heart Study offers direct measures of atherosclerosis, the underlying cause of most cardiovascular events (Lloyd-Jones, et al., 2009), which enable comparison with cognitive function.

Atherosclerosis is linked to stroke, cerebral angiopathy, and tortuosity of the brain's penetrating arteries, all of which have been associated with decrements in cognition (Rosano, Naydeck, Kuller, Longstreth, & Newman, 2005). There are suggestions in the literature, based largely on indirect methods of detection, that atherosclerosis can impact brain function even in the absence of overt strokes or transient ischemic attacks. For example, an examination of persons with autopsy-confirmed AD showed that large-vessel atherosclerosis was strongly associated with increased frequency of neuritic plaques and that amyloid angiopathy was associated with increased density of plaques and tangles (Honig, Kukull, & Mayeux, 2005). Since atherosclerosis is a generalized condition that affects medium-sized and large arteries throughout the body, it seems likely that measures of atherosclerosis in vessels outside the brain may to some degree reflect the state of the brain's vascular bed and cognitive functioning. Few

population-based studies have directly examined the relationship between subclinical atherosclerosis and cognition (Johnston, et al., 2004a; Muller, Grobbee, Aleman, Bots, & van der Schouw, 2007), and most studies have focused on the late stages of atherosclerosis in elderly demented populations with clinical CVD (Elias, Elias, Sullivan, Wolf, & D'Agostino, 2003). Therefore, the relationship between subclinical atherosclerosis and cognitive function has not been well examined, particularly among otherwise healthy individuals.

Atherosclerotic risk has been traditionally assessed using well-known predisposing factors to atherosclerosis, including hypertension (Tervo, et al., 2004), diabetes (Kumari & Marmot, 2005), increased abdominal fat (Lakka, Lakka, Salonen, Kaplan, & Salonen, 2001), and increased plasma lipids (Lloyd-Jones, et al., 2009). These components constitute a recognized clustering of factors known as the metabolic syndrome, which raises the risk of CVD (Grundy, Brewer, Cleeman, Smith, & Lenfant, 2004). However, there are varying definitions of the metabolic syndrome, and relationships between these factors and disease become increasingly complex with advancing age (Luchsinger & Gustafson, 2009; Ruitenberg, et al., 2001). As such, it may be useful to examine these risk factors separately (Muller, Tang, et al., 2007).

Until recently, atherosclerosis was detectable only by late clinical consequences such as heart attack or stroke. The predisposing factors to atherosclerosis described above are traditionally used to assess atherosclerosis risk for heart attack or stroke , such as in Framingham Risk scores (Wolf, D'Agostino, Belanger, & Kannel, 1991); however, they only indirectly indicate the presence of atherosclerosis. Imaging techniques such as computerized tomography and magnetic resonance imaging (MRI) are now able to provide direct measurement of atherosclerosis. Carotid intima media thickness (cIMT)

represents a marker of subclinical atherosclerosis (Bots, Hoes, Koudstaal, Hofman, & Grobbee, 1997), and the carotid artery has been a common target in prior studies because of its proximity to brain and its ease of access via ultrasound. Other direct atherosclerotic measures include determination of coronary artery calcium (CAC) content (Janowitz, 2001), amount of abdominal aortic plaque (Jaffer, et al., 2002), and abdominal aortic wall thickness (Li, et al., 2004). CAC may outperform cIMT, a more general indicator of atherosclerosis, as a predictor of coronary artery disease (Terry, et al., 2005). In addition, abdominal AWT might provide a better index of subclinical atherosclerosis than cIMT, given that autopsy studies have shown that the first atherosclerotic lesions begin in the abdominal aorta (McGill, et al., 2000).

There is little information on the relationship between cognitive performance and CAC, abdominal aortic plaque, or abdominal AWT. However, studies using the more commonly examined cIMT show that atherosclerosis may hasten the onset of cognitive dysfunction, increase its severity, or speed its progression. A cross-sectional study of 400 independently living men (40-80 years old) found that subjects with either subclinical or prevalent CVD had significantly lower Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975) scores (Muller, Grobbee, et al., 2007) than those subjects with no CVD. In a sample of 88 outpatients whose ages ranged from 56 to 85 years, atherosclerotic burden, as measured by cIMT, was significantly associated with brain white matter hyperintensity (WMI) volume and reduced attention, executive function, and information-processing speed (Cohen, et al., 2009). Increased cIMT was weakly associated with lower verbal learning performance (β = -0.07 per 0.1 mm increase CIMT [SE(β) = 0.03], p = 0.01), but not global cognition, in a community-based sample of middle-aged and older adults with subclinical atherosclerosis (Gatto, et al., 2009) and

was an independent predictor of poor memory and cognitive processing speed in a 12-year study of elderly Finnish women (Komulainen, et al., 2007). Romero et al. (2009) found that cIMT correlated inversely with verbal and nonverbal memory measures, and stenosis ≥ 50% was also associated with decreased executive function. In an investigation of 109 persons aged 55-85 years with various types of cardiovascular disease, increased cIMT was associated with significantly lower performance in the attention-executive-psychomotor domain independent of age, sex, cardiovascular risk, systolic blood pressure and history of coronary artery disease. By contrast, cIMT was not significantly related to language, memory, or visuospatial abilities (Haley, et al., 2007).

Presence of the ApoE4 genotype has been linked to both atherogenesis (Davignon, Cohn, Mabile, & Bernier, 1999) and impaired brain function (Corder, et al., 1993; Farrer, et al., 1997). A 14-year population-based study of individuals recruited in middle-age showed an association between ApoE4 genotype and two of three measures of cognition (Knopman, Mosley, Catellier, & Coker, 2009). ApoE4 was independently associated with an average yearly decline in scores on the Digit Symbol Substitution Test (Wechsler, 1981) of 0.10 points for carriers compared to non carriers and 0.17 points for diabetics compared to non diabetics, while stroke and hypertension were not associated. Stroke and ApoE4 genotype independently predicted greater annualized decline on the Delayed Word Recall Test (Knopman & Ryberg, 1989). Metabolic syndrome, hypertension, diabetes, and stroke (but not ApoE4) were independently associated with decline in the Word Fluency Test scores (Lezak, 1995). The combined presence of CVD and ApoE4 may diminish later-life cognitive performance and increase the prevalence of AD significantly more than expected from the independent effects of CVD or ApoE4 genotype alone (Haan, Shemanski, Jagust, Manolio, & Kuller, 1999).

The extent to which atherosclerosis is related to cognition is not fully understood, especially whether the atherosclerotic process has a direct effect on cognition that would be detectable prior to the onset of obvious cognitive impairment. The relationship between objective evidence of atherosclerosis and cognition has been studied in convenience samples and population-based studies of older adults; however, survival to older age may bias results through increased survival of individuals with lesser degrees of atherosclerosis. The relationship of atherosclerosis to cognitive functioning has not been examined in a population-based sample of adults with a wide range of ages or in ethnically diverse groups.

This study utilized a large, ethnically diverse community-based sample to investigate the relationship of cognitive functioning to direct measures of atherosclerosis. Direct and indirect measures of atherosclerosis from the first wave of the Dallas Heart Study (DHS-1) were compared to Montreal Cognitive Assessment scores (MoCA; Nasreddine et al., 2005) obtained 7-8 years later in DHS-II. It was hypothesized that higher levels of direct atherosclerosis measures (CAC, abdominal aortic plaque, and abdominal aortic wall thickness) would be moderately related to diminished cognitive performance at a later point in life, and that an increasing number of positive atherosclerotic indicators would have an incremental negative effect on MoCA scores.

Method

The Dallas Heart Study (DHS) is a population-based, multi-ethnic, longitudinal investigation of factors contributing to progression from health to being at risk for cardiovascular disease (Victor et al., 2004). In this study, African-Americans were over sampled to enhance minority representation and ensure approximately 50% African-American representation (Victor, et al., 2004). DHS provides a large, diverse sample in which to examine the possibility that subtle brain changes associated with subclinical atherosclerosis can be detected by cognitive testing. The first phase of the project was initiated in 1999 (DHS-I). DHS-I participants and spouses were recruited to DHS-II, which began in September 2007 and concluded in January 2010.

Participants

Participants were drawn from the stratified random sample of Dallas County residents obtained in DHS-I (N = 2,911) who returned for follow-up in DHS-II (N = 2,069). All participants were able to speak and comprehend English, provide informed consent and complete a valid MoCA test.

One participant was excluded because he requested that his data not be used. Forty entries were deleted due to missing data. Thirty-seven individuals were excluded due to positive stroke history and 1 person was removed due to unclear stroke history. Primarily Spanish-speaking participants were administered the MoCA in Spanish, and these participants (n = 86) were excluded as this study included only English-speakers. Following these exclusions, 1,904 participants were available for the current study analyses. Of those, 1,155 had data for all three direct measures of atherosclerosis (coronary artery calcium, abdominal aortic plaque, abdominal aortic wall thickness) obtained in DHS-I and completed cognitive testing as part of DHS-II.

Measures

Cognitive functioning was assessed using the Montreal Cognitive Assessment (MoCA), a measure that gathers a wide range of cognitive data over a short period of time. This 30-point screening tool requires approximately 10 minutes to administer and evaluates aspects of attention, orientation, language, verbal memory, visuospatial, and executive function. The MoCA items have been described in detail elsewhere (Nasreddine, et al., 2005) and can be viewed in Appendix E.

Coronary calcification was assessed using electron beam computed tomography (EBCT) with an Imatron C-150XP EBCT scanner (Imatron Inc., San Bruno, California), using a previously described protocol (Jain et al. 2004). This procedure was conducted on participants 30 years of age or older. The data were analyzed in a separate workstation (NeoImagery Industries, City of Industry, California). Results were expressed in Agatston units (Agatston et al. 1990) and the mean of the two consecutive scans was used as the final CAC score, unless only one scan was obtained. To minimize false-positive CAC classifications due to tissue-associated artifact, individuals with a mean EBCT score >10 Agatston U were classified as CAC-positive (Jain, et al., 2004). CAC scores were further categorized using a previously described classification scheme (Rumberger, Brundage, Rader, & Kondos, 1999): as none (<10), mild (≥10 to <100), moderate (≥100 to <400), and severe (≥400).

Abdominal aortic plaque scores were determined by abdominal MRI using a 1.5 Tesla whole-body MRI system [Intera, Philips Medical Systems] (de Lemos, et al., 2005). Six transverse slices of the infrarenal abdominal aorta were obtained using a free-breathing, ECG-gated, T2-weighted turbo spin-echo (black-blood) sequence. Images were analyzed by trained observers using the Magnetic Resonance Analytical Software

Systems (MASS) cardiac analysis software package (Version 4.2 beta, Medis Medical Imaging Systems, Inc). Adventitial and luminal borders were drawn for each slice using a free-hand manual contour drawing tool. Areas of increased signal intensity, luminal protrusion, and focal wall thickening were identified as atherosclerotic plaque and categorized as present or absent (Jaffer, et al., 2002).

Abdominal aortic wall thickness (AWT) was determined using the above-described MRI system. Slice thickness was 5 mm and interslice gap was 10 mm. Images were magnified to 400%; brightness and contrast settings were optimized for wall visualization, and the adventitial and luminal boundaries were drawn for each slice using a free-hand manual contour drawing tool. The AWT for each slice was calculated as the difference between the radius of a circle with area equal to that enclosed by the adventitial boundary, and the radius of a circle with area equal to that enclosed by the luminal boundary, as previously described (Rosero et al., in preparation). The mean AWT for each participant was calculated as the sum of AWT measurements for each slice, divided by the number of slices. Since there is no widely accepted clinical cut-off for AWT, the selection of a dichotomous threshold at the 75th percentile was retrospectively defined using the overall DHS-1 sample of approximately 6,000 subjects, as has been done by other DHS investigators (de Lemos, et al., 2003). The 75^{th} percentile cut-off was stratified by gender and age, as follows, and defined as "normal" or "elevated": ≥60 years (M = 2.32, F = 1.92), 55-59 (M = 2.24, F = 1.90), 50-54 (M = 2.12, F = 1.88), 45-49 (M = 1.94, F = 1.79), 40-44 (M = 1.92, F = 1.72), 35-39 (M = 1.75, F = 1.66), 30-34 (M = 1.72, F = 1.62), ≤29 (M = 1.61, F = 1.44).

Hypertension was defined as average systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg or use of antihypertensive medication. Diabetes was

defined by a fasting glucose level ≥126 mg/dl or use of any hypoglycemic medication. Hypercholesterolemia was defined as low-density lipoprotein cholesterol ≥ 160 mg/dl, total cholesterol ≥ 240 mg/dl, or the use of statin medication. Waist circumference was measured in centimeters on a horizontal plane 1 cm above the iliac crest. The National Cholesterol Education Program obesity threshold was used to determine abdominal obesity; 88 cm and 102 cm for women and men, respectively ["Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III)," 2001]. Apolipoprotein E genotyping was conducted, by a method described elsewhere (Emi, et al., 1988).

Procedures

DHS-I involved three separate visits, during which demographic and health-related information, measurements of blood pressure, weight, height, and waist-hip ratio, and venous blood and urine samples were obtained. Participants also underwent EBCT and MRI and APOE genotype testing. For DHS-II, information gathered during the course of a 1-day visit included social and medical history, physical examination, blood and urine sampling, CAC, MRI estimation of abdominal aortic plaque and vessel wall thickness, and brief cognitive testing using the MoCA.

Because MoCA testing was conducted during the participants' day-long visit, attempts were made to administer the test at the beginning of the day to minimize potential fatigue effects. It was performed by trained personnel, scored in the conventional manner, and double-checked for accuracy. We omitted the suggested 1-point correction for 12 years of education or less (Nasreddine, et al., 2005), as this did not seem to be an adequate adjustment for our sample. After scoring, the de-indentified

MoCA data were entered item-by-item in the DHS database.

Data Analysis

Statistical analyses were conducted using SPSS version 18.0 (SPSS, Inc., Chicago IL). The statistical assumptions for all analyses were examined to ensure the appropriateness of each analysis. Due to the large number of tests conducted, the more stringent p-value of ≤ 0.01 was the test of significance in all analyses. To assist with the determination of clinical relevance, the strength of significant correlation coefficients was designated as small (.10-.29), medium (.30-.49), and large (>.50) using standard criteria (Cohen, 1988).

Nominal data are reported as percentiles and continuous data as means with standard deviations and median values. Direct atherosclerosis measures were compared by gender and race using ANCOVA to control for education and age. Markedly skewed variables (CAC and abdominal aortic plaque) required $\log_{10}$ transformation to meet assumptions of parametric statistical testing when used as continuous variables; for clarity, we report the these data as antilogs.

