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Subclinical Atherosclerosis is Weakly Associated with Lower Cognitive Function in Healthy Hyperhomocysteinemic Adults without Clinical Cardiovascular Disease

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Abstract

OBJECTIVE—Atherosclerosis is the most common pathologic process underlying cardiovascular disease (CVD). It is not well known whether subclinical atherosclerosis is an independent risk factor for lower cognitive function among individuals without clinically evident CVD.

METHODS—We examined cross-sectional associations between subclinical atherosclerosis and cognitive function in a community-based sample of otherwise healthy adults with plasma homocysteine ≥8.5 μmol/L enrolled in the BVAIT study (n=504, mean age 61 years). Carotid artery intima-media thickness (CIMT), coronary (CAC) and abdominal aortic calcium (AAC) were used to measure subclinical atherosclerosis. Cognitive function was assessed with a battery of neuropsychological tests. A principal components analysis was used to extract five uncorrelated cognitive factors from scores on individual tests, and a measure of global cognition was derived. Multivariable linear regression was used to examine the association between subclinical atherosclerosis and cognitive function, adjusting for other correlates of cognition.

RESULTS—Increasing thickness of CIMT was associated with significantly lower scores on the verbal learning factor (β = −0.07 per 0.1 mm increase CIMT [SE(β)=0.03], p=0.01). CAC and AAC were not individually associated with any of the cognitive factors.

CONCLUSIONS—This study provides evidence that increasing CIMT is weakly associated with lower verbal learning abilities but not global cognition in a population of otherwise healthy middle-to-older aged adults with elevated plasma homocysteine but without clinically evident CVD. The association between CIMT and poor verbal learning may pertain particularly to men.

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Key Points

Subclinical atherosclerosis measured by CIMT is weakly associated with lower verbal learning abilities in healthy, cognitively intact middle-to-older aged adults.

Keywords

cognitive function; atherosclerosis; cardiovascular disease; memory; verbal learning

INTRODUCTION

Interest in the association between cardiovascular disease (CVD), its risk factors and cognitive impairment, cognitive decline and dementia(Elias and Robbins, 1991) has been building. Factors such as hypertension(Tervo et al., 2004), diabetes(Kumari and Marmot, 2005) and elevated homocysteine(Riggs et al., 1996) that are known to increase CVD risk, have also been linked to diminished cognitive function. Furthermore, there is a growing consensus that vascular disease is part of the pathology of Alzheimer's disease (AD), which accounts for the majority of cases of dementia, and that AD and vascular dementia, often considered the second most common type of dementia, may not be completely separate entities as previously believed(Launer, 2002).

While atherosclerosis is the most common pathologic process underlying CVD(Azen et al., 1996), few community-based studies have examined the relationship between atherosclerosis and cognition(Breteler et al., 1994, Cerhan et al., 1998, Johnston et al., 2004, Muller et al., 2007). Furthermore, most studies have focused attention on late stages of atherosclerosis when studying elderly demented populations with clinical CVD(Elias et al., 2001). As such, it is not well known whether subclinical atherosclerosis is an independent risk factor for impaired cognitive function among non-demented individuals without clinically evident CVD. Establishing a timeline for when atherosclerosis may begin to exert an effect on cognitive function is critical for an understanding of the mechanisms by which atherosclerosis may act as well as for developing and targeting appropriate interventions(Knopman et al., 2001).

To address these questions, we examined cross-sectional associations between subclinical atherosclerosis, using measures of carotid artery intima-media thickness (CIMT), coronary artery calcium (CAC) and abdominal aortic calcium (AAC), and cognitive function assessed with a battery of neuropsychological tests in a community-based sample of otherwise healthy cognitively intact hyperhomocysteinemic middle-aged and older adults.

METHODS

Study participants

Healthy hyperhomocysteinemic adults ≥ 40 years old who were randomized in the B-Vitamin Atherosclerosis Intervention Trial (BVAIT) were the focus of the present study. Data obtained for participants at their baseline visit prior to initiating the intervention were used in the current analysis.

