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Subclinical Atherosclerotic Calcification and Cognitive Functioning in Middle-Aged Adults: The CARDIA Study

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Abstract

Objective—Cardiovascular risk factors in middle-age are associated with cognitive impairment and dementia in older age. Less is known about the burden of calcified subclinical atherosclerosis and cognition, especially in midlife. We examined the association of coronary artery and abdominal aortic calcified plaque (CAC and AAC, respectively) with cognitive functioning in middle-aged adults.

Methods—This cross-sectional study included 2,510 black and white adults (age: 43–55 years) without heart disease or stroke who completed a year 25 follow-up exam (2010–11) as part of the Coronary Artery Risk Development in Young Adults Study. CAC and AAC were measured with non-contrast computed tomography. Cognition was assessed with the Digit Symbol Substitution Test (DSST) (psychomotor speed), Stroop Test (executive function), and Rey Auditory Verbal Learning Test (RAVLT) (verbal memory).

Results—A greater amount of CAC and AAC was associated with worse performance on each test of cognitive function after adjustment for age, sex, race, education, and study center. Associations were attenuated, but remained significant for the DSST and RAVLT following additional adjustment for vascular risk factors, including adiposity, smoking, alcohol use, dyslipidemia, hypertension, and diabetes. Compared to participants without CAC or AAC, those

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with both CAC and AAC, but not CAC or AAC alone was associated with lower DSST scores ($p<0.05$).

Conclusions—In this community-based sample, greater subclinical atherosclerotic calcification was associated with worse psychomotor speed and memory in midlife. These findings underscore the importance of a life course approach to the study of cognitive impairment with aging.

Keywords

atherosclerosis; heart disease; calcium score; cognition; subclinical disease; risk factors

The presence of cardiovascular risk factors in middle-age such as hypertension and diabetes are predictive of cognitive impairment [1, 2] and dementia in older age [3, 4]. There is accumulating evidence that subclinical atherosclerosis, which may partly reflect lifetime exposure to cardiovascular risk factors may also be involved in the development of aging-related cognitive impairment and dementia. [5–10] Calcified atherosclerotic plaque lesions represent advanced stages of the atherosclerotic process and are strongly associated with magnetic resonance imaging markers of vascular brain disease, including white matter lesions, cerebral infarcts, cerebral microbleeds, and worse white matter microstructural integrity. [5–8]

Few studies have determined whether calcified plaque burden in multiple vessel beds is associated with cognition. [6, 8] Furthermore, available evidence has come from studies of older adults, including the Rotterdam Study (mean age 69.5 years) and the Age, Gene, Environment Susceptibility-Reykjavik Study (mean age 76.3 years). It is becoming increasingly clear that dementia has a long preclinical period leading to calls for the study of risk factors and cognitive outcomes many years prior to the clinical diagnosis of disease. [11] If subclinical atherosclerosis early in life is identified as an important determinant of cognitive function, increased efforts to prevent or potentially reduce the burden of atherosclerosis may result in delays in aging-related cognitive decline and possibly dementia later in adulthood.

The present study was conducted to investigate whether the extent of calcified plaque in the coronary arteries and the abdominal aorta is associated with cognitive function in midlife in the Coronary Artery Risk Development in Young Adults (CARDIA) Study. The hypothesis was that a greater burden of calcified plaque would be associated with worse cognitive health in middle-age (43–55 years).

Materials and Methods

Study population

CARDIA is a multi-center, community-based, longitudinal cohort study of the development and determinants of cardiovascular disease over time in 5,115 young adults initially aged 18–30 years in 1985–1986. To date, participants have been re-examined approximately every 2–5 years. All participants provided written informed consent, and institutional review boards approved the study.

Of the 3,499 participants examined at year 25 (2010–2011) (72% of surviving cohort), 3,120 completed a computed tomography scan (CT) of the chest and abdomen. We excluded 233 participants without complete information on all three tests of cognitive function and 377 who reported a history of heart disease or stroke. The remaining 2,510 participants formed the sample population for the current analysis.

Clinical measurements

Standardized protocols for data collection and quality control were used across study centers. Participants were asked to fast for at least 12 h and to avoid smoking or engaging in heavy physical activity for at least 2 h prior to examination.