To determine if there was a relationship between direct measures of atherosclerosis and global cognition, partial Spearman correlations between the MoCA scores and coronary artery calcium scores, abdominal aorta plaque, and abdominal aortic wall thickness were conducted, controlling for the covariate of education and age. In order to determine if having more than one positive indicator of atherosclerosis resulted in a stronger relationship to cognitive function, participants were also grouped according to the number of direct indicators (CAC score > 10, presence of aortic plaque, or AWT $\geq$ 75^{th} percentile) present: 1, 2, and 3. For this analysis, only participants with data for all 3 indicators were used and those with 0 positive indicators (N = 517) were excluded due to

unequal sample size. The mean MoCA score among groups was compared using ANCOVA, controlling for education and age. A similar analysis was conducted using positive indirect measures of atherosclerosis (diabetes, hypertension, hypercholesterolemia, waist circumference > 102 cm for men and 88 cm for women): 1, 2, and 3 or 4 positive indicators (combined due to the small sample size of the 4 indicator group, N=23).

In addition to its use as a continuous variable, MoCA scores were divided into tertiles (lowest, middle, highest). We determined associations between lowest MoCA tertile and direct atherosclerosis measures (CAC scores, abdominal aorta plaque, and abdominal AWT), and traditional, indirect measures of atherosclerosis (hypertension, diabetes, hypercholesterolemia, and waist circumference) using a series of logistic regressions, with adjustment for demographic variables (age, education, gender, and race). Area under receiver operator characteristic (ROC) curve was estimated to assess the performance of the final adjusted model. The area may range from 0.0 to 0.50 (no discrimination between participants in lowest and highest tertile by model) to 1.00 (100% discrimination between participants in lowest and highest tertile by model). These analyses determined whether direct, physical measures of atherosclerosis predict cognitive functioning as well or better than indirect, traditional indicators of atherosclerosis, and what combination of these variables had the most predictive value.

To determine if the presence of the ApoE4 allele related to cognitive performance, mean MoCA scores for participants with and without an E4 allele were compared using ANCOVA, controlling for education. To explore whether the presence of ApoE4 strengthened the relationship between subclinical atherosclerosis and cognitive functioning, ApoE4 status was added as a variable of interest to the regression models

described above.

Results

Demographic characteristics. Descriptive information is presented in Table 1. The majority of participants were Black (54%) and female (58%). The average age at DHS-I was 42.96 years (SD = 10.52) and at DHS-II 50.87 (SD = 10.39). The sample had an average 13.6 years of education (SD = 2.7). Men had significantly more years of education [M (SD) = 13.90 (2.8)] than women [M (SD) = 13.36 (2.6), $t = 4.34$, $p < .001$]. Due to its small sample size (N = 41), the "Other" race group was excluded from group analyses when race was compared and in any logistic regression modeling, and these analyses did not differ with or without the inclusion of the "Other" race.

Health characteristics. Eight percent of participants were diabetic (see Table 1); slightly higher than the national estimate of 5% (WHO, 1999) due to the high proportion of Black participants, 14% of whom were diabetic. The rate of hypertension in this sample (31%) was comparable to the 30% prevalence in the general population (Lloyd-Jones, et al., 2009), while the rate of hypercholesterolemia (10%) was lower than the 20% estimate from the Centers of Disease Control (Fryar, Hirsch, Eberhardt, Yoon, & Wright). Approximately 58% of the sample was above the abdominal obesity threshold, with significantly more females (56%) affected than men (40%), compared to national estimates of 62% obese females and 42% obese males (Li, Ford, McGuire, & Mokdad, 2007). In regard to APOE status, E3/E3 was the most frequently occurring allele (55%), and 32% had at least one E4 allele, which is comparable to prior estimated frequencies in the general population (Hill, Bhattacharjee, & Neumann, 2007).

Atherosclerosis. CAC and abdominal aortic plaque scores were $\log_{10}$ transformed to conduct parametric analyses, and Tables 2 and 3 represent antilog data. Although the

transformation did not fully normalize the distribution of CAC and abdominal aortic plaque, additional ANCOVA analyses were conducted using their rank orders and results were similar to those with the log-transformed data.

Means, standard deviations, and medians for CAC for the overall sample and by gender and race are presented in Table 2. The average CAC score was 0.11 (SD = 114.3) and the median CAC score was .50. Although education only weakly correlated with CAC scores (rho = -.104, p = .010), there were differences by education group. Those with less than 12 years of education had significantly higher CAC [N = 168; M (SD) = 0.27 (138.04)] than those with 12 years [N = 404; M (SD) = 0.16 (125.89)] or ≥ 13 years of education [N = 841; M (SD) = 0.07 (102.33); F(2, 1410) = 7.52, p = .001]. Age and CAC scores were moderately correlated (rho = .417, $p \leq .001$). When CAC was dichotomized using the 10 Agatston unit as a cut-off, 15% of the sample had positive CAC. More men (28%) had CAC scores above the Agatston cut-off of 10 than women (14%), and males had significantly higher overall CAC than females [F(1, 1409) = 76.23, $p \leq .001$] after controlling for education and age. There were differences in CAC scores by race after controlling for education and age [F(2, 1375) = 5.26, p =.005], as Blacks had significantly higher CAC than Whites.

Means, standard deviations, and medians for abdominal aortic plaque for the overall sample and by gender and race are presented in Table 3. The average abdominal aortic plaque (mm^2) was 0.05 (SD = 164.3) and the median measurement was 0. Abdominal aortic plaque was not significantly associated with education (rho = -.040, p = .152), and although those with less than 12 years of education tended to have higher measurements than those with 12 or more years of education, the differences were not significant; F(2, 1281) = 4.08, p = .017. Age and abdominal aortic plaque were

moderately correlated (rho = .355, $p \leq .001$). When classified as either present or absent, 37% of the sample had detectable aortic plaque, which was more prevalent among men (41%) than among women (34%), and males had significantly higher overall abdominal aortic plaque than females [$F(1, 1281) = 11.45$, $p = .001$] after controlling for age. There were no significant differences by race; $F(2, 1281) = .696$, $p = .499$.

Means, standard deviations, and medians for abdominal AWT for the overall sample and by gender and race are presented in Table 4. The average abdominal AWT (mm) was 1.68 (SD = 0.3) and the median measurement was 1.65. Abdominal AWT was not significantly associated with education (r = -.051, $p = .065$), and although those with less than 12 years of education tended to have higher AWT than those with 12 or more years of education, the differences were not significant; $F(2, 1284) = 3.76$, $p = .024$. Age and AWT were moderately correlated (r = .383, $p \leq .001$). When AWT was dichotomized using the 75th percentile (1.83 mm) as a cut-off, 25% of the sample had elevated AWT. Men had significantly greater AWT (M = 1.77, SD = 0.3) compared to women (M = 1.62, SD = 0.3); $F(1, 1284) = 87.09$, $p \leq .001$. There were no significant differences by race after controlling for age; $F(2, 1253) = 3.81$, $p = .022$.

MoCA performance. The reliability of the MoCA in this sample was examined using Cronbach's alpha to measure consistency across scoring items. A Cronbach's alpha level of 0.60 is the minimal level that demonstrates consistency (Hartmann, 1977), and the MoCA was found to be adequately reliable (23 items; $\alpha = .67$). MoCA performance for the overall sample and by gender and race is presented in Table 5. The MoCA Total Score ranged from 7 to 30 points with a mean of 23.63 (SD = 4.3), compared to published normative data of a mean of 27.2 (SD = 3.0) for normal elderly controls

(Nasreddine, et al., 2005). The majority of the sample (65%) fell below the suggested 26-point cut-off score for mild cognitive impairment (Nasreddine, et al., 2005)

Education was moderately associated with MoCA performance (N = 1904, r = .43, $p < .001$), and age was weakly correlated with MoCA total score (r = -.199, $p \leq$ .001). After controlling for education and age, there was no difference in MoCA scores by gender; $F(1, 1900) = 5.26$, $p = .022$. After controlling for education and age, White participants obtained significantly higher MoCA total scores than all other groups and Black individuals scored lower than Hispanic subjects; $F(1, 1858) = 137.65$, $p \leq .001$.

Cognition and atherosclerosis. The relationship between direct measures of atherosclerosis was examined using Spearman's rho, controlling for education and age. CAC [rho (1409) = -.06, $p = .048$], abdominal AWT [rho (1283) = -.04, $p = .187$], abdominal aortic plaque [rho (1280) = -.06, $p = .052$], did not correlate with MoCA Total Score. When stratified by sex, the relationships between these measures of atherosclerosis and MoCA did not differ ($p \geq .152$). The correlational analysis was also conducted by race, and there were no significant relationships between measures of atherosclerosis and MoCA Total Score for any of the racial groups ($p \geq .114$).

Pearson product-moment correlations (using $\log_{10}$ transformed CAC and abdominal aortic plaque to correct for skewed distributions) were also conducted, and results did not differ from those presented for Spearman. When correlational analyses were conducted with only those participants greater than 50 years of age, who were thought to be more vulnerable to the effects of atherosclerosis, a small, but significant relationship was only found for MoCA Total Scores and abdominal aortic wall thickness (N = 355, r = -.16, $p = .004$).

Direct measures of atherosclerosis were also examined as categorical variables in relation to MoCA performance while controlling for education and age (see Table 6). The positive CAC group (>10 Agatston units) obtained slightly lower MoCA scores than the negative CAC group, though the difference was not significant; F(1, 1409) = 3.95, p = .047. Those with abdominal aortic wall thickness at or above the 75th percentile also obtained slightly lower MoCA scores than those below the 75th percentile, though the difference was not significant; F(1, 1282) = .009, p = .924. The group with abdominal aortic plaque obtained slightly lower MoCA scores than the group without plaque, though the difference was not significant; F(1, 1280) = 2.34, p = .126.

In order to determine if a greater number of positive atherosclerotic indicators resulted in lower MoCA scores, those with only 1 positive measure (CAC > 10 or aortic plaque or elevated AWT) was compared to those with two positive indicators and those with all three positive indicators (CAC > 10, present aortic plaque, and elevated AWT; see Table 7). Of the three direct atherosclerosis measures, abdominal aortic plaque was the most common positive indicator. After controlling for education and age, the 3-indicator group obtained lower MoCA Total Scores than the 1 and 2-indicator groups, though the differences were not significant; F(2, 633) = 1.40, p = .248, η^2 = .004. When the 0-indicator group was included, the results were also in the expected direction, with those in the 0-indicator group (N = 517) obtaining higher MoCA Total Scores [M (SD) = 23.89 (3.89)] than all other groups; F(3, 1149) = 1.09, p = .351, η^2 = .003. There was no correlation between MoCA total scores and number of positive atherosclerosis measures [rho (1151) = -.04, p = .216].

A similar analysis using indirect measures of atherosclerosis (diabetes, hypertension, hypercholesterolemia, waist circumference > 102 cm for men and 88 cm

for women) revealed that those individuals with more positive indicators (2-indicators, and 3 or 4 indicators) obtained successively lower MoCA Total Scores than the 1-indicator group, though the differences were not significant; $F(2, 1048) = 1.09$, $p = .335$, $\eta^2 = .002$ (see Table 8). Of the indirect atherosclerosis measures, diabetes was the most common positive indicator. When the 0-indicator group (N = 474) was included, the results were in the expected direction, with those in the 0-indicator group obtaining higher MoCA Total Scores [M (SD) = 24.10 (3.76)] than those with 2 indicators and 3 or 4 indicators; $F(3, 1521) = 1.14$, $p = .333$, $\eta^2 = .002$. There was a no correlation between MoCA total scores and number of positive vascular risk factors [rho (1523) = -.04, $p = .134$]. In order to determine if there was a differential impact of these factors in older individuals, the above analyses were repeated for older participants (greater than 50 years of age, n = 438), and there was a trend toward lower MoCA Total Scores with increasing numbers of direct or indirect atherosclerosis measures, though differences were not significant ($p \geq .024$).

In order to examine what variables contributed to MoCA performance, the MoCA Total Score was divided into tertiles, and the characteristics of the tertile groups are presented in Table 9. The Lowest tertile (N = 687) had an average MoCA Total Score of 18.97 (SD = 2.9) and ranged from 7 to 22 points. The Highest tertile (N = 659) had an average MoCA Total Score of 27.35 (SD = 1.2) and ranged from 26 to 30. The Lowest tertile was significantly older, less educated, and had a higher proportion of Black participants (74%), and a higher frequency of diabetes and hypertension compared with the Middle and Highest MoCA tertile groups. Direct measures of atherosclerosis by Lowest and Highest MoCA tertile can be seen in Table 10. After controlling for education, those in the Lowest MoCA Tertile had significantly higher CAC, abdominal

aortic plaque, and abdominal AWT ($p \leq .003$); however, these differences were removed after controlling for age ($p \geq .024$).

Logistic regression was used to examine the Lowest and Highest MoCA tertiles using demographic characteristics, indirect atherosclerosis risk factors, and direct measures of atherosclerosis to predict membership in the Lowest MoCA tertile. The unadjusted full model included the indirect and direct measures of atherosclerosis and ApoE4 allele status, using the forced entry method. The reduced, unadjusted model (Table 11) was determined using a backward stepwise method with alpha to enter = .10 and alpha to leave = .15. The full model was then adjusted for demographic variables, and the final adjusted model was determined using the backward stepwise method described above (see Table 12). Higher age, lower education, and male gender were most predictive of membership in the Lowest MoCA tertile ($p \leq .001$), while White race lowered the likelihood of being in this group ($p \leq .001$). The area under receiver operator characteristic curve was used to characterize the final adjusted model, which showed good discrimination between Lowest and Highest MoCA tertile (AUC = .851, $p \leq .001$, CI = .825 - .876; see Figure 1), using standard criteria (Hosmer, 1999). Using the final adjusted logistic regression model, a predicted score of ≥ .54 determined membership in the Lowest MoCA tertile with 76% sensitivity and 81% specificity.

ApoE4, cognition, and atherosclerosis. The frequency of ApoE4 was 0.15, which is comparable to the 0.14 observed in the general U.S. population (Mahley, 1988). The frequency was greater in Blacks (0.19) compared to White participants (0.13), which is consistent with prior reports (Farrer, et al., 1997; Hallman, et al., 1991) The impact of the E4 allele on cognitive performance was examined using ANCOVA to control for education. There was no difference in MoCA Total Scores between participants with an

E4 allele and those without an E4 allele; $F(1, 1643) = .078$, $p = .780$. The influence of E4 on direct atherosclerosis measures was also examined, with no differences in CAC, AWT, or aortic plaque ($p \geq .455$). Given that ApoE4 frequency varied by race, these analyses were also examined for Blacks and Whites separately, and results did not differ ($p \geq .180$).

Discussion

Much of the evidence for an association between cognitive functioning and atherosclerosis comes from studies of selective populations, such as the elderly (Kearney-Schwartz, et al., 2009; Vidal, et al., 2010) and those with advanced atherosclerosis (Lee & Yeh, 2007; Muller, et al.). Literature on subclinical atherosclerosis has only recently increased due to advances in imaging, and the majority of this work has utilized carotid measures of atherosclerosis (Muller, Grobbee, et al., 2007; Romero, et al., 2009). This is the first study to date to simultaneously examine direct measures of atherosclerosis (CAC, abdominal aortic plaque, abdominal AWT), along with traditional vascular risk factors for atherosclerosis (diabetes, hypertension, high cholesterol, abdominal obesity), in relationship to global cognitive function. In this population-based sample, there was little to no relationship between measures of subclinical atherosclerosis and MoCA scores obtained 7-8 years later.