Briefly, men and postmenopausal women ≥ 40 years old were eligible for BVAIT if they had Hcy ≥ 8.5 μmol/L. Of 5,309 individuals who were prescreened by telephone, 4,803 were ineligible (Hcy was < 8.5 μmol/L for 1,770 individuals) or refused to be enrolled. Exclusions were made for any clinical signs or symptoms of CVD (n=151), diabetes mellitus or fasting serum glucose ≥126 mg/dL (n=131), triglyceride (TG) levels ≥500 mg/dL (n=2), hypertension [systolic blood pressure (SBP) ≥160 mmHg and/or diastolic blood pressure (DBP) ≥100 mmHg)] (n=11), untreated thyroid disease (n=2), creatinine clearance <70 ml/min (n=4), a life threatening disease with prognosis <5 years (n=113), alcohol intake of >5 drinks per day/substance abuse (n=1), not a postmenopausal woman (n=356), or unwillingness to stop taking vitamin supplements (n=624). No cognitive or psychiatric

exclusion criteria were specified. A total of 506 subjects were randomized in BVAIT; all signed a written informed consent approved by the Institutional Review Board at the University of Southern California.

Measurement of Subclinical Atherosclerosis

CIMT—Using high resolution B-mode ultrasound, the right common carotid artery (CCA) was imaged using methods described previously(Hodis et al., 2001). An image analyst measured CIMT of the distal CCA far wall with automated computerized edge detection using an in-house software package (Prowin, patents 2005, 2006), as described elsewhere(Selzer et al., 2001). CIMT was the average of approximately 70–100 individual measurements between the intima–lumen and media–adventitia interfaces along a 1-cm length just distal to the carotid artery bulb. This method standardized the location and the distance over which intima–media thickness was measured and ensured that the same portion of the arterial wall was measured in each image and compared within and across all participants. The intraclass correlations for the IMT measurements using this method range from 0.97 to 0.99(Selzer et al., 2001).

Coronary and abdominal aortic calcium—Multidetector spiral computed tomography (MDCT) methodology using an Mx-8000 4-S-CT scanner (Philips, formerly Marconi, Cleveland, Ohio) was used to image the coronary arteries and thoracic abdominal aorta. High resolution scanning of the heart was begun at the level of the carina (determined from a scout film) and proceeded caudally through the cardiac apex. A single breath-hold (during inspiration) procedure was used. Simultaneous acquisition of 4 slices and fast rotation time restricted the breath-hold time to less than 15 seconds. Prospective electrocardiographic triggering (set at 50% of the expected next RR interval) in sequential slice mode at 120 kV and 165 mAs was used for scanning of the heart. Contiguous, non-interlaced slices were acquired with a table increment of 20 mm every series of 4 slices. Two sets of 28 contiguous 5 mm slices were obtained and reconstructed in a 35 cm field of view that included a tissue-equivalent calibration phantom pad under the participant's thorax (Detrano et al., 1994, Mahaisavariya et al., 1994). Following acquisition of the heart images, high resolution scanning of the abdomen was begun at the tip of the xyphoid process and proceeded caudally through the level of the umbilicus for a total scanning distance of 20.15 cm. A single breath-hold (during inspiration) procedure with a breath-hold time less than 15 seconds was used. Helical scanning mode at 120 kV and 180 mAs with a table speed of 3 cm/sec and pitch of 6 was used for scanning the abdomen. One set of 31 total slices 5 mm thick was reconstructed in a 30 cm field of view that included the calibration phantom pad under the participant's abdomen spanning from the xyphoid process to below the umbilicus (Detrano et al., 1994, Mahaisavariya et al., 1994). All scans were analyzed by image analysts without knowledge of treatment group using calcium scoring software developed by Reed et al. (Reed et al., 1994) and validated by Yaghoubi et al. (Yaghoubi et al., 1995). For each subject, a calcium score for the coronary arteries and for the abdominal aorta was derived using methods described elsewhere (Agatston et al., 1990).

