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Association of Vascular Health and Neurocognitive Performance in Overweight Adults with High Blood Pressure

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Abstract

To examine the relationship between vascular health, including flow-mediated dilation (FMD), intima medial thickness (IMT), and neurocognitive performance in a sample of 124 sedentary, middle-aged adults with high blood pressure (SBP 130–159 mmHg or DBP 85–99 mmHg) who were overweight or obese (body mass index 25.0 – 39.99 kgs/m^2). Patients completed a neuropsychological test battery including measures of Executive Function and Psychomotor Speed, along with measures of IMT and FMD. Hierarchical multiple regression analyses were used to investigate the association between vascular measures and neurocognitive performance after controlling for demographic factors and cerebrovascular risk factors. Higher levels of FMD predicted better Executive Function (b = 0.90, P = .045). Greater IMT tended to be associated with slower Psychomotor Speed (b = −0.82, P = .084), with the effect attenuated after controlling for FMD. Impaired FMD is associated with worse neurocognitive functioning among overweight adults with high blood pressure.

Introduction

Cerebrovascular disease is a major source of disability in the United States {Duron, 2008 6661 /id} and is associated with an increased risk of stroke {Lorenz, 2007 6697 /id}. It is well-known that the presence of cerebrovascular risk factors (CVRF), such as hypertension, hypercholesterolemia, diabetes, and tobacco use, are associated with microvascular ischemic brain changes {Jeerakathil, 2004 11 /id}, and previous evidence has shown that the presence of carotid plaque, atherosclerosis in the Circle of Willis, and intracranial stenosis are associated with similar brain changes {Uehara, 1999 45 /id}. Additionally, increasing evidence indicates that subtle vascular disease detected by peripheral measures may be associated with important changes in brain vasculature prior to any clinical event (e.g., stroke) and that the underlying relationship between vascular health and cerebrovascular damage may be continuous {Smith, 2007 6698 /id}.

Recent studies have shown that subclinical vascular disease is associated with poorer neurocognitive functioning on tests of frontal-subcortical function (i.e., executive function) {Cohen, 2009 6699 /id} as well as greater white matter hyperintensity burden {Hoth, 2007 20 /id}. We have previously reported that the relationship between CVRF, intima medial thickness (IMT), and neurocognitive functioning may be mediated by endothelial dysfunction, determined by impaired flow-mediation dilation (FMD) of the brachial artery, among adults with major depressive disorder {Smith, 2007 6698 /id}. However, the

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relationship of FMD, IMT, and neurocognition has not been examined among individuals with high blood pressure, a group at significantly elevated risk for neurocognitive dysfunction. We therefore examined these relationships among 124 overweight or obese adults with high blood pressure participating in the **E**xercise and **N**utrition interventions for **C**ardi**O**vascula**R** h**E**alth (ENCORE) study, the primary cardiovascular results {Blumenthal, 2010 6665 /id} and resulting neurocognitive changes recently have been reported {Smith, 2010 6737 /id}. Participants in the current study represent a subset of individuals who were enrolled in ENCORE and who had complete neurocognitive test data. The present sample was selected because individuals were overweight and had high blood pressure, both of which are known to be associated with vascular disease {Al, 2001 6739 /id;Vanhoutte, 1996 6740 /id} and neurocognitive dysfunction {Elias, 2003 37 /id;Wolf, 2007 6685 /id}.

Methods

As detailed elsewhere, the ENCORE study was designed to examine the effects of exercise and dietary modification on blood pressure and hemodynamic function {Blumenthal, 2010 6665 /id}. Inclusion criteria included blood pressure pre-hypertension or stage 1 hypertension (SBP 130–159 mmHg or DBP 85–99 mmHg), ≥ 35 years of age, BMI between 25.0 – 39.99 kgs/m^2, and sedentary lifestyle. Exclusion criteria included a history of cardiovascular disease or other significant medical co-morbidities that would limit the individual's ability to participate fully in the intervention and medications, including those for weight loss, hypertension, insulin, and certain psychotropic medications. Participants taking anti-depressants (N = 10) and/or psychostimulant medications (N =1) were included in our analyses, although results were unchanged when these participants were eliminated. Participants with a history of stroke, congestive heart failure, cardiovascular events (e.g. myocardial infarction), peripheral vascular disease, diabetes, and cancer diagnosis in the past two years were also excluded.

Neurocognitive Testing

Participants completed a neuropsychological test battery in order to assess performance in the domains of Executive Function and Psychomotor Speed. Neurocognitive tests were selected for the availability of multiple test versions, well-established psychometric properties, and accepted clinical utility. We selected a range of test instruments in order to provide a comprehensive assessment of Executive Function and Psychomotor Speed, which are multifaceted neurocognitive processes. Accordingly, our test battery included measures of information processing speed efficiency, sustained attention / vigilance, set-shifting ability, learning efficiency, and verbal fluency, which are all various facets of Executive Function and/or Psychomotor Speed.