There were differences in the degree of atherosclerosis by demographics, as expected. Older individuals and those with less education tended to have higher levels of atherosclerosis, as measured by CAC, abdominal aortic plaque, and abdominal AWT, as has been previously reported (Yan, et al., 2006). Men demonstrated a higher atherosclerotic burden, as measured by CAC, plaque, and AWT, compared to women. This is consistent with the observation that cardiovascular disease occurs later and with

lower frequency among women (Murabito, 1995). Hispanics were less affected by abdominal aortic plaque and AWT than either Blacks or Whites, and Blacks also showed greater CAC than other ethnicities, though racial differences disappeared after age was considered. Cognitive performance had a weak negative association with age, and was more strongly influenced by education. Higher MoCA scores were observed in Whites even after controlling for education and age, which may reflect differences in education quality or socioeconomic status for ethnic groups (Morgan, Marsiske, & Whitfield, 2008).

CAC, abdominal AWT, and abdominal aortic plaque were not correlated with scores on the MoCA, and the relationship between cognitive scores and atherosclerosis did not differ by gender or race. A somewhat greater relationship between AWT and MoCA scores ($r = -.16$) was seen in individuals over age 50, though the weak strength of the finding is likely of minimal clinical significance. When MoCA scores were compared between positive and negative CAC, present versus absent aortic plaque, and AWT above or below the 75^{th} percentile, results were in the expected direction, with lower cognitive performance in groups with positive atherosclerotic measures, though this finding was attenuated by age and education.

The relationship between CAC and cognitive performance has not been widely examined, and results differ based on study design with significant associations being found in older samples. Increasing CAC was associated with decreased cognitive speed of processing, and executive function in an Icelandic cohort of 4,250 men and women with an average age of 76 years, though this finding was removed by age and education (Vidal, et al., 2010). In a population-based study of 409 individuals aged 65 and older, those with higher CAC were more likely to have mild cognitive impairment (Rosano, et

al., 2005). However, in a cross-sectional study of middle-to-older aged adults with subclinical atherosclerosis, CAC was not associated with lower performance on any of the neuropsychological measures administered (Digit Symbol, Block Design, Letter Number Sequencing, Trails-B, Category Fluency, Boston Naming Test, CVLT, Logical Memory, Judgment of Line Orientation; Gatto et al., 2009). Even fewer published data on cognition and aortic plaque and AWT are available for comparison with the current findings, which used a middle-aged sample with few subjects over 60 years of age.

Interestingly, the presence of ApoE4 did not significantly impact cognitive performance as has been previously reported (Small, Rosnick, Fratiglioni, & Backman, 2004). Also unexpectedly, the influence of vascular factors on cognition did not significantly increase with age, though when the relationships between MoCA scores and direct measures of atherosclerosis were compared by age quartiles, there was a trend toward significant correlations with CAC ($r = -.13$, $p = .012$) and AWT ($r = -.14$, $p = .015$) in the oldest group (ages 52-65). These findings may be related to differences in the populations studied and in the measures employed. It is possible that a healthy survivor effect partially accounts for these findings, such that less healthy participants would have been more likely to drop out in the interval between the assessment of atherosclerosis and MoCA testing (Arrighi & Hertz-Picciotto, 1994; Paramsothy, et al.; Philips, de Lemos, Patel, McGuire, & Khera, 2007).

Although there were differences between the highest and lowest MoCA Tertile groups, such as increased prevalence of diabetes and higher abdominal AWT in the lowest MoCA Tertile group, those factors were not the most predictive of MoCA performance. Regression modeling highlighted demographic factors of age, gender, education, and race as the key predictors of lowest and highest MoCA Tertile. Slightly

lower MoCA scores were obtained with successively greater number of positive indicators of atherosclerosis (e.g. CAC ≥10) and traditional risk factors for atherosclerosis (e.g. diabetes). Thus, even though the relationships between individual factors and cognition were not significant, a combination of factors, or cumulative effects of these burdens, may contribute to cognitive vulnerability over time, though differences were marginal after considering demographic factors.

Despite the large sample size and unselected nature of this cohort, the present study has limitations, the foremost being the lack of baseline cognitive testing and the 7-8-year interval between measurement of atherosclerosis and MoCA testing. This study focused on vascular risk at one time point, and the potential development of additional vascular risk during the interval between DHS-I and DHS-II was not examined. The implications of such changes are unclear; however, our findings of only modestly lower MoCA scores with increasing positive or elevated risk factors would suggest such an effect would be minimal. It is possible that concurrent atherosclerosis measurements or change scores over time may show a greater relationship with cognitive functioning than what was seen in the present study, and those data are forthcoming.

Although large, population-based studies are valuable, the interpretability of the results may be limited by factors inherent to the cross-sectional community-based design, which limits conclusions regarding within-person change or direction of causality. The DHS sample was relatively well educated and had a majority of minority participants, so these findings may not generalize to less educated populations or those with a different ethnic composition. A comparison of healthy individuals to a group with clearly defined atherosclerosis may help identify differences in cognitive function. In addition, this study focused on measures of atherosclerosis in fairly young and healthy sample, in which the

prevalence of clinically relevant CAC, aortic plaque, and abdominal AWT among participants was relatively low, which may have reduced our ability to observe associations. It may be that the levels of CAC, aortic plaque, and abdominal AWT in this sample had not yet reached a threshold that would result in notable decrements in cognition. Further, duration of the vascular factors may play a key role in determining the risk of cognitive loss (Rosano, et al., 2005) and since the length of time a participant had a positive indicator was unknown, some individuals may have recently developed a risk factor while others may have carried that burden for years. However, the impact of this is unclear as positive indicators were present for at least 7 years between DHS-I and II. Finally, there was no formal assessment of dementia or traumatic brain injury in DHS-I, so those conditions could not be ruled out as a potential confound for MoCA performance.

The MoCA itself has limitations. First, it is a relatively new measure. Although it has been reported to be more sensitive than tests such as the MMSE in detecting MCI (Zadikoff, et al., 2008), it is a screening tool for global cognition and may not be sensitive enough to show the cognitive effects of subtle biological processes. A study comparing the internal consistency reliability and validity of the MoCA in 3 samples (healthy individuals in a preventive medicine clinic, DHS Dallas community residents, and clinical patients in a neurology clinic) found reliability was low in the first 2 samples, but high in the clinical sample, suggesting that the MoCA may be a better assessment tool among impaired individuals than in largely normal samples (unpublished data). In addition, normative data for the MoCA are limited to Canadian Caucasians and its validity in other populations is not known. Further studies of subclinical atherosclerosis

and cognition using more comprehensive and sensitive neuropsychological tests would be helpful.

It may also be useful to follow individuals with a higher atherosclerotic burden longitudinally to determine how cognitive performance changes over time in relationship with atherosclerosis measures. This may aid in establishing when atherosclerosis begins to exert effects on cognition, which would have implications for the development and targeting of appropriate interventions. As previously mentioned, the results of DHS-II measurements of atherosclerosis will become available for comparison to concurrent MoCA testing, and factors such the rate of change in atherosclerosis will be examined in relation to cognitive performance.

In summary, there was no relationship between direct measures of atherosclerosis and cognitive testing approximately 8 years later in this population-based sample. The majority of participants were in mid-life, a time in which vascular risk factors such as hypertension (Launer, Masaki, Petrovitch, Foley, & Havlik, 1995), hypercholesterolemia (Solomon, et al., 2007), and abdominal obesity (Whitmer, et al., 2008) have been shown to increase cognitive vulnerability in later life. Although CAC, abdominal aortic plaque, and abdominal aortic wall thickness were not predictors of global cognitive performance, it is not yet known if early-life development or prolonged elevations of these biological measures may play a role in the development or earlier expression of cognitive impairment with advancing age.

TABLES

Table 1. *Characteristics of the DHS Sample*

	N	Min	Max	M
DHS 1 Age	1904	18	65	42.96 (10.52)
DHS 2 Age	1904	26	74	50.87 (10.39)
Education	1904	1	20	13.59 (2.69)
Female N (%)	1103 (58)			
Race N (%)				
Black	1019 (54)			
White	637 (33)			
Hispanic	207 (11)			
Other	41 (2)			
MoCA Total Score	1904	7	30	23.36 (4.03)
CAC Score (Agatston units)*	1414	0	7444	52.55 (310.4)
CAC Category N (%)				
None <10	1127 (80)			
Mild 10-99	169 (12)			
Moderate 100-399	81 (5)			
Severe ≥400	37 (3)			
Abdominal Aortic Plaque Area (mm^2) *	1284	0	588	23.12 (59.4)
Detectable Plaque N (%)	471 (37)			
Abdominal Aortic Wall Thickness (mm)	1287	1	3.47	1.68 (.30)
>75^{th} percentile N (%)	325 (25)			
Waist Circumference (cm)	1564	56	164	99.55 (17.04)
> 88 cm for females N (%)	615 (56)			
>102 cm for males N (%)	296 (40)			
Diabetic N (%)	157 (8)			
Hypertensive N (%)	578 (30)			
Hypercholesterolemia N (%)	195 (10)			
ApoE4 N (%)	530 (32)			

* Log_{10} transformed scores were used in parametric analyses.

Table 2. *Coronary Artery Calcium (Agatston Units) by Gender and Race, Controlling for Education and Age*

		Coronary Artery Calcium[1]		
		Male	Female	Overall
Black	M	0.42 (135.9)	0.07 (83.2)	0.14 (108.7) [3]
	Median	1.55	.50	.59
White	M	0.21 (144.7)	0.02 (84.8)	0.06 (126.1)
	Median	0.95	0	0
Hispanic	M	0.28 (112.3)	0.02 (63.3)	0.07 (96.9)
	Median	1.36	0	0
Total	M	0.29 (135.1) [2]	0.04 (84.2)	0.11 (114.3)
	Median	1.13	0	.50

[1] CAC was log transformed to conduct ANCOVA; these data are the backtransformed values.
[2] Males had significantly higher CAC than females, $F(1, 1409) = 76.23$, $p \leq .001$
[3] Blacks had significantly higher CAC than Whites, $F(2, 1375) = 5.26$, $p = .005$

Table 3. *Abdominal Aortic Plaque (mm^2) by Gender and Race, Controlling for Age*

		Abdominal Aortic Plaque [1]		
		Male	Female	Overall
Black	M (SD)	0.11 (218.6)	0.04 (152.4)	0.06 (178.1)
	Median	0	0	0
White	M (SD)	0.11 (228.9)	0.04 (137.6)	0.06 (181.1)
	Median	0	0	0
Hispanic	M (SD)	0.02 (124.9)	0.02 (84.9)	0.02 (99.3)
	Median	0	0	0
Total	M (SD)	0.10 (214.9) [2]	0.04 (138.0)	0.05 (164.3)
	Median	0	0	0

[1] Abdominal aortic plaque was log transformed to conduct ANCOVA; these data are the backtransformed values.
[2] Males had significantly higher abdominal aortic plaque than females, $F(1, 1280) = 11.45$, $p = .001$.

Table 4. *Abdominal Aortic Wall Thickness (mm) by Gender and Race, Controlling for Age*

		Abdominal AWT		
		Male	Female	Overall
Black	M (SD)	1.65 (.3)	1.65 (.3)	1.70 (.3)
	Median	1.76	1.62	1.67
White	M (SD)	1.78 (.3)	1.63 (.3)	1.70 (.3)
	Median	1.74	1.61	1.68
Hispanic	M (SD)	1.67 (.2)	1.53 (.2)	1.59 (.2)
	Median	1.70	1.51	1.58
Total	M (SD)	1.77 (.3) [1]	1.63 (.3)	1.68 (.3)
	Median	1.74	1.61	1.65

[1] Males had significantly higher abdominal AWT than females, $F(1, 1284) = 87.09$, $p \leq .001$

Table 5. *MoCA Total Score by Gender and Race, Controlling for Education and Age*

	Male		Female		Overall	
	N	M	N	M	N	M
Black	389	21.81 *(3.41)*	630	22.42 *(3.44)*	1019	22.11 *(3.54)* [1]
White	299	24.81 *(3.51)*	338	25.33 *(3.46)*	637	25.07 *(3.56)* [1]
Hispanic	87	23.26 *(3.41)*	120	24.16 *(3.45)*	207	23.71 *(3.50)*
Total	775	23.29 *(4.18)*	1087	23.97 *(4.25)*	1863	23.63 *(4.27)*

[1]White group significantly higher than all other groups and black group significantly lower than Hispanic group, $p \leq .001$.

Table 6. *MoCA Total Score by Categorical Atherosclerosis Measures, Controlling for Education and Age*

	Mean	Std. Deviation	N
Coronary Artery Calcium			
≥ 10	22.35	4.40	287
< 10	23.69	3.87	1126
Abdominal Aortic Wall Thickness			
≥ 75th percentile	23.41	4.13	325
< 75th percentile	23.68	3.88	961
MRI Aortic Plaque			
Present	23.03	4.15	471
Absent	23.95	3.78	813

Note. No significant differences in MoCA scores.

Table 7. *MoCA Total Score by Number of Direct Atherosclerosis Measures (Positive CAC, Present Aortic Plaque, Elevated AWT), Controlling for Education and Age*

				95% Confidence Interval	
	N	Mean	SD	Lower Bound	Upper Bound
One Indicator	388	23.65	3.82	23.29	24.05
Two Indicators	186	23.13	3.90	22.50	23.64
Three Indicators	64	21.88	5.10	20.69	23.25

Note. No significant differences between groups.

Table 8. *MoCA Total Score by Number of Indirect Measures of Atherosclerosis (Diabetes, Hypertension, Hypercholesterolemia, Abdominal Obesity), Controlling for Education and Age*

				95% Confidence Interval	
	N	Mean	SD	Lower Bound	Upper Bound
One indicator	574	23.55	3.64	23.25	23.84
Two indicators	334	22.91	3.63	22.52	23.30
Three or Four Indicators	145	22.41	3.65	21.82	23.01

Note. No significant differences between groups.