Measurement of Cognitive Function

A battery of cognitive and neuropsychological tests(Lezak et al., 2004) was administered in a standardized order to all subjects by one trained psychometrist. The battery was designed to assess a broad array of cognitive functions and abilities, particularly episodic memory and executive tasks thought to be vulnerable to aging, and included the following tests:

- Symbol Digit Modalities Test (SDMT)
- Trail Making Test Part B (Trails-B)

- Judgment of Line Orientation, Form H (JLO)
- Block Design [Wechsler Adult Intelligence Scale, 3rd Edition (WAIS-III)]
- Letter-Number Sequencing [Wechsler Memory Scale, 3rd Edition (WMS-III)] (LNS)
- Category fluency (animal naming, 60 seconds) (Animals)
- Boston Naming Test, 30-item version (BNT)
- Shipley Institute of Living Scale (Shipley), Abstraction Subset
- California Verbal Learning Test, 2nd edition (CVLT-II), immediate recall (IR) and delayed recall (DR)
- Logical Memory I and II (paragraph recall, IR and DR) (WMS-III)
- Faces I (IR) and II (DR) (WMS-III)

The Center for Epidemiologic Studies Depression Scale (CES-D) scale (Radloff, 1977) was used to assess mood, and the American National Adult Reading Test (AMNART) (Grober and Sliwinski, 1991) was used as a measure of pre-morbid cognitive function.

Of the 506 randomized subjects, two did not have cognitive testing; 504 (99.6%) subjects were included in the present study. Of the 504 subjects, 7 (1.4%) did not have measures of AAC, either due to technical problems that prevented reading or scoring of the scan (n=4) or missing phantom scores (n=3), and thus were not included in analyses that used AAC.

Biochemical and Behavioral Factors

Blood pressure, body height and weight were measured and body mass index (BMI) was calculated (kg/m^2). Blood samples were drawn after a minimum 8-hour fasting period. Total fasting Hcy was determined in plasma using reverse phase HPLC with a C18 column on a Waters HPLC instrument equipped with a WISP automatic injector and attached to a fluorimeter(Araki and Sako, 1987). A solution containing 40 nmol/ml Hcy was used as a standard and for column calibration. For quality control, pooled plasma spiked with different quantities of Hcy was used. Coefficient of variation for the assay was 7.8%.

Total cholesterol, total TG, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) (calculated) were measured by standardized enzymatic assay methodology(Lipid Clinics Research Program 1974). Fasting serum glucose levels were measured using the glucose oxidase technique on a Beckman Glucose II analyzer (Beckman Instruments, Brea, California). Smoking questionnaires were used to determine smoking status.

Statistical Analysis

Characteristics of subjects and mean values for CVD risk factors were summarized. For subjects (n=24) who were unable or refused to complete one or more tests in the battery due to reasons unrelated to their cognitive status, age-gender- and education-specific mean values from the BVAIT study population were imputed. Small reductions (on the order of 1.2% – 1.6%) in variances of the tests resulted from imputations, which were made for < 0.7% of the total number of tests. Results did not appreciably differ when subjects with imputed values were excluded from analyses. Mean CIMT was analyzed as a continuous variable, and a variable was created for CIMT categorized into quartiles. CAC and AAC were categorized as either present or absent (calcium score >0 versus 0). A composite ordinal variable indicating burden of subclinical atherosclerosis was created by summing a

dichotomous CIMT variable (≥3rd quartile vs. < 3rd quartile; to capture those with the thickest CIMT), CAC and AAC, and ranged from 0 (no on all three) to 3 (yes for all three).

For data reduction purposes, a principal components analysis with an orthogonal varimax rotation was performed on the 14 cognitive tests in the neuropsychological battery and consecutive uncorrelated factors were extracted. Following methods of Cattell(Cattell, 1966), a scree plot of successive eigenvalues was used to identify at what number of principal components the plot leveled off; this led to a decision to retain five factors. The five factors accounted for 72.4% of the total variance, and for descriptive purposes, each were assigned a name that reflected high factor loadings of individual cognitive tests (i.e., loadings with an absolute value > 45). The resulting factors generally reflected cognitive abilities in areas of 1) executive function (high factor loadings on SDMT, Trails-B, LNS, JLO, Block Design and Shipley), 2) verbal learning (CVLT- IR and DR), 3) logical memory (paragraph recall - IR and DR), 4) visual episodic memory (Faces I and II), and 5) semantic memory (Animals and BNT). For each subject, a factor score for each of the five component factors was calculated. In addition, we created a measure of global cognition, which was calculated as the weighted sum of scores on each of the individual tests in the neuropsychological battery; weighting of each test was based on the sum of the inverse covariances of scores with other tests. The resulting measure was then divided by its standard deviation (SD) so as to interpret results per SD of global cognition and ensure a consistent interpretation of results with those of the five cognitive factors.