Computerized tomography

Noncontrast CT images were acquired via multidetector scanners using a standardized protocol. [12] To measure coronary artery calcified plaque (CAC), contiguous 2.5–3-mm-thick transverse images from the root of the aorta to the apex of the heart were obtained. For the abdominal aorta, 1–1.25-mm-thick transverse images 15-cm proximal to the superior end plate of the sacrum were acquired. Participants were scanned over a hydroxyl-apatite phantom to monitor image brightness and noise, as well as to adjust for scanner differences across field centers. A calcium score in Agatston units (AU) [13] was calculated for each calcified lesion and the scores summed across all lesions within a given artery and across all arteries (left anterior descending, left main, circumflex, and right coronary) to obtain the total CAC score. For abdominal aortic calcified plaque (AAC), calcium in the wall of the distal abdominal aorta in a 60-mm segment centered at the aortic bifircation was measured. CAC and AAC were classified as present (>0 AU) or absent. Severity was categorized by a score of 0, 1–99, 100–399, and ≥400 AU. To characterize the burden of systemic calcified plaque, we also jointly classified participants by presence or absence of CAC and AAC as having neither CAC nor AAC, CAC only, AAC only, and both CAC and AAC.

Cognitive function assessment

The Digit Symbol Substitution Test (DSST), a subtest of the Wechsler Adult Intelligence Scale (3rd edition), assesses an array of cognitive domains, most prominently visual motor speed, sustained attention, and working memory. It is a paper-and-pencil task requiring timed translation of numbers to symbols using a key given at the top of the test page. The DSST has been used extensively to measure cognitive function in cognitively intact individuals; its score is well correlated with measures of physical function and future cognitive decline; and might be less sensitive to educational level than other tests. [14, 15] The range of scores is 0 to 133, with increasing scores indicating better performance.

The Stroop Test evaluates the ability to view complex visual stimuli and to respond to one stimulus dimension while suppressing the response to another dimension, an “executive” skill largely attributed to frontal lobe function. [16] The Stroop task involved 2 congruent and 1 incongruent trials. In the first congruent trial, participants read a list of color words printed in black ink in a box containing 40 smaller rectangular boxes. In the second congruent trial, participants named the colors of the rectangular boxes. In the final incongruent trial, participants named the color of the ink in which the word named a different color than the ink within each box. Each trial was scored by summing the number of errors and the time required to complete each trial. An interference score was calculated by subtracting the score on the incongruent trial from the second congruent trial. Interference provides a measure of how much additional executive processing is needed to respond to an incongruent trial; thus, a higher interference score indicates worse performance on the task

The Rey Auditory Verbal Learning Test (RAVLT) assesses the ability to memorize and to retrieve words (verbal memory). The RAVLT has been used extensively in epidemiologic research and has been found to be sensitive to neurological impairment in a wide variety of patients. Scores of verbal learning and memory also correlate strongly with executive function. [17] Testing consisted of 5 oral presentations of a list of 15 concrete nouns (List A) with free recall, one presentation of a 15-word interference list (List B), one short delay free

recall of List A, and one long 10 minute delay free recall of List A. Results from the long delay (10 min) free recall were used in analyses. The range of scores is 0 to 15, with increasing scores indicating better performance.

Other measurements

Education was represented as years of schooling. The CARDIA Physical Activity History questionnaire queried the amount of time per week spent in 13 categories of physical activities over the past 12 months. [18] Cigarette smoking status was classified as current or former/never. Total daily alcohol consumption was calculated from an interviewer-administered questionnaire. Symptoms of depression were assessed with the 20-item Center for Epidemiologic Studies Depression scale (CES-D). [19]

Body weight was measured to the nearest 0.2 kg with a calibrated balance-beam scale. Height was measured with a vertical ruler to the nearest 0.5 cm. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured after a 5-minute rest on the right arm of seated participants at three 1-minute intervals using a standard automated blood pressure measurement monitor (OmROn model HEM907XL; Omron). Plasma total cholesterol, HDL cholesterol, and triglyceride concentrations were measured by enzymatic methods at Northwest Lipids Research Laboratory (Seattle, WA). HDL cholesterol was measured after dextran-magnesium precipitation. LDL-cholesterol was estimated by the Friedewald equation. Glucose was assayed using hexokinase coupled to glucose-6-phosphate dehydrogenase (Millipore, Inc, Bellerica, MA).

Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medications. Dyslipidemia was defined as use of lipid lowering medications or meeting ATP III guidelines for low HDL-cholesterol (women: ≤ 50 mg/dL; men: ≤ 40 mg/dL), high LDL-cholesterol (≥160 mg/dL), or high triglycerides (≥ 200 mg/dL). Diabetes was determined based on a combination of measured fasting glucose levels (≥126 mg/dl); self-report of oral hypoglycemic medications or insulin; a 2-hour postload glucose ≥200 mg/dl; or a glycated hemoglobin A_{1c} ≥6.5%. [20]

Statistical analysis

Participant characteristics overall and according to the presence or absence of CAC or AAC were described using means, medians, and proportions as appropriate. We used linear regression models and χ^2 analyses to test for differences by presence of CAC or AAC for continuous and categorical characteristics, respectively. The Wilcoxon rank-sum test was used for characteristics with skewed distributions. Multivariable linear regression models were used to estimate the association between CAC or AAC and each measure of cognitive function after adjusting for potential confounding factors, including age, sex, race, educational level, and study center. A second model adjusted additionally for factors that may lie earlier in the causal pathway, including BMI, smoking status, alcohol use, dyslipidemia, hypertension, and diabetes. Alternative models which adjusted simultaneously for HDL- and LDL-cholesterol, triglycerides, systolic blood pressure, fasting glucose, and use of medications for dyslipidemia, hypertension, and diabetes (separately) as opposed to the clinical classification of these conditions produced similar results. Tests for a linear trend were determined by entering the CAC or AAC score into the model as an ordinal term. The Tukey-Kramer test of multiple comparisons was used to compare mean cognitive function scores according to categories of both CAC and AAC. Tests of statistical significance were 2-tailed, with an alpha level of 0.05. SAS version 9.3 (Cary, NC) was used to perform all analyses.

Results

Of the 2,510 eligible participants without a history of heart disease or stroke, 46.1% were black and 54.9% were women. Overall, 27.3% of participants had any CAC, 51.7% had AAC, and 20.4% had both CAC and AAC. Most of those with CAC had an Agatston score of 1–99 (19.5% of all participants), while 5.7% and 2.2% had a score of 100–399 and ≥400 AU, respectively. For AAC, 28.6%, 12.4%, and 10.7% had an Agatston score of 1–99, 100–399, and ≥400 AU, respectively.

Table 1 shows the characteristics of participants according to the presence of CAC and AAC. CAC was associated with older age; male sex; white race; less education; higher alcohol consumption; current smoking; higher physical activity; lower HDL-cholesterol; and higher LDL-cholesterol, triglycerides, and systolic and diastolic blood pressure. The prevalence of dyslipidemia, hypertension, and diabetes were higher among those with CAC. Similar results were observed for AAC, except race and physical activity showed no association. Depression scores were not associated with CAC or AAC.

Mean scores on the DSST, Stroop Test, and RAVLT were 70.3±15.9 symbols (range: 8 to 125), 22.5±10.5 sec+errors (range: −23 to 127), and 8.4±3.2 words (range: 0 to 15). Table 2 displays multivariable-adjusted mean scores for the DSST, Stroop Test, and RAVLT according to CAC score. Mean scores were lower for the DSST and RAVLT, and higher for the Stroop Test among participants with higher CAC score ($p<0.001$, 0.03, and 0.03, respectively). Adjustment for vascular risk factors in model 2 attenuated these associations; however, higher CAC score remained associated with lower scores on the DSST ($p=0.02$). Further adjustment for physical activity or CES-D scores showed similar results (data not shown).

Table 3 shows multivariable-adjusted mean scores for the DSST, Stroop Test, and RAVLT according to AAC score. Higher AAC score was associated with poorer performance on each measure of cognitive function ($p<0.01$, for all). Further adjustment for vascular risk factors attenuated these associations; however, AAC remained associated with lower scores on the DSST ($p=0.008$) and RAVLT ($p=0.04$). Further adjustment for physical activity or CES-D scores showed similar results (data not shown).

We also examined the joint association of the presence of both CAC and AAC with each measure of cognitive function (Table 4). Compared to those with neither CAC nor AAC, those with both performed worse on the DSST ($p <0.001$) and RAVLT ($p<0.05$). Adjustment for vascular risk factors attenuated these associations; however, the association with the DSST remained ($p<0.05$). No other significant differences were identified.

Discussion

In this community-based study of individuals free of known coronary and cerebrovascular disease, we found a graded association between a greater burden of CAC and AAC and worse performance on a test of processing speed, attention, and working memory in midlife. Greater severity of AAC was also associated with worse performance on a test of verbal memory in midlife. In addition, those with more systemic calcified atherosclerosis, reflected by the simultaneous presence of both CAC and AAC, had poorer processing speed. These associations were independent of demographic characteristics, major vascular risk factors, and depressive symptoms. These findings suggest that calcified atherosclerotic plaque burden may provide additional information over vascular risk factors in predicting cognitive performance in middle-aged adults.