Table 9. *Characteristics of the DHS Sample by MoCA Tertiles*

	Lowest (N = 687)	Middle (N = 558)	Highest (N = 659)	Overall (N = 1904)	Statistic	*p*
MoCA Total Score						
M	18.97 *(2.9)*	24.06 *(.80)*	27.35 *(1.2)*	23.36 *(4.0)*	$F(2)= 65.88$	<.001
Range	7-22	23-25	26-30	7-30		
Gender N (%)						
Male	296 *(43)*	239 *(43)*	266 *(40)*	801 *(42)*	$\chi^2 = 1.13$	.569
Female	391 *(57)*	320 *(57)*	392 *(60)*	1103 *(58)*		
Education M	12.39 *(2.4)*	13.47 *(2.5)*	14.95 *(2.5)*	13.59 *(2.7)*	$F(2) = 182.70$	<.001
Age M	45.47 *(9.8)*	42.42 *(10.3)*	40.8 *(10.)*	42.96 *(10.5)*	$F(2) = 35.29$	<.001
Race N *(%)*						
Black	507 *(74)*	315 *(56)*	197 *(30)*	1019 *(54)*	$\chi^2(6) = 350.78$	<.001
White	88 *(13)*	159 *(28)*	390 *(59)*	637 *(33)*		
Hispanic	80 *(11)*	70 *(13)*	57 *(9)*	207 *(11)*		
Other	12 *(2)*	15 *(3)*	14 *(2)*	41 *(2)*		
Waist Circumference						
M	101.74 *(17.3)*	99.63 *(16.2)*	97.32 *(17.2)*	99.55 *(17.0)*	$F = 3.69$	<.025
APOE4						
N *(%)*	187 *(11)*	163 *(10)*	180 *(11)*	530 *(28)*	$\chi^2 = .382$	.826
Diabetic						
N *(%)*	74 *(13)*	45 *(9)*	38 *(7)*	157 (*9)*	$\chi^2 = 12.16$	.002
Hypertensive						
N *(%)*	278 *(41)*	166 *(30)*	134 *(21)*	578 *(31)*	$\chi^2 = 65.96$	<.001
Hypercholesterolemic						
N *(%)*	77 *(5)*	51 *(3)*	67 *(4)*	195 *(12)*	$\chi^2 = 2.03$	.363

Table 10. *Direct Measures of Atherosclerosis for Lowest and Highest MoCA Tertile Groups, Controlling for Education and Age*

	MoCA Tertile		Mean	SD
Coronary Artery Calcium Agatston Unit (N) [1]	Lowest	(497)	0.19	162.18
	Highest	(493)	0.06	158.49
Aortic Plaque Area mm^2 (N) [1]	Lowest	(419)	0.12	223.87
	Highest	(472)	0.03	223.87
Aortic Wall Thickness mm (N)	Lowest	(421)	1.72	.34
	Highest	(474)	1.65	.37
Number of Positive Indicators (N)	Lowest	(226)	1.60	.74
	Highest	(189)	1.48	.74

[1] CAC and abdominal aortic plaque was log transformed to conduct ANCOVA; these data are the backtransformed values.
Note. No significant differences between groups.

Table 11. *Logistic Regression Predicting Membership in Lowest MoCA Tertile*

						Odds	95% C.I.	
		B	S.E.	df	p	Ratio	Lower	Upper
Unadjusted Model	High Cholesterol	-0.15	0.23	1	.504	0.86	0.55	1.34
	Hypertensive	0.53	0.18	1	.003	1.70	1.20	2.40
	Diabetic	0.15	0.29	1	.614	1.16	0.66	2.05
	Abdominal Obesity	-0.04	0.15	1	.784	0.96	0.71	1.29
	E4 Allele	0.01	0.16	1	.961	1.01	0.74	1.38
	CAC ≥ 10	0.17	0.20	1	.391	1.19	0.80	1.75
	Abdominal Aortic Plaque	0.34	0.16	1	.041	1.40	1.01	1.93
	Abdominal Aortic Wall Thickness ≥ 75th percentile	0.30	0.19	1	.119	1.35	0.93	1.97
Reduced Unadjusted Model	Hypertensive	0.62	0.16	1	.000	1.85	1.34	2.55
	Abdominal Aortic Plaque	0.45	0.15	1	.003	1.57	1.17	2.12

Note. n = 775

Table 12. Logistic Regression Predicting Membership in Lowest MoCA Tertile, Adjusted for Demographic Variables

		B	S.E.	df	p	Odds Ratio	95% C.I. Lower	Upper
Adjusted Model	Education	-0.39	0.05	1	.001	0.68	0.62	0.74
	Age	0.05	0.01	1	.001	1.05	1.02	1.07
	Male	0.72	0.21	1	.001	2.05	1.36	3.09
	Race			2	.001			
	Black	0.67	0.32	1	.029	1.96	1.07	3.58
	White	-1.78	0.33	1	.001	0.17	0.09	0.32
	High Cholesterol	-0.33	0.29	1	.266	0.72	0.40	1.29
	Diabetic	-0.61	0.38	1	.109	0.54	0.26	1.15
	Hypertensive	0.19	0.25	1	.433	0.82	0.51	1.34
	Abdominal Obesity	-0.36	0.21	1	.087	0.70	0.47	1.05
	E4 Allele	-0.35	0.21	1	.097	0.71	0.47	1.07
	CAC ≥ 10	-0.20	0.30	1	.491	0.83	0.46	1.46
	Abdominal Aortic Plaque	0.40	0.22	1	.071	1.49	0.97	2.30
	Abdominal Aortic Wall Thickness ≥ 75th percentile	0.24	0.26	1	.374	1.27	0.75	2.14
Final Adjusted Model	Education	-0.41	0.03	1	.001	0.67	0.62	0.71
	Age	0.08	0.01	1	.001	1.08	1.06	1.10
	Male	0.59	0.15	1	.001	1.81	1.34	2.44
	Race			2	.001			
	Black	0.59	0.23	1	.011	1.81	1.15	2.65
	White	-1.84	0.26	1	.001	0.16	0.10	0.27

Note. n = 1319

FIGURES

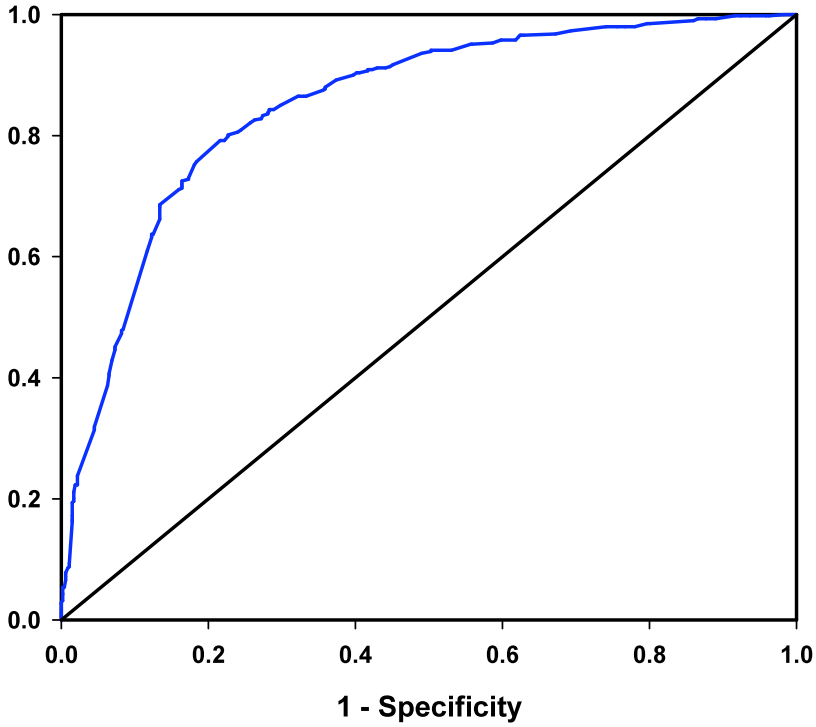


Figure 1. Area Under the Curve Receiver Operating Characteristics for the Final Adjusted Logistic Regression Model, Discriminating Between Lowest and Highest MoCA Tertile

Note. A LR predicted score of 0.54 provides a "best" cut-off score with a sensitivity of 0.757 and specificity of 0.816.

SECTION 2

APPENDIX A

Additional Background

Cardiovascular pathology was once considered to have little impact on the human brain, given the brain's capacity for vascular autoregulation and sustained cerebral perfusion even under adverse hemodynamic conditions (Lassen, 1964). Cognitive dysfunction secondary to cardiovascular disease (CVD) was generally thought to result largely from acute stroke or brain ischemia due to cardiac events such as arrhythmias with compromise of cardiac output (Newman, Kirchner, et al., 2001). Such cerebrovascular events have also been shown to increase the severity of dementia and hasten its age of onset (Snowdon, et al., 1997), thereby adding to the notion that CVD-related processes may directly or indirectly impact brain function. In addition, manifestations such as white matter intensity and infarcts have been linked to amnestic mild cognitive impairment (MCI) and non-amnestic MCI, respectively (Luchsinger, et al., 2009). However, CVD is now frequently associated with cognitive dysfunction in the absence of clinically identified stroke (Inzitari, et al., 2000; Looi & Sachdev, 2000; Paul, et al., 2005). Furthermore, CVD appears to be part of the pathology of both vascular dementia and Alzheimer's disease (AD), which accounts for the majority of dementia cases in older adults (Gatto, et al., 2009).

Several underlying CVD processes have been associated with cognitive impairment, including reduced cardiac output (Jefferson, et al., 2007) and abnormalities of systemic vascular function (Gunstad, et al., 2006; Haley, et al., 2007; Hoth, Poppas, Moser, Paul, & Cohen, 2008). Atherosclerosis is the most common pathologic process underlying CVD (Azen, et al., 1996) and an obvious cause of brain malfunction when

associated with strokes. Atherosclerosis was historically considered the leading cause of "senility," or dementia among the elderly, until it was discovered that most of these cases were due to Alzheimer's disease (Caplan, 1995). There are strong suggestions in the literature, based largely on indirect methods of detection, that atherosclerosis can have impact on brain function even when it is subclinical (i.e., in the absence of overt strokes, transient ischemic attacks, peripheral artery disease, or angina).

The remainder of this appendix will explore additional evidence linking measures of generalized atherosclerosis to cognitive dysfunction, as well as provide further background on direct and indirect measures of atherosclerosis. In addition, the Montreal Cognitive Assessment (Nasreddine, et al., 2005) will be reviewed in more detail.

Atherosclerosis

Pathology

Atherosclerosis, the principal cause of CVD in adults, progresses over time and commonly manifests in mid-to-late life as heart attack or stroke. Chronic inflammation appears to play a role in atherosclerosis, involving the gradual development of cholesterol-filled plaques in arterial walls that reduce or block blood flow, or the acute rupture of a plaque followed by aggregation of platelets and formation of an intravascular clot (Zipes et al., 2005), both resulting in vascular occlusion. Occasionally, arterial walls rupture because of atherosclerotic changes, resulting in hemorrhagic stroke.

The cause of atherosclerosis is not fully known, but factors such as high blood pressure and high cholesterol seem to cause subtle injury to artery walls. The process is thought to begin when an injured arterial wall creates chemical signals that cause certain types of white blood cells to attach to the endothelium of the artery. These cells migrate into the arterial wall and are transformed into foam cells that collect cholesterol and

trigger growth of smooth muscle cells in the artery wall. The build-up of these fat-laden foam cells forms patchy deposits, or plaques. Of importance for detection, plaques eventually accumulate radio-opaque calcium (Zipes et al., 2005).

Atherosclerosis has known genetic risk factors in common with AD. The best-characterized genetic polymorphism associated with AD is the E4 allele of apolipoprotein E (Corder, et al., 1993; Farrer, et al., 1997). ApoE4 has long been a known risk factor for atherosclerosis, myocardial infarction, and stroke (Davignon, Gregg, & Sing, 1988). ApoE4 polymorphisms enhance the extent of neuronal damage from cerebral ischemia (DeCarli, et al., 1999), the vascular complications of diabetes (Ukkola, et al., 1993), and the risk of dementia in relation to smoking (Carmelli, Swan, Reed, Schellenberg, & Christian, 1999). The carotid ultrasound disease assessment study (CUDAS) of healthy individuals found a significant association between ApoE4 polymorphism and increased incidence of carotid plaque but not of carotid intima media (cIMT) thickening (Beilby, et al., 2003). In contrast, Altamura et al. (2007) found that the ApoE4 promoted cIMT but had no effect on carotid plaque in a dementia cohort. The combined presence of CVD and ApoE4 may diminish later-life cognitive performance and increase the prevalence of AD significantly more than expected from the independent effects of CVD or ApoE4 genotype alone (Haan, et al., 1999).

Finding a link between subclinical atherosclerosis and brain function would have public health relevance in that aggressive attempts to reduce the risk for atherosclerosis and to treat presymptomatic atherosclerosis could contribute to maintaining optimal cognitive function throughout life and perhaps to slowing the cognitive decline associated with diseases such as AD. Furthermore, establishing when atherosclerosis begins to exert

effects on cognition would be helpful in the development and targeting of appropriate interventions (Knopman, et al., 2001).

Relationship to Cerebrovascular Health and Cognition

Cognitive function, particularly in areas of processing speed, flexibility, and memory, tends to decline with advancing age (Salthouse, 1996), but it is not known if the decline over time is due to the aging process itself and/or the greater effects of various diseases that affect the brain, such as AD and cerebral atherosclerosis. The Freedom House Study, a 3-year longitudinal examination of 547 non-institutionalized septuagenarians and octogenarians, reported variability in rates of change on various measures, with greatest declines seen on the Executive Interview (Royall, Mahurin, & Gray, 1992), a measure of frontal dysfunction, and the Trail-Making Test (Reitan, 1955), a popular test of processing speed and mental flexibility. The investigators postulated that the clinical heterogeneity in rates of cognitive change might reflect the combined effects of age and comorbid conditions affecting cognition, though such conditions were not examined (Royall, Palmer, Chiodo, & Polk, 2005).

Atherosclerosis is one such condition that may hasten the onset of cognitive dysfunction, increase its severity, or speed its progression. There are different mechanisms through which atherosclerosis could affect cognitive function. Endothelial cells are one component of the blood-brain barrier, and early stage atherosclerosis is represented by endothelial dysfunction (Libby, 2001). The disruption of endothelial function caused by atherosclerosis could make the blood-brain barrier more permeable and thereby compromise the barrier's ability to protect the brain from toxins and other substances that may have a cumulative effect (Skoog, et al., 1998).