Multivariable linear regression methods used the five factor scores and the global cognitive measure as dependent variables to examine the association with subclinical atherosclerosis and atherosclerosis burden. Separate models were run for the combination of each cognitive measure with CIMT (continuous, quartiles categories and dichotomous forms), CAC, AAC, and the composite variable indicating atherosclerosis burden. Beta coefficients (β) and their standard errors were estimated from regression models to assess the association between atherosclerosis and cognition. For the continuous CIMT variable, β represented the average unit change in the factor score per 0.1 mm of CIMT. For other categorical atherosclerosis variables, βs represented differences from the mean of a reference group (subjects with atherosclerosis at the lowest level or without atherosclerosis as defined by the variable). We first assessed individual correlations between the measure of global cognition and demographic covariates. Those covariates that were significant univariate correlates were then entered individually into a model of the association between the subclinical atherosclerosis and global cognition, and their effect on the β estimate for the atherosclerosis measure was assessed. Models were adjusted for demographic characteristics that changed the β estimate by at least 10% including: age (40–46, 47–54, 55–60, 61–66, 67–74 and ≥75 years), gender, race/ethnicity (indicator variables for Caucasian, African-American, Latino and Asian-American/Pacific Islander/Native American), highest educational level achieved (high school or less, some college, Bachelor's degree and graduate/professional degree), household income (<30,000, 30,000–49,999, 50,000–69,999, 70,000–99,999 and ≥100,000 dollars/year) and mood (CES-D = 0, 1–3, 4–8, 9–20 and >20). Since we found that education was a stronger correlate of cognitive function than the AMNART, and given that AMNART scores and educational level were collinear when modeled simultaneously, we chose to include education in our final models. Continuous variables including LDL-C, SBP and fasting Hcy that were associated with cognitive function in our population, but for which a clearly linear relationship could not be established, or for which previous investigators have reported non-linear associations with cognition (Robbins et al., 2005b, Yaffe et al., 2004) were categorized and modeled as a series of indicator variables. Given their established role as CVD risk factors and their demonstrated associations with cognitive function, potential confounding by LDL-C, Hcy, SBP, and smoking was controlled for by including these factors in the regression models. Given the number of hypothesis tests

planned, yet the exploratory nature of our analyses, we set a *priori* $\alpha = 0.01$. We explored whether gender, age and education level were effect modifiers by including interaction terms for each of these variables with the independent subclinical atherosclerosis variable in the models. If the interaction was significant (p-value of <0.05), additional models were run by the stratifying factor. All analyses used SAS version 9.0 (SAS Institute Inc., Cary, NC, USA.).

RESULTS

Characteristics of study subjects and mean values of CIMT, CAC and AAC are summarized in Table 1. The majority of the study subjects were men (61.1%), non-Hispanic White (64.7%) and highly educated (59.3% with a Bachelor's or graduate degree). Most subjects were overweight (mean BMI = 28.1 kg/m^2); 38% reported having smoked currently or in the past; 115 (22.8%) of participants reported current use of anti-hypertensive medications and 155 (30.8%) reported current use of lipid-lowering medications.

Increasing thickness of CIMT was associated with significantly lower scores on the verbal learning factor ($\beta = -0.07$ per 0.1 mm increase in CIMT [SE(β)=0.03], p=0.01), but not in other areas of cognitive function (Table 2). Compared to subjects with CIMT in the lowest quartile (<0.65 mm), subjects with CIMT in the highest quartile (≥0.83 mm) performed lower on verbal learning ($\beta = -0.26$ [SE(β)=0.12], p=0.04). The presence of CAC or AAC was not significantly individually associated with lower scores on any of the cognitive factors, or on the measure of global cognition (results not shown). Global cognitive abilities were lower, but not significantly, among individuals with evidence of subclinical atherosclerosis at three vascular sites (i.e., the greatest burden) compared to individuals with evidence at two or less sites (Table 2).