In a recent analysis of the Age, Gene, Environment Susceptibility-Reykjavik Study cohort of men and women (mean age 76.3 years), greater burden of CAC was independently associated with worse performance on tests of memory, processing speed, and executive function, as well as higher odds for dementia. [8] In the Rotterdam Study (mean age 69.5 years), greater calcified plaque in several locations, including the coronary arteries and aortic arch was associated with poorer performance on tests designed to measure a range of cognitive domains. [6] Several, [9, 10, 21–23] but not all [24] available population-based studies primarily of older adults incorporating other measures of subclinical atherosclerosis, including carotid intima-media thickness and ankle-brachial index, have reported similar findings. Our results are consistent with those of previous studies and extend this evidence to a younger cohort. Future studies are needed to determine whether atherosclerosis in midlife is associated with accelerated aging-related cognitive decline and dementia through older adulthood.

The mean differences that we observed in cognitive test scores between those with and without CAC or AAC were modest; nevertheless, effect sizes of this magnitude may be clinically relevant. For example, in our study population every 1-year increase in age was associated with 0.56 less symbols substituted correctly on the DSST and 0.03 less words recalled correctly on the RAVLT (data not shown). Therefore, the effect sizes we observed between those with a CAC or AAC score of ≥400 AU and those without CAC or AAC correspond to an age difference of about 4–13 years. In addition, in a 3-year follow-up study of individuals with minimal cognitive impairment, a 1-point difference in baseline DSST score was significantly associated with a higher risk of Alzheimer's disease. [25] In another study of community-dwelling adults aged >70 years, a 1-point difference in baseline DSST score was associated with a 3% higher risk of dementia. [26]

We found that risk factors for vascular disease attenuated the association of CAC and AAC with psychomotor speed and memory, and statistically explained the association with executive functioning. Existing studies, including the Framingham Offspring Study [22] and the Baltimore Longitudinal Study of Aging [9] have shown that vascular risk factors explain the association of carotid atherosclerosis with executive function, but not psychomotor speed, memory, or other domains of cognition. These findings suggest an important role for these vascular risk factors in the relationship between atherosclerosis and cognitive function. Other common metabolic, inflammatory, and dietary risk factors may represent additional indirect mechanisms by which calcified atherosclerosis influences cognitive functioning. [27, 28] As mentioned earlier, calcified plaque has been shown to be associated with greater white matter lesion volume, worse white matter microstructural integrity, cerebral infarcts, and cerebral microbleeds. [5–8] Additional direct mechanisms by which calcified plaque might be associated with worse cognitive function include chronic cerebral hypoperfusion, increased parenchymal oxidative stress, and common genetic vulnerability to atherosclerosis of large and small vessels. [29]

Important strengths of our study include a population-based sampling method; a biracial cohort; extensive data on potential confounders; a large sample size well balanced with respect to age, sex, race, and education that permitted simultaneous adjustment for multiple variables; detailed assessments of atherosclerosis and vascular risk factors; and the standardized data collection protocols and rigorous quality control of the CARDIA study. Nevertheless, at least two limitations deserve mention. First, we assessed calcified plaque and cognitive function at only a single time in midlife and therefore we were unable to determine whether atherosclerosis or its change over time was associated with delays in aging related cognitive decline. In addition, this is an observational analysis, and residual confounding, particularly by socioeconomic status, may be present. Conversely, our results were robust to adjustment for midlife educational attainment, making it improbable that the

observed associations are owing completely to residual confounding by socioeconomic status.

In conclusion, our findings indicate that greater calcified atherosclerotic plaque burden in the coronary arteries or abdominal aorta is associated with worse performance on tests of processing speed and verbal memory in midlife. Furthermore, this association appears independent of vascular risk factors. These findings highlight the importance of a life course approach to the study of cognitive impairment with aging. Additional long-term studies are needed to determine the influence of subclinical atherosclerosis early in life on aging-related cognitive decline and dementia through older age. These studies will help to determine the implications for interventions that seek to delay or potentially reduce atherosclerosis and improve vascular health decades prior to the appearance of clinical signs and symptoms.

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1. We determine the independent association of calcification with cognition
2. Greater calcification in midlife independently associated with cognitive function
3. A life course approach to the study of cognitive impairment with aging is needed

Table 1

Characteristics of participants according to the presence or absence of coronary artery calcified plaque or abdominal aortic calcified plaque, year 25, CARDIA (n = 2,510).