Another proposed mechanism involves diminished oxygen delivery due to

reduced blood flow. For example, greater cerebral blood flow velocity has been linked to lower prevalence of cognitive decline (Ruitenberg, et al., 2001). Certain brain areas have been shown to be vulnerable to the effects of hypoperfusion, particularly the hippocampus (Roman, 2004), which is associated with learning and memory (Johnston, et al., 2004b). Gatto et al. (2009) speculated that cognitive differences in middle-age may be associated with small decreases in oxygen supply associated with subclinical atherosclerosis, while the larger declines in cognitive function in later life may be attributable to the cumulative effects of hypoperfusion over time. In a review of cerebrovascular disease and dementia, it was suggested that brain insults from cardiovascular risk factors and atherosclerotic processes may manifest as subtle cognitive impairment with particular effects on frontal mediated cognitive functioning (DeCarli, 2003)

Relationship to Demographic Factors – Race, Gender, Education

Rates of cardiovascular disease vary by race. Traditional coronary heart disease risk factors are higher in Blacks than other groups, particularly for hypertension, obesity, and diabetes, in addition to higher rates of coronary heart disease mortality than Whites (Thom, et al., 2006). However, several studies (Lee, O'Malley, Feuerstein, & Taylor, 2003; Tang, et al., 1995) though not all (Bild, et al., 2005; Jain, et al., 2004), have found substantially higher prevalence and quantity of coronary artery calcification among middle-aged and older US White populations than among Blacks. Carotid IMT findings are mixed, with suggestions that Blacks have thicker common cIMT but thinner internal cIMT compared to Whites (Manolio, et al., 1995). The limited data available on other ethnic groups also suggest that differences in the prevalence of coronary calcification exist among Whites, Hispanics, and Asians, with Whites having higher atherosclerotic

burden (Budoff, Yang, Shavelle, Lamont, & Brundage, 2002).

The inconsistencies surrounding race, atherosclerosis, and CVD are not well understood, but may be the result of multiple genetic, acquired, and/or socioeconomic factors, and potentially to differences in study methodology. For instance, low income (Salonen, Seppanen, Rauramaa, & Salonen, 1988) and Medicaid status (Sacco, et al., 1997) have been associated with increased carotid atherosclerosis, perhaps because of decreased access to adequate treatment. Some researchers have speculated on genetic explanations for racial differences; it has been suggested that genes account for 74.9% of phenotypic variation in artery wall thickness, an atherosclerotic indicator (Duggirala, Gonzalez Villalpando, O'Leary, Stern, & Blangero, 1996). A recent report identified a relationship between a common polymorphism for the soluble epoxide hydrolase gene and coronary calcification in Blacks but not Whites (Fornage, et al., 2004). Other contributors for higher coronary calcification in Blacks may be differences in vitamin D metabolism (Doherty, et al., 1997), race differences in tissue calcification and bone mineral density (Henry & Eastell, 2000), and diet (Tell, et al., 1994).

There is evidence in older populations that men have a higher potential for cerebral and cardiovascular changes with consequent effects on cognitive function in the presence of CVD risk factors (Meyer, et al., 1999). It is widely recognized that women, relative to men of the same age, are more protected from the adverse effects of CVD risk factors on morbidity and mortality as CVD occurs later and with lower frequency among women (Murabito, 1995). These gender differences are not yet fully explained, with most research focusing primarily on estrogen and the association of menopause to a rise in CVD. However, the evidence for a protective effect of estrogen in women has been called into question by recent data suggesting that hormone-replacement therapy may not

be protective and may initially increase risk of CVD events in women with clinical atherosclerosis (Mosca, et al., 2001). Another possible explanation for gender differences may be the adverse effects of androgens in men (Rossouw, 2002). Other risk factors can mediate the gender difference; for example, factoring in diabetes, which is more common in women, eliminated the cardiovascular advantage of women over men (Murabito, 1995).

Epidemiological studies have shown a strong inverse relationship of education to clinical CVD (Kaplan & Keil, 1993; Leino, Raitakari, Porkka, Taimela, & Viikari, 1999). The negative association between education and disease may be related to a variety of factors, such as symptom recognition, access to treatment, general health behaviors, and adherence to medical treatment (Yan, et al., 2006). Education level may also serve as a proxy for a host of correlated variables (e.g. early health care utilization, quality of living environment, etc). Education is also inversely related to known cardiovascular risk factors, including smoking, blood pressure, obesity, and physical activity (Iribarren, et al., 1996; Leino, et al., 1999). These risk factors also influence subclinical atherosclerosis (Chambless, et al., 2002).

Population-based research on education and subclinical CVD has been initiated recently due to advances in noninvasive measurement of atherosclerosis, with most studies using cIMT as the key atherosclerotic indicator. Carotid IMT was inversely associated with education in 12,476 middle-aged men and women (Ranjit, et al., 2006), and this inverse relationship has been replicated (Lemelin, et al., 2009; Rosvall, et al., 2006). In a group of postmenopausal women, greater levels of educational attainment were associated with lower levels of coronary and aortic calcification (Gallo, Matthews, Kuller, Sutton-Tyrrell, & Edmundowicz, 2001). In a population-based study of 4,487

individuals age 45-75, men with 10 and less years of formal education had a 70% increase in calcification score and the respective increase for women was 80% after adjustment for age (Dragano, et al., 2007). In a large biracial cohort of young adults (N= 2913) followed for 15 years, education was inversely associated with prevalence of coronary artery calcium (CAC) after adjusting for age, sex, and race, with particularly higher prevalence for individuals with less than high school completion (Yan, et al., 2006).

Statistical tools have been developed to predict the likelihood of cardiovascular events occurring within 10 years, including the Framingham Coronary Risk (Wilson, et al., 1998) and Framingham Stroke Risk algorithms (Wolf, et al., 1991). These algorithms will not be described in detail but they take into account the multifactorial contributions of the demographic variables outlined above as well as the conditions discussed in the following section. In the Framingham Offspring Study, more than 2,000 men and women who were free of stroke or dementia were assessed for 10-year stroke risk using the Framingham Stroke Risk Profile. Employing stroke risk as the predictor variable and separate analyses for each cognitive performance measure as the outcome variable with statistical correction for age, education, and sex, there was an inverse relationship between increments in 10-year risk of stroke and cognitive performance [tests included nonverbal memory (Delayed Recall; Wechsler, 1997b: $\beta = -0.141$, $p < 0.001$), visual organization (Hooper, 1983: $\beta = -0.138$, $p < 0.001$), abstract reasoning (Similarities; Wechsler, 1997a: $\beta = -0.111$, $p = 0.005$), and visual scanning and mental set shifting (Trail-Making Test; Reitan and Wolfson, 1993; $\beta = -0.138$, $p < 0.0001$]; (Elias, et al., 2004), highlighting the combined effects of demographic and vascular risk factors on cognitive performance in various domains.

Atherosclerosis is associated with cardiovascular and cerebrovascular health, as well as cognitive function. These associations are mediated by age, gender, race, and education. Multiple cognitive domains have been shown to be impacted by the atherosclerotic process, and there is no clear consensus on the mechanisms underlying the connection between atherosclerosis and cognition. Atherosclerotic burden has been traditionally measured or estimated indirectly using known vascular risk factors, which are also linked to cognitive performance and dementia. Four of these risk factors, or indirect measures of atherosclerosis, are reviewed below.

Indirect Evidence of Atherosclerosis

Hypertension

Hypertension impacts approximately a third of the general adult population. Its prevalence increases with age, affecting up to 77% of individuals over age 70 (Munro, et al., 1994). Longstanding hypertension is a risk factor for CVD and consequently for vascular dementia. The pathologic processes by which hypertension contributes to cognitive dysfunction are numerous. Sustained hypertension may result in brain pathology associated with cerebrovascular remodeling, impaired vasodilation and autoregulation, lacunar infarcts, amyloid angiopathy, and cerebral white matter changes (Manolio, Olson, & Longstreth, 2003; Pantoni & Garcia, 1997). High blood pressure can result in severe atherosclerosis, leading to cerebral hypoperfusion (Skoog & Gustafson, 2006).

Studies that have examined midlife hypertension have reported that it is a risk factor for later development of dementia (Launer, et al., 1995), possibly reflecting its association with late-life atherosclerosis and vascular mechanisms of dementia (Breteler, 2000; Skoog, Kalaria, & Breteler, 1999). In a population-based study of 382 Swedish 70-

year-olds, persons who later developed severe cognitive impairment had significantly higher blood pressure (BP) in mid-life (10-15 years before the clinical onset of obvious impairment) than those who did not develop severe cognitive impairment (Skoog, et al., 1996). Similarly, in a 20-year prospective study of 1,449 persons aged 65-79 years at follow-up, there was a significant relationship between mid-life hypertension and the subsequent development of AD (Kivipelto, et al., 2001). In a longitudinal analysis of 918 persons, hypertension was associated with an increased risk of MCI after adjusting for age and sex (Reitz, Tang, Manly, Mayeux, & Luchsinger, 2007). Others have not found an association between hypertension and cognitive functioning in older populations (Farmer, et al., 1990).

Studies of older populations, especially over age 75, generally report that low blood pressure (BP) is also a risk factor for developing dementia (Guo, Viitanen, Fratiglioni, & Winblad, 1996; Okumiya, et al., 1997; Ruitenberg, et al., 2001; Skoog, et al., 1996). In a prospective study of 488 community-dwelling elderly individuals over age 75, mildly to moderately elevated systolic BP was associated with reduced risk for AD, while subjects with persistent low BP over 2 years had higher risk of developing AD (Verghese, Lipton, Hall, Kuslansky, & Katz, 2003). It has also been reported that blood pressure may decline in the preclinical stage of AD (Skoog, 2003). It may be that the structural and functional cardiovascular modifications associated with aging (e.g. arterial stiffness) require higher pressures to maintain adequate cerebral perfusion (Pearce, 1996).

Hypertension has been found to be associated with Alzheimer-type pathology, including early presence of both neuritic plaques, neurofibrillary tangles, and lower brain weight, in the brains of non-demented and demented persons with hypertension (Sparks, 1997) and could play a causal role in cognitive decline beyond its relationship to stroke.

In a study comparing individuals (ages 70-89) with untreated hypertension to normotensive participants, deficits in processing speed, episodic and working memory, and executive function were observed in the hypertension cohort, while there were no significant differences in attention (Saxby, Harrington, McKeith, Wesnes, & Ford, 2003). Hypertension may be mainly related to an increased risk of nonamnestic forms of cognitive impairment, such as frontal-executive cognitive impairment (DeCarli, 2003).

Numerous studies have investigated the association between antihypertensive drug use and the risk of dementia. In the Cache County Study, a longitudinal investigation of dementing illnesses in an elderly population (Breitner, et al., 1999), a protective effect of antihypertensive drugs was observed regardless of duration of use (Khachaturian, et al., 2006). In a cohort of 2,574 Japanese men, the risk of dementia was reduced by 6% with each additional year of antihypertensive treatment (Peila, White, Masaki, Petrovitch, & Launer, 2006). As part of the Rotterdam Study, a prospective, population-based investigation of age-related disorders (Hofman, et al., 2007), the duration of antihypertensive use and risk of dementia in 6,249 individuals ≥55 years of age was examined. Antihypertensive use was associated with a reduced risk of dementia, with an 8% risk reduction per year of use for persons <75 years of age and 4% risk reduction in those >75 (Haag, Hofman, Koudstaal, Breteler, & Stricker, 2009). Other than the blood pressure-lowering effect of antihypertensive drugs, it has been suggested that certain antihypertensive drugs can differentially affect brain pathology (Marx, 2007); however, Haag et al. (2009) did not observe differences among types of antihypertensive drugs.

Diabetes

Diabetes mellitus affects approximately 5% of the population, with Type 2

diabetes accounting for 85% of cases (WHO, 1999). Patients with diabetes have a threefold increase in risk for all cardiovascular diseases (Resnick, Harris, Brock, & Harris, 2000). Hyperinsulinemia is a risk factor for atherosclerosis, which has a higher rate of development in diabetics (Kumari & Marmot, 2005). Diabetes is associated with dyslipidemia and hyperinsulinemia, both of which are related to poor cognitive performance (Kalmijn, Feskens, Launer, Stijnen, & Kromhout, 1995). Type 2 diabetes has been associated with risk for AD (Luchsinger, Tang, Stern, Shea, & Mayeux, 2001; Peila, Rodriguez, & Launer, 2002).

In a study of middle-aged individuals, an association was found between poor cognitive performance and diabetes, independent of age or hypertension (Kumari & Marmot, 2005). A review article reported that in 13 out of 19 studies examined, Type 2 diabetes subjects had significantly lower scores on at least one cognitive test, with particular effects for verbal memory and complex information processing (Strachan, Deary, Ewing, & Frier, 1997). The mechanism(s) by which diabetes affects cognition are not known, but could be related to hyperglycemia, hyperinsulinemia, or other metabolic factors (Kumari, Brunner, & Fuhrer, 2000).

Hypercholesterolemia

Three major classes of lipoproteins are found in the serum of a fasting individual: low density lipoproteins (LDL), high density lipoproteins (HDL), and very low density lipoproteins (VLDL), which together are referred to as total cholesterol ["Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report," 2002]. An estimated 102 million adults in the United States have total blood cholesterol values of 200 mg/dL and higher, and of these about 36 million

American adults have levels of 240 or above (American Heart Association, 2006).

There is extensive evidence that individuals with higher cholesterol levels have more atherosclerosis and CVD than do those having lower levels (Karpe, et al., 2001; McGill, McMahan, Malcom, Oalmann, & Strong, 1997; Wilson, et al., 1998). Any LDL cholesterol above 100 mg/dL appears to be atherogenic, and the prevalence of elevated levels in large part accounts for the high development of atherosclerosis in the United States (Lloyd-Jones, Larson, Beiser, & Levy, 1999).

The relationship between high cholesterol and neuropsychological function has been widely studied, yet evidence remains inconsistent. Several epidemiological studies showed an association between higher cholesterol and higher dementia prevalence (Evans, et al., 2000; Pappolla, et al., 2003), whereas others failed to find a relationship (Tan, et al., 2003). Familial hypercholesterolemia has been linked to higher incidence of mild cognitive impairment (Zambon, et al.). High cholesterol in mid-life has been linked to a 66% increase in AD risk late in life (Solomon, et al., 2007). At later age, the correlation between dementia and cholesterol levels is no longer consistent (Ghribi, 2008). Differences in the literature may be due to the clinical stage of dementia, use of statin drugs, and time of cholesterol measurement. The mechanisms underlying the relationship between cholesterol and cognitive decline remain to be clarified, though suggested processes include altered cholesterol metabolism in the brain (van den Kommer, et al., 2009), increased Aβ production (Sparks, et al., 1994), or by compromising the blood brain barrier (Bjorkhem, Cedazo-Minguez, Leoni, & Meaney, 2009).

Abdominal Obesity

Abdominal obesity is linked to the development of atherosclerosis and associated

with accelerated progression of atherosclerosis (Lakka, et al., 2001). In a study of healthy individuals without CVD, waist circumference and weight gain since adolescence were the strongest predictors of early atherosclerosis (Stamatelopoulos, et al., 2007). Abdominal obesity is a stronger risk factor for vascular and metabolic disease than total body obesity (Onat, et al., 2004), even for those who are not overweight (Whitmer, Gunderson, Quesenberry, Zhou, & Yaffe, 2007), perhaps due to greater metabolic activity in visceral adiposity than subcutaneous adipose tissue (Altomonte, Harbaran, Richter, & Dong, 2003). Abdominal obesity can be measured using waist circumference, which is the best anthropometric measure of visceral fat and a potentially better indicator of health risk than body mass index (Han, Sattar, & Lean, 2006). Waist circumference is also more strongly related to total fat and disease risk than waist-to-hip ratio, as waist circumference is minimally related to height, so correction for height does not improve its relation with abdominal fat or poor health (Dobbelsteyn, Joffres, MacLean, & Flowerdew, 2001).