Given the significant inverse association between CIMT and verbal learning and the significant main effects of age, gender and education on cognition, effect modification by these factors was explored. Associations between CIMT and verbal learning differed significantly by gender (p for interaction =0.02) but not by age or education (p-values interaction >0.05). An association between increasing CIMT and poorer verbal learning was detected in men ($\beta = -0.10$ per 0.1 mm increase CIMT [SE(β)=0.03], p=0.004) but not in women. Compared to men with CIMT <3rd quartile, men with the thickest CIMT (CIMT ≥3rd quartile) scored almost 1/3 SD lower on verbal learning ($\beta = -0.31$ [SE(β)=0.13], p=0.016) (Table 3).

DISCUSSION

This study provides evidence that increasing thickness of CIMT is weakly associated with lower verbal learning abilities but not global cognition among healthy cognitively intact middle-toolder aged individuals without clinically evident CVD but with elevated Hcy. The observed association remained robust after adjustment for CVD risk factors suggesting that CIMT may be an independent correlate of verbal learning. The association between CIMT and poor verbal learning may pertain particularly to men. Arterial calcium measures of subclinical atherosclerosis were not associated with lower cognitive function in any area assessed. Results from this study also suggest that individuals with the greatest burden of subclinical atherosclerosis may have lower global cognitive abilities compared to those with less burden. Taken together, our findings suggest that in healthy, non-demented adults, early subclinical atherosclerosis (i.e., increasing thickness of CIMT) is associated with lower verbal learning, whereas later stage subclinical atherosclerosis (calcifications of the arteries) is not. We did not find evidence that subclinical atherosclerosis was associated with executive function, logical, visual or semantic memory.

The associations observed in this population were small. Lower verbal learning performance per 0.1 mm CIMT corresponds to approximately 7% of an SD in the factor score, which is still well within the range of what is considered clinically “normal”(Norman et al., 2000). The difference in verbal learning performance (nearly 30% of a SD lower) was more pronounced comparing individuals with CIMT in the highest quartile to the lowest. Stratified analyses suggest that the association between subclinical atherosclerosis and cognition may differ by gender, with an association between increasing CIMT and lower verbal learning apparent for men but not for women. This observation could be explained by the possibility that a threshold in the level of CIMT exists which must be reached for cognition associations to be observed, and that this threshold was reached in men but not women in the study population. This possibility is supported by the fact that mean CIMT was greater for male than female subjects.

While list-learning and recall, and story-learning and recall are both measures of verbal memory and a reasonable assumption would be that these two tests would be represented by a common factor, these tests loaded on different factors. However, no neuropsychological task measures only a single cognitive process, and cognitive skills involved in list-learning are not identical to skills in story-learning, which places a greater emphasis on thematic (conceptual) organization. Thus, the loading of these tests on two separate factors is not surprising.

Given the number of statistical tests performed, we cannot rule out the possibility that the association detected between increasing CIMT and lower verbal learning was due to chance. However, by employing a principal components analysis to derive uncorrelated cognitive factors, we minimized multiple statistically significant findings due to correlated outcomes. Furthermore, we adjusted the α level in our hypotheses testing of main effects to be more conservative. Finally, as our objectives were to address questions about different stages of subclinical atherosclerosis and different areas of cognition, multiple analyses were necessary.

Atherosclerosis could be acting through one or more possible mechanisms to exert an effect on cognitive function. Endothelial dysfunction represents the earliest stage of atherosclerosis(Libby, 2001). Endothelial cells make up one component of the blood-brain barrier (BBB), which functions to maintain a constant intracerebral milieu critical for proper brain function(Hof et al., 1999). By disrupting the function of endothelial cells, atherosclerosis could theoretically increase permeability of the BBB(McCarron et al., 2006, Skoog et al., 1998). Breaches to this barrier could allow neurotoxins and other substances from which the brain is normally protected into the cerebral environment. Over time, the cumulative effect of these substances within the brain could result in detectable losses of cognitive abilities.

The diminished delivery of oxygen resulting from reductions in blood flow is another possible mechanism by which atherosclerosis may affect cognition. One study (Ruitenberg et al., 2005) showed that greater cerebral blood flow velocity was related to a lower prevalence of cognitive decline, suggesting that cerebral hypoperfusion may precede and contribute to the onset of cognitive dysfunction and dementia. It is possible that deficits in certain cognitive domains, such as verbal learning, may be explained by their association with areas of the brain that are more vulnerable to the effects of cerebral hypoxemia resulting from vascular disease. Areas of the brain irrigated by long penetrating arteries such as the hippocampus are less able to tolerate the effects of hypoperfusion(Roman, 2004). An fMRI study of CVLT performance (the test with high factor loadings on the verbal learning factor) showed that an area of the brain most active during tasks associated with this test was the hippocampus(Johnson et al., 2001). Thus, in populations that are cognitively normal,

small decreases in oxygen supply to the brain associated with subclinical atherosclerosis may explain some of the differences in cognitive performance in middle age, and the cumulative effect of small decrements over time may contribute to observable declines in cognitive function.