	Coronary artery calcified plaque		Abdominal aortic calcified plaque	
	Present	**Absent**	**Present**	**Absent**
n (%)	686 (27.3)	1,824 (72.7)	1,297 (51.7)	1,213 (48.3)
Age, years	51.1 (3.3)	49.6 (3.7) *	50.6 (3.6)	49.5 (3.7) *
Men, %	67.1	36.8 *	52.2	37.5 *
Black, %	41.0	48.0 †	47.8	44.4
Education, years	15.4 (2.6)	15.7 (2.5) †	15.3 (2.6)	15.9 (2.5) *
Alcohol use, ml/day	4.8 (0, 17.5)	2.4 (0, 13.0) *	2.7 (0, 16.7)	2.4 (0, 12.2) †
Body mass index, kg/m^2	30.6 (7.0)	29.9 (7.0) †	30.7 (6.7)	29.4 (7.2) *
Current smoker, %	23.4	13.3 *	23.1	8.5 *
Physical activity, exercise units	322 (151, 528)	270 (125, 480) *	278 (129, 488)	290 (142, 498)
CES-D, score	8 (4, 12)	7 (4, 12)	8 (4, 13)	7 (4, 12)
HDL cholesterol, mg/dL	53.9 (17.6)	59.4 (17.6) *	55.5 (16.9)	60.5 (18.4) *
LDL cholesterol, mg/dL	116.4 (35.5)	111.9 (31.1) †	115.9 (34.4)	110.2 (29.9) *
Triglycerides, mg/dL	108 (76, 157)	88 (65, 128) *	100 (74, 145)	86 (62, 125) *
Systolic blood pressure, mmHg	122.8 (16.2)	118.2 (15.6) *	121.8 (16.1)	116.9 (15.2) *
Diastolic blood pressure, mmHg	76.3 (10.8)	74.3 (11.4) *	76.5 (11.1)	73.2 (11.2) *
Fasting glucose, mg/dL	104.1 (31.2)	96.7 (23.2) *	100.8 (27.4)	96.5 (23.9) *
Dyslipidemia, %	40.7	31.5 *	39.4	28.3 *
Hypertension, %	41.7	28.7 *	38.4	25.6 *
Diabetes, %	15.9	10.2 *	14.5	8.8 *

Presented as the mean (standard deviation) or median (interquartile range) unless otherwise stated.

* p-value < 0.001 vs. neither CAC nor AAC

† p-value < 0.05 vs. neither CAC nor AAC

Table 2

Multivariable-adjusted mean (95% confidence interval) Digit Symbol Substitution Test (DSST), Stroop Test, and Rey Auditory Verbal Learning Test (RAVLT) scores according to coronary artery calcified plaque, year 25, CARDIA (n = 2,510).

	Coronary artery calcified plaque score (Agatston units)				
	0 (n=1,824)	**1–99 (n=489)**	**100–399 (n=142)**	**≥400 (n=55)**	**p-trend**
DSST (symbols)					
Model 1	70.0 (69.3, 70.6)	68.9 (67.6, 70.1)	66.6 (64.3, 68.8)	65.9 (62.3, 69.5)	< 0.001
Model 2	68.0 (66.8, 69.1)	67.6 (66.1, 69.1)	65.2 (62.6, 67.7)	64.6 (60.6, 68.6)	0.02
Stroop Test (sec+errors)					
Model 1	22.5 (22.0, 23.0)	23.2 (22.3, 24.0)	23.8 (22.2, 25.4)	24.3 (21.7, 26.9)	0.03
Model 2	23.3 (22.5, 24.1)	23.8 (22.8, 24.9)	24.1 (22.4, 25.8)	25.0 (22.3, 27.8)	0.11
RAVLT (words)					
Model 1	8.3 (8.2, 8.5)	8.1 (7.8, 8.3)	7.8 (7.4, 8.3)	8.0 (7.3, 8.8)	0.03
Model 2	8.1 (7.8, 8.3)	7.9 (7.5, 8.2)	7.9 (7.3, 8.4)	8.0 (7.1, 8.8)	0.23

Model 1 was adjusted for age, sex, race, educational attainment, and study center.