Several studies have evaluated the relationship of abdominal obesity to cognitive performance, and abdominal obesity has implications for cognitive dysfunction even for those who are not overweight (Gustafson, Rothenberg, Blennow, Steen, & Skoog, 2003; Whitmer, et al., 2008). After adjusting for diabetes and hypertension, a study of elderly Koreans found that a BMI ≥ 25 was associated with impaired cognitive function, and that the effects of BMI on cognition were particularly marked among those with abdominal obesity (Jeong, Nam, Son, Son, & Cho, 2005). In a sample of 90 healthy, stroke-and dementia-free adults ages 54-81, both abdominal obesity and BMI predicted diminished performance on tests of motor speed and executive function but did not affect memory (Waldstein & Katzel, 2006). As part of the Health, Aging, and Body Composition Study,

higher total and abdominal adiposity was associated with greater cognitive decline in men (Kanaya, et al., 2009), as measured by the MMSE (Folstein, et al., 1975). Similarly, the Framingham Heart Study found that obesity and hypertension had a cumulative effect on cognitive functioning in men but not women, with men showing decreased performance on verbal and nonverbal memory tasks (Elias, et al., 2003).

Jagust et al. (2005) showed that abdominal obesity in elderly Latinos was related to decreased hippocampal volume and increased white matter hyperintensities, neurodegenerative findings that are associated with impaired cognition (Wu, et al., 2002). A longitudinal study of over 6,000 individuals found that abdominal obesity in midlife resulted in a threefold increased risk of dementia, independent of diabetes and cardiovascular comorbidities (Whitmer, et al., 2008). However, the effects of both AD-associated weight loss and age-related changes in body composition present methodological challenges for evaluating the role of abdominal obesity in development of dementia (Stewart, et al., 2005).

Direct Evidence of Atherosclerosis

Coronary Artery Calcium

Calcium is deposited early in the formation of atherosclerotic plaque, and coronary artery calcification has long been recognized as an important marker of atherosclerosis (Blankenhorn & Stern, 1959). Coronary artery calcium (CAC) scores provide a measure of the total coronary plaque burden or extent of calcium deposits in the walls of the coronary arteries (Simon, Giral, & Levenson, 1995), and reflect generalized atherosclerosis in both cerebral and peripheral vascular beds (Rosano, et al., 2005). CAC has been shown to outperform carotid intima-media thickness, a more general indicator of atherosclerosis, as a predictor of coronary artery disease (Terry, et al., 2005). No specific

value indicates that a lesion is calcified. Therefore, an arbitrary level of +130 Hounsfield units (H) has been chosen based on the premise that the attenuation of soft tissues is about +50 H, and +130 H is enough of an increase that any structure with that value probably contains calcium (Simons, et al., 1992). CAC scores are derived from electron beam computed tomography (EBCT) scans and are expressed in an Agatston score, which measures the amount of calcium at each lesion and summed over all lesions (Agatston, et al., 1990).

A recent review of EBCT in asymptomatic individuals proposed guidelines for the interpretation of CAC scores (Rumberger, et al., 1999). Although a negative or extremely low calcium score (≤10) cannot fully exclude the presence of atherosclerosis, it does indicate a less than 5%-10% likelihood of a coronary obstructive lesion, regardless of age and gender. Of individuals with a negative CAC score, 80%-90% were found to have angiographically "normal" coronary arteries (Fallavollita, Brody, Bunnell, Kumar, & Canty, 1994; Rumberger, Sheedy, Breen, Fitzpatrick, & Schwartz, 1996). CAC scores of 11 to 100 indicate mild atherosclerotic plaque burden, although the likelihood of associated significant obstructive disease (50% stenosis or greater) is low (20% or less). Individuals with CAC scores of 101 to 400 have moderate coronary plaque and a high likelihood of associated moderate non-obstructive coronary disease. CAC scores ≥400 reflect advanced plaque disease and high risk for the development of symptomatic ischemic disease (He, et al., 2000). In a study of 367 originally asymptomatic subjects who were followed for 3 to 6 years, the mean baseline CAC score was 76 for those with no cardiac events versus 399 for subjects with a cardiac event (e.g. angina, myocardial infarction), $p < 0.01$ (Agatston, et al., 1994).

Coronary calcification increases with age and differs by gender, with women

lagging behind men in prevalence and CAC scores, reflecting the lower incidence of atherosclerotic disease in pre-menopausal women. The relationship between age, gender, and CAC scores was examined in a population of 1,898 asymptomatic individuals (Janowitz, Agatston, Kaplan, & Viamonte, 1993). In women younger than 50 years, CAC scores >10 were extremely uncommon but were seen in about 25% of similarly aged men. Between ages 50 and 59 years, CAC scores for women (M = 63, SD = 487) were significantly lower than the average scores for men in that age range (M = 140, SD = 384), which held true for all age groups. Women between 60 and 69 years had CAC scores similar to men a decade younger.

Prior studies of the effect of age and gender on coronary calcification suggest the correlation between age and increased CAC scores reflects the increased incidence of atherosclerosis with advancing age, and that CAC scores have similar predictive values in men and women after matching for severity of artery disease (Rumberger, et al., 1999). Although CAC scores may reflect similar overall atherosclerotic plaque burdens, regardless of age and gender, the clinical prognostic value of CAC scores varies as a function of these demographic variables. For example, a CAC score of 100 in a 40-year-old woman may reflect a more premature or aggressive atherosclerotic process than a similar score in a 60-year- old man (Rumberger, et al., 1994).

The impact of race on CAC is unclear, with some reports of higher CAC prevalence in Whites than in Blacks. Tang and colleagues (2005) found that Blacks had a significantly lower prevalence of coronary calcium than did Whites or Asians, and Whites had greater CAC than Blacks or Hispanics (Budoff, et al., 2002). Lower coronary atherosclerotic burden was found in Blacks compared to Whites in 283 high-risk subjects (Doherty, Tang, & Detrano, 1999) and in 999 low-risk subjects (Lee, et al., 2003).

Similar observations have also been made in older subjects, ages 67 to 99 years (Newman, et al., 2002; Newman, Naydeck, et al., 2001). In contrast, findings from the population-based Dallas Heart Study suggest a similar prevalence of CAC in Blacks and Whites (Jain, et al., 2004). Furthermore, there are significant age-by-race interactions with respect to CAC (Bild, et al., 2005).

In the Multi-Ethnic Study for Atherosclerosis (MESA), the CAC scores of 6,814 participants between 45 to 84 years of age who identified as White, Black, Hispanic, or Chinese were examined (McClelland, Chung, Detrano, Post, & Kronmal, 2006). For women, Whites had the highest percentile of CAC and Hispanics generally had the lowest, although in the oldest age group, the Chinese women had the lowest values. Overall, Chinese and Black women were intermediate, with their order dependent on age. For men, Whites consistently had the highest percentiles, and Hispanics had the second highest (in contrast to women). Blacks were lowest at the younger ages, and Chinese were lowest at older ages. In this study of individuals free of clinical CVD, median CAC increased 14 Agatston units for women and 21 for men over a 2-year period to an overall mean of 46 Agatston units (36 for women, 54 for men). The traditional risk factors associated with both CAC incident risk and progression were age, male gender, White race, diabetes mellitus, hypertension, and higher body mass index, with diabetes being the strongest predictor of increased CAC (Kronmal, et al., 2007).

The relationship between coronary calcification and cognitive performance has not been widely examined. A population-based study of 409 individuals aged 65 and older found that those with higher levels of CAC were more likely to have impaired cognition (Rosano, et al., 2005) and brain MRI abnormalities (e.g., subcortical infarction and higher volume of white matter hyperintensities). However, in a cross-sectional study

of middle-to-older aged adults with subclinical atherosclerosis, CAC was not associated with lower performance on any of the neuropsychological measures administered (Digit Symbol, Block Design, Letter Number Sequencing, Trails-B, Category Fluency, Boston Naming Test, CVLT, Logical Memory, Judgment of Line Orientation; Gatto et al., 2009).

Abdominal Aortic Plaque & Wall Thickness

Atherosclerotic burden, as indicated by aortic plaque, is more prevalent in the abdomen than in other vascular beds. Abdominal aortic plaque is present early in life and increases with age for both sexes (Jaffer, et al., 2002). In the Framingham Heart Study, atherosclerotic plaque was defined as luminal protrusions of ≥1 mm in radial thickness and further classified as type A (maximal radial thickness ≤2.5 mm) or type B (thickness >2.5 mm). A group with CVD had more than 3 times the total aortic plaque volume than the no-CVD group and this difference remained significant after adjusting for sex, age, hypertension, diabetes, and hyperlipidemia (Oyama, et al., 2008). The development of atherosclerotic disease in the aorta is most common among individuals over the age of 60 (Heinzlef, Cohen, & Amarenco, 1997) and the risk of cerebrovascular disease increases notably in the presence of aortic plaque greater than 4 mm in thickness (Amarenco, et al., 1994). Abdominal plaque prevalence in this sample was greater in women than men across age groups, suggesting greater prevalence of subclinical atherosclerosis in women despite higher rates of clinical CVD in men. Abdominal aortic plaque is measured via aortic MRI. Quantifying the extent of raised aortic plaque has been used widely, as it is thought to be a direct measure of disease burden and an indicator of disease progression (Taniguchi, et al., 2004). However, such atherosclerotic lesions may take several decades to develop, while aortic wall thickening occurs earlier (Corti, et al., 2005).

Aortic wall thickness (AWT) has not been as extensively investigated as the

thickness of the carotid intima-media (cIMT). The measurement of the thickness of the cIMT represents a marker of subclinical atherosclerosis (Bots, et al., 1997), and the carotid artery has been a common target in prior studies because its relatively superficial location on the neck can be easily visualized by ultrasound. However, autopsy studies have shown that the first atherosclerotic lesions actually begin to develop in the abdominal aorta (McGill, et al., 2000); therefore, measuring abdominal AWT might provide a better index of subclinical atherosclerosis.

Relatively little is known about the age, sex, and ethnic distributions of abdominal AWT in the general population. In a multiethnic population-based cohort, Li et al. (2004) examined the distribution of aortic wall thickness by race, sex, and age and found that both average and maximal abdominal AWT increased with age. Additionally, abdominal AWT was higher in men than in women, while there were no significant differences by race. The Dallas Heart Study, a multiethnic population-based probability sample, found that AWT increased with age across ethnic groups (Rosero et al., in preparation). After adjusting for age, there were no ethnic differences in AWT among men, who had significantly higher AWT than women in all ethnic groups (p<.001 each). With age, AWT increased most slowly in White women and most rapidly in Black men. The median AWT in this cohort varied from 1.55 mm for Hispanic women to 1.79 mm for Black men.

There is little information on the relationship between cognitive functioning and either abdominal aortic plaque or abdominal AWT. However, the more commonly studied cIMT has been associated with poorer performance in the attention-executive-psychomotor domain (Trail Making Test, Letter Search, Stroop, COWAT, Grooved Pegboard, Digit Span, and Digit Symbol; p <.05), independent of age, education, sex, and

cardiovascular risk factors such as hypertension (Haley et al., 2006). Healthy individuals with greater cIMT showed significant decline over 2 years on measures of verbal and nonverbal memory (CVLT, Rey-Osterrieth) and semantic fluency (Wendell, Zonderman, Metter, Najjar, & Waldstein, 2009).

Summary

The extent to which subclinical atherosclerosis is associated with cognitive change is not fully understood, nor whether the atherosclerotic indicators discussed above have a direct effect on cognition that would be detectable prior to the onset of obvious cognitive impairment. The relationship between objective evidence of subclinical atherosclerosis and cognition has been studied in convenience samples and population-based studies of older adults; however, survival to older age may bias results through increased survival of individuals with lesser degrees of atherosclerosis. The relationship of subclinical atherosclerosis to cognitive functioning has not been examined in a population-based sample of adults with a wide range of ages or in ethnically diverse groups. This study utilizes a large, community-based sample to investigate the relationship of cognitive functioning and the subtle brain changes associated with subclinical atherosclerosis. Direct and indirect measures of subclinical atherosclerosis were examined in relationship to scores on the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) obtained 7-8 years later. Details about the development, scoring, and utilization of the MoCA are presented below.

The Montreal Cognitive Assessment

A copy of the MoCA protocol is presented in Appendix E. The MoCA is a measure that gathers a wide range of cognitive data over a short period of time. This 30-point screening tool requires approximately 10 minutes to administer and evaluates

aspects of attention, orientation, language, verbal memory, visuospatial, and executive function. The short-term memory recall task involves two learning trials of five words and delayed free recall after approximately 5 minutes (5 points). The delayed recall portion also utilizes categorical and multiple-choice cuing, although this is not incorporated into the total score. Visuospatial abilities are assessed using a clock-drawing task (3 points) and a three-dimensional cube copy (1 point). Executive function is assessed using a short number-letter alternation task adapted from the Trail Making Test Part B task (1 point), a phonemic fluency task (1 point), and a two-item verbal abstraction task (2 points). Attention, concentration, and working memory are evaluated using a sustained attention task (target detection using tapping; 1 point), a serial subtraction task (3 points), and digits forward and backward (1 point each). Language is assessed using a three-item confrontation naming task (lion, camel, rhinoceros; 3 points), repetition of two syntactically complex sentences (2 points), and the aforementioned verbal fluency task. Orientation to time and place is also evaluated (6 points).

Nasreddine et al. (2005) developed the MoCA based on clinical intuition regarding cognitive domains affected by mild cognitive impairment (MCI; Peterson et al., 2005). The measure was administered to patients with mild AD and MCI, as well as normal elderly controls. Test-retest reliability was measured on 26 participants with an average of 35 days between measurements. The mean change score was 0.9 (2.5) points with a correlation of 0.92, $p<.001$. Internal consistency yielded a Cronbach's alpha of 0.83, and item analysis identified trail-making, cube drawing, clock drawing, naming, delayed recall, fluency, abstraction, and orientation discriminated reliably between all three groups. The AD group performed the most poorly, followed by the MCI group. The digit span, sustained attention, and serial calculation tasks discriminated between AD

and normal control groups. AD and MCI groups performed similarly on sentence repetition, and MCI participants were most impaired on delayed recall. Therefore, all items successfully discriminated between at least two of the groups, and the majority of items differentiated between groups in a step-wise manner (Nasreddine et al., 2005).

A cut-off score of 26 was established as the best balance between sensitivity and specificity. The MoCA demonstrated excellent sensitivity for detecting MCI (90%) and AD (100%), and good specificity for identifying normal controls (87%). Norms are available based on a preliminary Canadian sample (N = 90) with a mean age ± standard deviation of 72.84 ± 7.03 and mean education and standard deviation of 13.33 ± 3.40. The normative study employed a 1-point correction for education at or below 12 years.