A third possibility is that CIMT may be a surrogate measure for intracranial atherosclerosis and its resultant localized pathology of infarction or ischemia due to blockage or deterioration of cerebral arterioles(Chui et al., 2000). This is consistent with the fact that CIMT predicts stroke risk(Bots et al., 2007), and would suggest that individuals with greater carotid atherosclerosis may also have more cerebral atherosclerosis, which individually leads to declines in cognition.

Other population-based studies that used CIMT as a measure of atherosclerosis reported associations between atherosclerosis and cognitive function. In the ARIC study (adults aged 45–64 years), CIMT was cross-sectionally correlated with psychomotor performance in men and women, and with verbal learning in women after adjustment for basic demographic factors(Cerhan et al., 1998), but not longitudinally after 6 years(Knopman et al., 2001). In contrast, we found evidence of an association between CIMT and decreased verbal learning in men but not in women.

In a study of 400 Dutch middle-aged and elderly men aged 40–80 years(Muller et al., 2007), increased CIMT was significantly associated with lower memory (combined verbal and visual). Investigators in that study used the Rey verbal learning test to assess verbal memory, and the Doors test to assess visual memory. Our observed association between lower verbal learning and increasing CIMT among men is partly in line with these findings, although visual memory was not associated with CIMT in our sample.

A limitation of this cross-sectional study is the inability to address directionality of associations. We controlled for a number of factors including education and income that could be associated with both cognitive function and subclinical atherosclerosis in order to minimize their contribution to the observed associations. While we cannot rule out the possibility that a third factor not considered could be responsible for the detected associations, the fact that the association was specific to the verbal learning area of cognition makes this scenario less believable. Strengths of this study include the battery of neuropsychological tests that allowed an examination of a broad range of cognitive abilities, as well as highly reliable and well-validated measures of subclinical atherosclerosis. This study is limited by small numbers of elderly adults >80 years old and women aged 40–49 years given the selection criteria for postmenopausal women. Therefore, the findings of the study may not be generalizable to elderly adults and to premenopausal women. In addition, given that BVAIT selected healthy subjects with Hcy ≥8.5 μmol/L, results may not be generalizable to populations with lower Hcy. Previous research has shown that elevated Hcy is associated with atherosclerosis(Boushey et al., 1995, Refsum et al., 1998) as well as with deficits in cognitive performance, cognitive decline and dementia(Robbins et al., 2005a). It is therefore possible that given study selection criteria, we may have been more likely to detect an association, if one existed, between subclinical atherosclerosis and lower cognitive function. It is important to note, however, that mean Hcy levels in the study population (10.3 μmol/L) are still within what is considered the normal range(Malinow et al., 1999). Finally, selection criteria for our study excluding individuals with a history of CVD and diabetes may limit the generalizability of our findings. These selection criteria may have also limited our ability to detect an association between subclinical atherosclerosis and lower cognitive function if it is the combination of atherosclerosis across a spectrum of CVD risk factors that is important to detect an effect on cognition function.

In summary, our findings suggest that in a population of otherwise healthy middle-to-older aged hyperhomocysteinemic adults without clinically evident CVD, 1) CIMT but not CAC or AAC, is associated with lower verbal learning abilities but not other areas of cognitive function through mechanisms independent of standard CVD risk factors assessed in this study; 2) this association may pertain only to men perhaps because they met a threshold level of CIMT necessary for an association with cognition to be observed. An implication of this study is that interventions aimed at reducing the risk of atherosclerosis may have an added benefit of preventing future decrements in cognitive function. Additional studies are needed to further elucidate the relationship between subclinical atherosclerosis and cognitive function among healthy adults without clinically evident CVD.