Model 2 was adjusted additionally for body mass index, smoking status, alcohol use, dyslipidemia, hypertension, and diabetes. An alternative model which adjusted simultaneously for HDL- and LDL-cholesterol, triglycerides, systolic blood pressure, fasting glucose, and use of medications for dyslipidemia, hypertension, and diabetes (separately) as opposed to the clinical classification of these conditions produced similar results.

Table 3

Multivariable-adjusted mean (95% confidence interval) Digit Symbol Substitution Test (DSST), Stroop Test, and Rey Auditory Verbal Learning Test (RAVLT) scores according to abdominal aortic calcified plaque, year 25, CARDIA (n = 2,510).

	Abdominal aortic calcified plaque score (Agatston units)				
	0 (n=1,213)	**1–99 (n=718)**	**100–399 (n=311)**	**≥400 (n=268)**	**p-trend**
DSST (symbols)					
Model 1	70.6 (69.8, 71.3)	69.1 (68.1, 70.1)	68.6 (67.1, 70.1)	66.4 (64.8, 68.1)	<0.001
Model 2	68.7 (67.3, 70.0)	67.3 (65.9, 68.8)	67.0 (65.2, 68.8)	66.2 (64.4, 68.1)	0.008
Stroop Test (sec+errors)					
Model 1	22.5 (21.9, 23.0)	22.3 (21.6, 23.0)	23.8 (22.7, 24.8)	24.1 (22.9, 25.3)	0.008
Model 2	23.4 (22.4, 24.3)	23.1 (22.1, 24.1)	24.2 (22.9, 25.4)	24.0 (22.7, 25.3)	0.28
RAVLT (words)					
Model 1	8.4 (8.2, 8.5)	8.4 (8.2, 8.6)	8.0 (7.7, 8.3)	7.7 (7.3, 8.0)	<0.001
Model 2	8.1 (7.9, 8.4)	8.2 (7.9, 8.5)	7.8 (7.5, 8.2)	7.7 (7.3, 8.1)	0.04

Model 1 was adjusted for age, sex, race, educational attainment, and study center.

Model 2 was adjusted additionally for body mass index, smoking status, alcohol use, dyslipidemia, hypertension, and diabetes. An alternative model which adjusted simultaneously for HDL- and LDL-cholesterol, triglycerides, systolic blood pressure, fasting glucose, and use of medications for dyslipidemia, hypertension, and diabetes (separately) as opposed to the clinical classification of these conditions produced similar results.

Table 4

Multivariable-adjusted mean (95% confidence interval) Digit Symbol Substitution Test (DSST), Stroop Test, and Rey Auditory Verbal Learning Test (RAVLT) scores according to the presence or absence of coronary artery calcified (CAC) and abdominal aortic calcified (AAC) plaque, year 25, CARDIA (n = 2,510).

	Presence or absence of CAC and AAC			
	Neither (n=1,039)	**CAC only (n=174)**	**AAC only (n=785)**	**Both CAC and AAC (n=512)**
DSST (symbols)				
Model 1	70.6 (69.8, 71.5)	70.3 (68.3, 72.3)	69.2 (68.2, 70.1)	67.4 (66.1, 68.6) *
Model 2	68.6 (67.2, 70.0)	68.6 (66.3, 71.0)	67.4 (66.1, 68.7)	66.3 (64.8, 67.8) †
Stroop Test (sec+errors)				
Model 1	22.4 (21.8, 23.0)	23.0 (21.5, 24.4)	22.6 (22.0, 23.3)	23.5 (22.7, 24.4)
Model 2	23.3 (22.4, 24.3)	23.9 (22.3, 25.5)	23.3 (22.4, 24.2)	24.0 (23.0, 25.0)
RAVLT (words)				
Model 1	8.4 (8.2, 8.5)	8.3 (7.9, 8.8)	8.3 (8.1, 8.5)	7.9 (7.7, 8.2) †
Model 2	8.1 (7.8, 8.4)	8.2 (7.7, 8.7)	8.1 (7.8, 8.4)	7.8 (7.5, 8.1)

* p-value < 0.001 vs. neither CAC nor AAC

† p-value < 0.05 vs. neither CAC nor AAC

Model 1 was adjusted for age, sex, race, educational attainment, and study center.

Model 2 was adjusted additionally for body mass index, smoking status, alcohol use, dyslipidemia, hypertension, and diabetes. An alternative model which adjusted simultaneously for HDL- and LDL-cholesterol, triglycerides, systolic blood pressure, fasting glucose, and use of medications for dyslipidemia, hypertension, and diabetes (separately) as opposed to the clinical classification of these conditions produced similar results.