The MoCA's ability to detect early cognitive decline over a 6-month period in a group with stroke or TIA (N=110) and a symptom-free group with increased cerebrovascular risk (N = 45) was compared to the MMSE (Popovic, Seric & Demarin, 2007). In this study, cognitive decline was detected earlier when the MoCA was used (1-point education factor included). Median MoCA scores declined from 26 to 20 points in the stroke/TIA group and from 29 to 24 points in the symptom-free/at-risk group. One-third of individuals with increased vascular risk, but without stroke or TIA, had cognitive impairment on the MoCA after the six-month follow-up period. The investigators suggested that use of MoCA could aid to early recognition of discrete cognitive disturbances in both symptomatic and asymptomatic individuals with increased CV risk.

In a study of the MoCA's discriminant validity as a global cognition assessment instrument for the detection of MCI or dementia in Parkinson's disease, the MoCA was superior to the MMSE as a screening instrument due to greater range of scores (19 points versus 9 points) and better specificity (64% accurately diagnosed versus 54%; Hoops et

al., 2009). Similarly, Zadikoff et al., (2007) reported the MoCA to be more sensitive to cognitive impairment than the MMSE in a PD population. In a sample with memory symptoms due to AD, MCI, or psychiatric illness, the MMSE correctly excluded 100% of patients with psychiatric illness compared to the modest 50% specificity of the MoCA (Smith, Gildeh, & Holmes, 2007). However, the MoCA did well at identifying cases of MCI and dementia in patients who scored above a 25 on the MMSE and would otherwise have been missed.

APPENDIX B

Hypotheses

Overall Aim: To investigate the relationship between global cognitive functioning and direct measures of atherosclerosis.

Aim 1: To investigate the relationship between cognitive functioning and previously obtained measures of coronary artery calcium volume, abdominal aorta plaque volume, and abdominal aortic wall thickness.

Hypothesis 1: Scores on a cognitive screening tool (Montreal Cognitive Assessment; MoCA) will show a small, negative correlation with coronary artery calcium scores, abdominal aorta plaque scores, and abdominal aortic wall thickness measurements.

Hypothesis 2: Participants with multiple positive indicators of atherosclerotic burden will obtain lower MoCA scores than participants with a single indicator.

Aim 2: To identify which direct and indirect measures of atherosclerosis contribute to cognitive functioning.

Hypothesis 3: Direct measures of atherosclerosis (coronary artery calcium deposits, abdominal aorta plaque, and abdominal aortic wall thickness) will predict membership in the Lowest MoCA Tertile after controlling for demographic factors and other covariates such as history of diabetes, hypertension, and waist size.

Hypothesis 4: The traditional indirect measures of atherosclerosis (hypertension, diabetes, hypercholesterolemia, and waist circumference) will

predict membership in the Lowest MoCA Tertile after controlling for demographic factors.

Aim 3: To determine if the presence of the ApoE4 allele strengthens the relationship between subclinical atherosclerosis and cognitive functioning.

Hypothesis 5: Participants with the ApoE4 allele will obtain lower MoCA scores than participants without the E4 allele.

Hypothesis 6: The addition of ApoE4 status will strengthen the relationship between measures of atherosclerosis and cognitive performance.

Exploratory Aim: To determine if there are differences in the above analyses with age (comparing those 50 years old and younger to a group of older subjects), as well as gender and race.

APPENDIX C

Additional Data Analyses & Results

Additional descriptive characteristics of the sample stratified by gender and race can be viewed in Tables 13 and 14, respectively. Men had more education than women, and Blacks were more highly represented in females. Men had higher frequency of atherosclerotic burden, as measured by positive direct indicators of CAC, abdominal aortic plaque, and abdominal AWT. Women had higher rate of abdominal obesity (> 88 cm waist). White individuals had more education than Blacks or Hispanics, and Hispanics were also less educated than Blacks. Higher MoCA scores were seen in the White group compared to other ethnicities, and Hispanics had higher scores than Blacks. The Black group had higher rates of abdominal obesity, E4 allele, and hypertension, while Whites had lower rate of diabetes.

Aim One

In order to determine if having multiple elevated or positive measures of atherosclerosis resulted in lower MoCA performance, participants were grouped by the number of positive indicators of atherosclerotic burden. The expectation was that those with multiple positive indicators would obtain lower MoCA scores than participants with only a single indicator. These groups were compared using ANCOVA, and results were discussed in Section 1 and presented in Tables 7 and 8. Given the unequal group sizes, this analysis was also conducted using the Kruskal-Wallis non-parametric test across ordered groups, and the differences in MoCA scores among the indicator groups were significant (p = .003). That significant differences were observed in this non-parametric analysis, but not in the ANCOVA, is likely due to the effects of covariates (age and

education) that are unaccounted for in the Kruska-Wallis test. Section 1 presents the results using 0, 1, 2, and 3–indicator groups. Due to the relatively small group size of the 3-indicator group (N = 63), it was combined with the 2-indicator group (N = 203) to improve the group size in comparison to the larger 1-indicator group (N = 323) and the ANCOVA results did not vary; $F(1, 587) = 3.63$, $p = .057$.

Correlations and ANCOVA analyses were conducted to examine the relationship between MoCA scores and CAC, plaque, and AWT, and these results were discussed in Section 1 and showed no significant correlations for any measure, as well as marginally lower MoCA scores in the expected direction when the categorical variables (CAC >10, detectable aortic plaque, >75th AWT) were compared. These analyses were repeated using both by age quartile groups and with only participants over 50 years of age, and there was no significant difference in MoCA scores by number of either direct [$F(3, 327) = 3.18$, $p = .024$] or indirect measures of atherosclerosis [$F(3, 432) = 1.87$, $p = .161$].

Examination of a possible threshold effect was further analyzed with receiver operating characteristics area under the curve statistics to determine if each direct atherosclerotic variable (CAC, plaque, AWT) had a threshold point that discriminated between Lowest and Highest MoCA Tertile. Each variable showed poor to fair discriminative ability (AUC between 56-58%, see Table 15 and Figure 2), using standard criteria (Hosmer, 1999).

Aim Two

Logistic regression was used to determine the model of demographic characteristics, indirect atherosclerosis risk factors, and direct measures of atherosclerosis that best predicted membership in the Lowest MoCA tertile. These results were discussed in Section 1 and presented in Table 12. These factors were also examined in separate

backward hierarchical logistic regression. The model examining demographic variables alone can be viewed in Table 16, and shows the predictive value of education, age, and male gender, and race, similar to the Section 1 final full model. Two separate logistic regressions were conducted using the categorical direct (CAC above 10, present plaque, AWT >75th percentile) and indirect (high cholesterol, diabetes, hypertension, and abdominal obesity) variables, which are presented in Table 17 and Table 18. The model with the direct measures was a non-significant model, highlighting the weak predictive value of these variables for MoCA performance. The model for indirect variables was also relatively weak, but highlighted hypertension as a significant predictor of falling in the Lowest MoCA Tertile. These analyses were repeated with CAC defined ordinally as none (<10), mild (10-99), moderate (100-399), and severe (>400), and results did not vary. Finally, a multivariate regression using the transformed CAC and aortic plaque, as well as AWT, to predict the continuous MoCA Total Score was conducted (see Table 19). In this analysis, only CAC was significant ($p < .001$) and the model was very weak, explaining only 2% of the variance. These supplementary analyses show that regardless of the model and type of regression, demographic characteristics were identified as the strongest predictive variables of MoCA performance.

The adjusted logistic regression model obtained in Section 1 and presented in Table 12 was repeated separately for males and females to determine if there was a different predictive model by gender, and results did not differ from the overall model; although age was retained for females but not in model for males (see Tables 20 and 21). Separate regression models for Black and White groups also highlighted only demographic variables, though the importance of these factors varied by race (see Table

22 and 23), as only education was related to the White group's membership in the Lowest tertile while education, male gender, and age were important for Blacks.

Although the majority of analyses focused on the Lowest MoCA tertile compared to the Highest MoCA tertile, the Middle and Highest tertiles were also combined in order to further explore how individuals in the Lowest tertile (<22 points) differed from those with higher MoCA scores. The frequency of high cholesterol, hypertension, diabetes, abdominal obesity, CAC >10, present aortic plaque, and AWT >75th percentile in the Lowest Tertile versus all other subjects was compared using chi-square. There were no differences in cholesterol and abdominal obesity, but there was a higher than expected occurrence of all other direct and indirect atherosclerosis indicators in the Lowest tertile ($p \leq .003$). This is similar to prior analyses comparing the Lowest and Highest tertiles.

Exploratory Analyses

An examination of the MoCA subdomains and atherosclerotic measures was conducted to determine if individual indicators of atherosclerosis had a relationship with a particular domain of cognition. MoCA items were divided into four subdomains, based on the original description of MoCA design (Nasreddine, et al., 2005). The Memory domain consisted of delayed free recall, cued recall, and multiple-choice recall and ranged from 0-5 points. The Attention domain included digit span, serial 7s, and letter vigilance (range 0-7 points). The Language domain consisted of naming, sentence repetition, and verbal fluency and ranged from 0-6 points. The Executive Function domain included trail-making, cube, clock, and abstraction (range 0-7).

The correlations between the subdomains and the MoCA Total Score were $r = .69$ (Language Domain), $r = .73$ (Attention Domain) and $r = .76$ (Executive Function Domain). Interestingly, the Memory domain was less correlated with the MoCA Total

Score (r = .40). Table 24 shows the correlational relationship between MoCA subdomain scores and CAC, aortic plaque, and AWT after controlling for education. Only the Language domain showed an association with any of the atherosclerotic measures, abdominal aortic plaque, but the relationship was negligible.

Other exploratory analyses were done using an additional abdominal aortic plaque variable, the measurement of the percentage of plaque in the abdominal aorta, rather than the measurement of plaque size (mm^2), as discussed in Section 1. Means, standard deviations, and medians for abdominal aortic plaque percent for the overall sample and by gender and race are presented in Table 25. The average abdominal aortic plaque (%) was 34.9 (SD = 4.69) and the median measurement was 34.6%. Plaque percent was significantly associated with education (r = -.11, $p \leq .001$), and with age (r = -.21, $p \leq .001$). Females had significantly higher overall abdominal aortic plaque percent than males [$F(1, 1283) = 20.10$, $p = .001$] after controlling for education and age. There were no significant differences by race; $F(2, 1252) = .948$, $p = .388$. Plaque percent was not related to MoCA scores (r = -.03, $p = .363$.). When added to the regression models discussed in Section 1 and in this Appendix, plaque percent did not alter the results.

A summary of this study's hypotheses and findings can be viewed in Table 26.

APPENDIX D

Additional Tables and Figures

Table 13. *Demographic Information for DHS Participants by Gender*

	Male (N = 801)	Female (N = 1103)	Statistic	*p*
Age M (SD)				
DHS-1	43.08 *(10.3)*	42.88 *(10.7)*	$t(1902) = .404$	.687
DHS-2	50.98 *(10.1)*	50.80 *(10.6)*	$t(1902) = .379$	.705
Education M (SD) [1]	13.90 *(2.7)*	13.36 *(2.6)*	$t(1901) = 4.34$	<.001
Race - N (%) [2]				
Black	389 *(49)*	630 *(57)*	$\chi^2(3) = 20.21$	<.001
White	299 *(37)*	338 *(31)*		
Hispanic	87 *(11)*	120 *(11)*		
Other	26 *(3)*	15 *(1)*		
MoCA Total Score M (SD)	23.29 (3.9)	23.41 (4.0)	$t(1902) = -.659$	<.510
Coronary Artery Calcium N (%) [3]				
>10 Agatston Units	173 (28)	114 (14)	$\chi^2(1) = 43.12$	<.001
Present Aortic Plaque N (%) [3]	224 (41)	247 (34)	$\chi^2(1) = 6.55$	.010
Aortic Wall Thickness N (%) [3]				
>75th percentile	193 (35)	129 (18)	$\chi^2(1) = 51.53$	<.001
Waist Circumference N (%) [4]				
>102 cm or >88 cm	296 (45)	615 (68)	$\chi^2(1) = 87.56$	<.001
ApoE4- N (%)	208 (30)	322 (34)	$\chi^2(1) = 2.49$	.114
Hypertensive - N (%)	230 (29)	348 (32)	$\chi^2(1) = 1.67$	.197
Diabetic - N (%)	69 (10)	88 (9)	$\chi^2(1) = .280$	.597
Hypercholesterolemia - N (%)	87 (13)	108 (11)	$\chi^2(1) = .691$	.406

[1] Males significantly more education.
[2] Females significantly higher number of Blacks.
[3] Males significantly higher prevalence of positive CAC, plaque, and AWT.
[4] Females significantly higher prevalence abdominal obesity.