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Table 1

Baseline Characteristics for BVAIT Subjects with Cognitive Testing (n=504)

Variable	Mean ± SD or Number (%)
Age (years)	60.8 ± 9.9
40–49	71 (14.1%)
50–59	147 (29.2%)
60–69	182 (36.1%)
70–79	95 (18.9%)
80+	9 (1.8%)
Gender	
Male	308 (61.1%)
Female	196 (38.9%)
Race/Ethnicity	
Non-Hispanic White	326 (64.7%)
Non-Hispanic Black	75 (14.9%)
Hispanic	55 (10.9%)
Asian/Pacific Island/Native American	48 (9.5%)
Educational Level	
High school or less	60 (11.9%)
Some college	145 (28.8%)
Bachelor's degree	131 (26.0%)
Graduate/professional degree	168 (33.3%)
Current/Former Smoker	191 (38.0%)
Body-Mass Index (kg/m^2)	28.1 ± 5.0
Blood Pressure (mmHg)	
Systolic	129.6 ± 16.9
Diastolic	80.8 ± 10.4
Current use of anti-hypertensives	115 (22.8%)
Total Cholesterol (mg/dL)	221.2 ± 39.4
LDL Cholesterol (mg/dL)	138.5 ± 36.4
HDL Cholesterol (mg/dL)	56.8 ± 15.2
Triglycerides (mg/dL)	134.4 ± 132.0
Current use of statins	155 (30.8%)
Glucose (mg/dL)	100.0 ± 11.9
Homocysteine (nmol/mL)	10.3 ± 3.0
CIMT (mm)	0.75 ± 0.15
Aortic Calcium, present*	347 (70.0%)
Coronary Calcium, present	222 (44.1%)
CES-D score	6.3 ±6.7

Variable	Mean ± SD or Number (%)
Depression (CES-D >16)	37 (7.3%)

* n=497

† n=500

Table 2

Associations between Cognitive Factor Scores and Subclinical Atherosclerosis Measures from Multivariable Linear Regression Models* for 504 BVAIT Subjects

	Cognitive Factor β(SE), p-value†											
Subclinical Atherosclerosis Measure	***Executive Function***		***Verbal Learning***		***Logical Memory***		***Visual Memory***		***Semantic Memory***		***Global Cognition***	
Mean CIMT (per 0.1 mm)	0.02 (0.03)	0.44	−0.07 (0.03)	0.01	− 0.01 (0.03)	0.81	0.03 (0.03)	0.38	− 0.04(0.03)	0.15	−0.02(0.03)	0.44
Composite score‡ 3 vs. 0–2	−0.07(0.12)	0.57	0.01 (0.13)	0.94	−0.17 (0.14)	0.22	−0.05 (0.14)	0.71	−0.16 (0.13)	0.22	−0.19 (0.11)	0.09

*Adjusted for age, gender, race/ethnicity, education, income, CES-D score, Hcy, SBP, LDL-C, smoking status

†p-value for comparison of one category to reference category

‡n=498, composite score dichotomized at 3 versus 0, 1 and 2

Table 3

Associations between Subclinical Atherosclerosis and Cognitive Performance from Gender Stratified Multivariable Linear Regression Models

Subclinical Atherosclerosis	**Verbal Learning factor**		
Measure	**β [SE(β)], p-value**		
Gender			
	Male (n=308)	**Female (n=196)**	***p(interaction)***
Mean CIMT (per 0.1 mm)	−0.10 (0.03), 0.004	0.04 (0.07), 0.56	0.02
CIMT ≥0.83 mm vs. <0.83 mm	−0.31 (0.13), 0.016	0.19 (0.17), 0.26	0.006

Appendix 1

Baseline Cognitive Test Scores for BVAIT Participants (n=504) by Age Group and Gender