Table 14. *Demographic Information for DHS Participants by Race*

	Black (N = 1019)	White (N = 636)	Hispanic (N = 207)	Other (N = 41)	Statistic
Age M (SD)[1]					
DHS-1	42.85 (10.5)	44.48 (10.5)	39.27 (10.0)	40.85 (9.40)	$F(3) = 13.81$
DHS-2	50.85 (10.4)	52.27 (10.3)	47.12 (9.9)	48.73 (10.1)	$F(3) = 13.73$
Education M (SD) [2]	13.07 (2.1)	14.78 (2.7)	12.14 (3.4)	15.30 (2.5)	$F(3) = 91.63$
Gender - N (%) [3]					
Male	389 (38)	299 (47)	87 (42)	26 (63)	$\chi^2(3) = 20.21$
Female	630 (62)	338 (53)	120 (58)	15 (37)	
MoCA M (SD) [4]	21.94 (4.0)	25.72 (2.8)	23.05 (3.7)	23.68 (3.60)	$F(3) = 141.57$
Coronary Artery Calcium N (%)					
>10 Agatston Units	109 (21)	144 (21)	28 (18)	6 (18)	$\chi^2(3) = 1.01$
Present Aortic Plaque N (%)	183 (38)	234 (37)	41 (30)	13 (40)	$\chi^2(3) = 4.22$
Aortic Wall Thickness N (%)					
>75th percentile	117 (24)	175 (29)	22 (16)	8 (27)	$\chi^2(3) = 8.82$
Waist Circumference N (%) [5]					
>102 cm or >88 cm	521 (66)	284 (50)	95 (55)	11 (31)	$\chi^2(3) = 45.03$
ApoE4 - N (%) [6]	323 (38)	157 (27)	44 (24)	6 (16)	$\chi^2(3) = 31.33$
Hypertension [7] N (%)	388 (39)	139 (22)	43 (21)	8 (20)	$\chi^2(3) = 64.77$
Diabetes [8] N (%)	106 (12)	27 (5)	18 (10)	6 (16)	$\chi^2(3) = 26.42$
Hypercholesterolemia N (%)	92 (11)	81 (14)	17 (9)	5 (14)	$\chi^2(3) = 4.41$

[1] Whites were older than Blacks and Hispanics; Hispanics younger than all other groups, $p<.001$
[2] Whites were more educated than Blacks and Hispanics; Hispanics less than all other groups, $p<.001$
[3] Other group had higher proportion of men, $p<.001$
[4] Whites had higher MoCA scores, and Hispanics higher scores than Blacks, $p<.001$
[5] Blacks had higher rate of abdominal obesity as measured by waist circumference, $p<.001$.
[6] Blacks had higher rate of the E4 allele, $p<.001$
[7] Blacks had higher rate of hypertension, $p<.001$
[8] Whites significantly lower rate of diabetes, $p<.001$

Table 15. *Receiver Operating Characteristic Area Under the Curve by Direct Measure of Atherosclerosis*

			Asymptotic 95% CI	
	Area	*p*	Lower Bound	Upper Bound
Coronary Artery Calcium	.585	.001	.549	620
Abdominal Aortic Plaque	.579	.001	.542	.617
Abdominal Aortic Wall Thickness	.564	.001	.526	.602

Table 16. *Logistic Regression Predicting Membership in Lowest MoCA Tertile for Demographic Variables*

							95% C.I.	
		B	S.E.	df	Sig.	Odds Ratio	Lower	Upper
Full Model	Education	-0.41	0.03	1	.001	0.67	0.62	0.71
	Age	0.08	0.01	1	.001	1.08	1.06	1.10
	Male	0.59	0.15	1	.001	1.81	1.34	2.44
	Race			2	.001			
	Black	0.59	0.23	1	.011	1.81	1.15	2.65
	White	-1.84	0.26	1	.001	0.16	0.10	0.27

Table 17. *Logistic Regression Predicting Membership in Lowest MoCA Tertile for Direct (Categorical) Atherosclerosis Measures*

							95% C.I	
		B	S.E.	df	Sig.	OR	Lower	Upper
Model	CAC >10	0.30	0.19	1	.116	1.34	0.93	1.94
	Present Aortic Plaque	0.31	0.16	1	.049	1.37	1.00	1.87
	AWT <75th percentile	0.31	0.19	1	.095	1.37	0.95	1.97

Table 18. *Logistic Regression Predicting Membership in Lowest MoCA Tertile for Indirect Atherosclerosis Measures*

							95% C.I	
		B	S.E.	df	Sig.	OR	Lower	Upper
Full Model	High Cholesterol	0.01	.19	1	.956	1.01	0.69	1.48
	Diabetes	0.36	0.23	1	.117	1.43	0.91	2.24
	Hypertension	0.80	0.14	1	<.001	2.23	1.68	2.96
	Abdominal Obesity	0.13	0.13	1	.327	1.14	0.88	1.47
Reduced Model	Hypertension	0.80	0.14	1	<.001	2.30	1.75	3.03

Table 19. *Multiple Regression Predicting MoCA Total Score for Direct (Continuous, Transformed) Measures of Atherosclerosis*

		Unstandardized Coefficients		Standardized Coefficients			95.0% C.I.	
		B	Std. Error	Beta	t	Sig	Lower Bound	Upper Bound
Full Model [1]	Constant	23.87	0.84		28.58	<.001	22.24	25.51
	CAC	-0.22	0.06	-0.11	-3.68	<.001	-0.34	-0.10
	Aortic Plaque	-0.11	0.06	-0.06	-1.91	.056	-0.23	0.00
	Aortic Wall Thickness	-0.40	0.46	-0.03	-0.86	.389	-1.30	0.51
Reduced Model [2]	CAC	-0.23	0.06	-0.12	-4.01	<.001	-0.35	-0.12
	Aortic Plaque	-0.14	0.05	-0.08	-2.56	.011	-0.24	-0.03

[1] R^2 = .026
[2] R^2 = .025

Table 20. *Logistic Regression Predicting Membership in Lowest MoCA Tertile For Men*

		B	S.E.	df	Sig.	Odds Ratio	95% C.I. Lower	95% C.I. Upper
Adjusted Model	Education	-0.33	0.06	1	<.001	0.72	0.64	0.82
	Race			2	<.001			
	Black	1.10	0.50	1	.028	3.01	1.13	8.01
	White	-1.45	0.52	1	.005	0.23	0.08	0.65
	Age	0.04	0.02	1	.086	1.04	0.99	1.09
	High Cholesterol	0.18	0.43	1	.671	1.20	0.52	2.77
	Diabetes	-0.46	0.61	1	.447	0.63	0.19	2.07
	Hypertension	0.25	0.40	1	.524	1.29	0.59	2.82
	Abdominal Obesity	-0.40	0.33	1	.217	0.67	0.35	1.27
	ApoE4	0.53	0.35	1	.128	1.70	0.86	3.38
	CAC >10	-0.06	0.38	1	.881	0.94	0.45	2.00
	Aortic Plaque	-0.48	0.36	1	.180	0.62	0.31	1.25
	Aortic Wall Thickness > 75th percentile	0.71	0.38	1	.066	2.03	0.96	4.31
Reduced Model	Education	-0.33	0.06	1	<.001	0.72	0.64	0.81
	Race			2	<.001			
	White	-1.53	0.52	1	.003	0.22	0.08	0.60

Note. n = 315

Table 21. *Logistic Regression Predicting Membership in Lowest MoCA Tertile For Women*

		B	S.E.	df	Sig.	Odds Ratio	95% C.I. Lower	Upper
Adjusted Model	Education	-0.45	0.06	1	<.001	0.64	0.56	0.73
	Race			2	<.001			
	Black	0.37	0.40	1	.361	1.44	0.66	3.16
	White	-1.70	0.43	1	<.001	0.18	0.08	0.42
	Age	0.06	0.02	1	<.001	1.06	1.03	1.10
	High Cholesterol	-0.42	0.41	1	.296	0.65	0.30	1.45
	Diabetes	-0.50	0.49	1	.310	0.61	0.23	1.59
	Hypertension	0.03	0.30	1	.923	1.03	0.57	1.87
	Abdominal Obesity	-0.19	0.28	1	.490	0.82	0.48	1.43
	ApoE4	0.20	0.27	1	.457	1.22	0.72	2.05
	CAC >10	-0.15	0.42	1	.723	0.86	0.38	1.96
	Aortic Plaque	-0.52	0.28	1	.060	0.59	0.34	1.02
	Aortic Wall Thickness > 75th percentile	-0.04	0.37	1	.923	0.96	0.47	1.98
Reduced Model	Education	-0.44	0.06	1	<.001	0.64	0.57	0.73
	Race			2	<.001			
	White	-1.66	0.42	1	<.001	0.19	0.08	0.43
	Age	0.06	0.02	1	<.001	1.06	1.03	1.10

Note. n = 486

Table 22. *Logistic Regression Predicting Membership in Lowest MoCA Tertile For Whites*

						Odds	95% C.I.	
		B	S.E.	df	Sig.	Ratio	Lower	Upper
Adjusted Model	Education	-0.36	0.07	1	<.001	0.70	0.61	0.80
	Male	0.51	0.35	1	.141	1.67	0.84	3.30
	Age	0.30	0.02	1	.192	1.03	0.99	1.07
	High Cholesterol	-0.33	0.48	1	.489	0.72	0.28	1.83
	Diabetes	-0.21	0.86	1	.805	0.81	0.15	4.37
	Hypertension	-0.52	0.50	1	.292	0.59	0.22	1.57
	Abdominal Obesity	-0.09	0.36	1	.798	0.91	0.45	1.84
	CAC >10	0.29	0.46	1	.521	1.34	0.55	3.27
	Aortic Plaque	0.67	0.37	1	.068	1.96	0.95	4.04
	Aortic Wall Thickness > 75th percentile	0.14	0.41	1	.732	1.15	0.52	2.55
	ApoE4	0.94	0.46	1	.042	0.39	0.16	0.97
Reduced Model	Education	-0.34	0.06	1	<.001	0.71	0.63	0.81

Note. n = 325

Table 23. *Logistic Regression Predicting Membership in Lowest MoCA Tertile For Blacks*

		B	S.E.	df	Sig.	Odds Ratio	95% C.I. Lower	95% C.I. Upper
Adjusted Model	Education	-0.42	0.07	1	<.001	0.65	0.57	0.75
	Male	0.97	0.32	1	.003	2.63	1.40	4.95
	Age	0.07	0.02	1	<.001	1.08	1.03	1.12
	High Cholesterol	-0.32	0.41	1	.443	0.73	0.33	1.63
	Diabetes	-0.45	0.46	1	.318	0.63	0.26	1.55
	Hypertension	0.39	0.31	1	.215	1.47	0.80	2.72
	Abdominal Obesity	-0.11	0.30	1	.716	0.90	0.50	1.61
	CAC >10	-0.58	0.44	1	.186	0.56	0.24	1.32
	Aortic Plaque	0.26	0.31	1	.414	1.29	0.70	2.39
	Aortic Wall Thickness > 75th percentile	0.23	0.40	1	.955	1.02	0.47	2.25
	ApoE4	0.12	0.29	1	.682	1.12	0.64	1.97
Reduced Model	Education	-0.44	0.07	1	<.001	0.64	0.56	0.74
	Male	1.21	0.32	1	<.001	3.34	1.79	6.24
	Age	0.08	0.02	1	<.001	1.08	1.04	1.12

Note. n = 353.

Table 24. *Spearman Correlations (rho) for MoCA Subdomains and Direct Atherosclerosis Measures, Controlling for Education and Age*

Domain	Statistic	Coronary Artery Calcium Agaston Unit	Aortic Plaque Area mm^2	Aortic Wall Thickness mm
Attention	rho	0.01	-0.02	0.02
	p	.78	.43	.55
Executive Function	rho	-0.05	-0.04	-0.02
	p	.04	.11	.36
Language	rho	-0.05	-0.07	-0.03
	p	.09	.01*	.30
Memory	rho	0.04	-0.02	-0.03
	p	.18	.42	.32

Note. df=1149

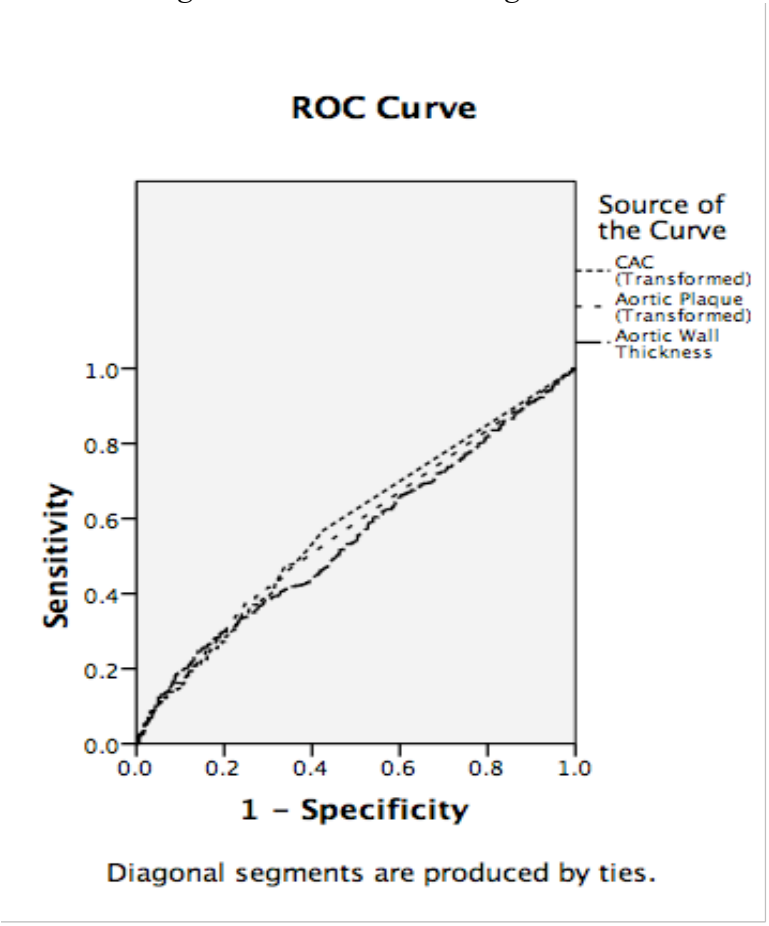
Table 25. *Abdominal Aortic Plaque (%) by Gender and Race*

		Abdominal AWT Percentage		
		Male	Female	Overall
Black	M (SD)	34.13 (4.8)	35.44 (4.3)	34.95 (4.5)
	Median	33.43	35.01	34.62
White	M (SD)	34.20 (5.2)	35.51 (4.8)	34.94 (5.0)
	Median	33.54	35.10	34.44
Hispanic	M (SD)	33.56 (3.9)	35.14 (4.0)	34.75 (4.0)
	Median	34.28	34.19	34.24
Total	M (SD)	34.24 (4.9)	35.44 (4.5)	34.93 (4.6)
	Median	33.76	34.97	34.55

Table 26. *Summary of Hypotheses and Findings*

Aim	Hypothesis	Summary	Supported?
I	Hyp. 1	MoCA and Athero will show small negative correlation	No
	Hyp. 2	Multiple + indicators will result in lower MoCA than a single indicator	Partially
II	Hyp. 3	Direct measures will predict Lowest Tertile	No
	Hyp. 4	Indirect measures will predict Lowest Tertile	No
III	Hyp. 5	ApoE4 will result in lower MoCA	No
	Hyp. 6	ApoE4 will augment athero and MoCA relationship	No

Figure 2. Area Under the Curve Receiver Operating Characteristics for Coronary Artery Calcium, Abdominal Aortic Plaque, and Abdominal Aortic Wall Thickness Discriminating Between Lowest and Highest MoCA Tertile



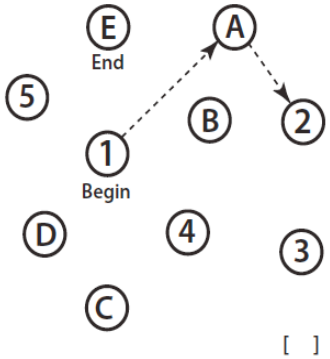
APPENDIX E

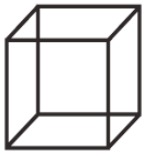
MoCA Protocol

MONTREAL COGNITIVE ASSESSMENT (MOCA)

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

VISUOSPATIAL / EXECUTIVE





Copy cube

[ ] [ ]

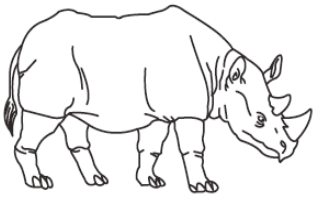
Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

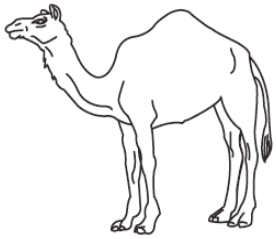
POINTS __/5

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

 Version 7.1 www.mocatest.org Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

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