Cognitive Test	Age Group and Gender (Mean ± SD)									
	40–49 (n=71)		50–59 (n=147)		60–69 (n=182)		70–79 (n=95)		80+ (n=9)	
	men (n= 64)	women (n=7)	men (n=87)	women (n=60)	men (n=97)	women (n=85)	men (n=55)	women (n=40)	men (n=5)	women (n=4)
AMNART	32.6 (7.9)	29.1 (8.6)	30.9 (8.8)	31.7 (8.7)	31.1 (8.8)	31.6 (8.3)	32.6 (7.8)	30.0 (8.1)	26.8 (11.3)	26.8 (13.7)
Symbol Digit	58.1 (8.7)	60.7 (8.1)	53.6 (9.0)	55.4 (8.3)	49.6 (8.5)	50.5 (9.2)	46.8 (8.4)	46.8 (8.4)	42.4 (4.0)	29.5 (12.9)
Paragraph Recall - IR†	4.9 (1.0)	4.7 (1.1)	4.7 (1.1)	4.7 (1.2)	4.5 (1.3)	4.4 (1.4)	4.2 (1.2)	4.2 (1.2)	4.6 (0.5)	4.8 (1.3)
Paragraph Recall - DR†	4.9 (0.9)	4.4 (1.3)	4.6 (1.1)	4.7 (1.1)	4.3 (1.3)	4.3 (1.3)	4.3 (1.1)	4.3 (1.1)	3.8 (1.3)	4.3 (1.3)
Faces1 - IR†	34.9 (4.2)	36.3 (4.0)	34.6 (4.3)	35.3 (4.3)	33.3 (4.5)	34.5 (4.3)	31.3 (4.7)	31.3 (4.7)	32.2 (3.6)	31.5 (3.7)
Faces2 - DR†	37.1 (4.5)	38.6 (3.9)	36.6 (4.0)	36.9 (4.5)	35.5 (4.6)	36.7 (4.2)	33.8 (4.6)	33.8 (4.6)	29.4 (3.0)	29.0 (7.0)
California Verbal Learning Test - IR†	27.5 (5.2)	28.6 (3.5)	24.7 (5.3)	26.6 (6.2)	24.4 (6.2)	27.0 (5.6)	19.5 (5.7)	19.5 (5.7)	18.6 (5.2)	22.0 (3.6)
California Verbal Learning Test - DR†	9.0 (3.1)	10.9 (1.7)	7.7 (3.0)	9.0 (3.3)	7.5 (3.3)	8.7 (3.1)	5.7 (2.6)	5.7 (2.6)	3.4 (2.5)	7.5 (2.6)
Letter-Number Sequencing	10.4 (2.4)	11.0 (3.2)	10.3 (2.4)	10.0 (2.1)	9.3 (2.3)	9.2 (2.4)	8.9 (2.3)	8.9 (2.3)	8.6 (1.5)	7.0 (2.3)
Judgment of Line Orientation	24.5 (5.1)	20.9 (5.3)	25.1 (4.4)	23.3 (5.4)	23.6 (5.5)	21.4 (6.1)	25.3 (3.8)	25.3 (3.8)	22.4 (6.5)	17.0 (8.0)
Boston Naming Test	27.6 (2.2)	27.1 (2.7)	27.8 (2.3)	27.5 (2.0)	26.8 (2.6)	26.7 (2.2)	26.9 (2.6)	26.9 (2.6)	28.0 (2.9)	23.8 (5.1)
Trail Making, Part B	65.0(23.4)	53.1(13.6)	80.4(37.4)	71.1(24.3)	90.0(44.4)	87.6(48.7)	93.1(42.2)	93.1(42.2)	100.2(24.0)	134.3(33.8)
Block Design [Scaled Score]	33.4 (9.8) [11.8(2.7)]	33.4 (7.2) [11.9(2.0)]	30.1 (9.9) [11.8(3.1)]	30.3 (9.3) [12.1(2.9)]	27.8(10.1) [12.8(3.2)]	25.0 (9.1) [11.1(2.8)]	29.5 (9.4) [14.0(3.1)]	29.5 (9.4) [11.7(2.5)]	27.2 (8.6) [13.8(3.0)]	14.3 (11.6) [10.0(3.7)]
Animal Naming	32.6(11.3)	24.7 (7.8)	32.3 (9.3)	30.3 (9.2)	28.8 (9.5)	29.9(10.1)	28.0 (9.3)	25.5(10.2)	22.0 (7.3)	26.0 (7.2)
Shipley Institute of Living Abstraction Scale, PtII	15.8 (3.0)	15.0 (3.5)	14.7 (3.7)	14.3 (3.3)	13.5 (4.3)	13.1 (4.5)	12.7 (3.8)	12.7 (3.8)	11.8 (5.5)	9.3 (4.5)

†IR: Immediate Recall, DR: Delayed Recall