Executive Function subtests included the Trail Making Test (B-A) {Reitan, 1979 391 /id}, the Stroop Test (Word, Color, and Color-Word sections) {Stroop, 1935 392 /id}, the Verbal Paired Associates test {Wechsler, 1987 22 /id}, the Controlled Oral Word Association Test (COWAT) {Wechsler D., 1956 395 /id}, the Digit Span test {Wechsler, 1987 22 /id}, and the Verbal Fluency Test (Animal Naming) {Lezak, 1995 398 /id}. Psychomotor Speed subtests included the Ruff 2 & 7 Test {Ruff R.M., 1992 23 /id}, and the Digit Symbol Substitution Test {Wechsler, 1997 6199 /id}. In addition, both the Stroop Test and the COWAT also loaded on our Psychomotor Speed variable. Details regarding the administration and scoring of these tests are provided elsewhere {Smith, 2010 6737 /id}.

Blood Pressure and Medical Screening Information

Clinic blood pressure (BP) was measured using a standardized cuff size, position, environment, and time of day. After five minutes of quiet rest, four seated BP readings were

obtained using a standard mercury sphygmomanometer and stethoscope, each two minutes apart for four screening sessions conducted over a 3–4 week period. Additional medical history information was obtained from a standard medical screening examination. Cerebrovascular risk was estimated using the Framingham Stroke Risk Profile (FSRP), which is a risk assessment tool used to assess the 10-year incidence of stroke {D'Agostino, 1994 2972 /id} and was determined at the time of a baseline physical examination. Risk factors used to assess stroke risk include SBP, diabetes mellitus, cigarette smoking, cardiovascular disease, and atrial fibrillation. Because age served as a covariate in our final analyses, it was not included in calculating FSRP scores. No participants reported a prior history of stroke. High-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol were measured enzymatically (LabCorp, Research Triangle Park, NC). HDL cholesterol was estimated by assay of the supernatant remaining after precipitation of serum LDL with dextran sulfate plus magnesium chloride. Participants fasted for 12 hours before this assessment.

Measures of Vascular Health

Carotid artery IMT was measured using a high-resolution B-mode ultrasound vascular imaging system (Acuson Aspen, Mountain View, CA) with a 10-Mhz linear array transducer. Ultrasound examinations of the far wall of the left and right common carotid arteries (CCAs) were used to acquire longitudinal images spanning 2 cm proximal to the carotid bulb. IMT of the far wall of the left and right CCAs was measured over a 1-cm segment using edge detection software (Carotid Analyzer 5.0.5, Medical Imaging Applications LLC, Iowa City, IA). Far wall measurements only were used as near wall measurements have been shown to have limited reliability.

Flow mediated dilation (FMD) and nitroglycerin mediated dilation (GTN-D) of the brachial artery were assessed in the morning, after overnight fasting. Longitudinal B-mode ultrasound images of the brachial artery, 4 to 6 cm proximal to the antecubital crease, were obtained using an ultrasound platform (Aspen, Mountain View, CA) with a 10-MHz linear array transducer. Images were obtained under the following conditions: a) after 10 minutes of supine relaxation; b) during reactive hyperemia, induced after inflation for 5 minutes to suprasystolic pressure (200 mm Hg) of a pneumatic occlusion cuff placed around the forearm; c) after an additional 10 minutes relaxation period in the supine position; and d) after the administration of 400 μg sublingual glyceryl trinitrate (GTN). End-diastolic images were stored to a magnetic-optical disk and arterial diameters were measured as the distance between the proximal and distal arterial wall intima media interfaces, using PC-based software (Brachial Analyzer Version 4.0, Medical Imaging Applications LLC, Iowa City, IA). Peak hyperemic flow was assessed by Doppler velocity measurement during the first 10 seconds post deflation of the occlusion cuff, and hyperemic flow response was defined as percent change in flow relative to resting baseline. Peak FMD response was assessed from 10 to 120 seconds post deflation of the cuff, with peak arterial diameter quantified using polynomial curve fitting. FMD was defined as the maximum percent change in arterial diameter relative to resting baseline. GTN-D was defined as peak percent change in arterial diameter assessed 3 to 5 minutes after the administration of GTN. FMD provides a putative measure of endothelial function {Celermajer, 1992 6738 /id}, whereas GTN-D is interpreted as measuring a more general vascular response.

Data Reduction and Analysis

To minimize the number of statistical tests in the present analysis, we used principle axis factor analysis to combine information from the 10 individual neuropsychological tests into three cognitive domain scores. A Scree test was used to determine the total number of factors retained for analysis. A minimum loading of 0.40 was required and Promax rotation

was used. We selected a Promax rotation, an oblique factor rotation method, in order to account for the interrelationships between our measures of executive function and processing speed. Based on these results, we created unit-weighted composite scores by standardizing the individual neuropsychological test scores and then summing all subtests relevant to a given domain. These composites were then used as the criterion variable in the regression models described below.

Separate hierarchical multiple regression analyses were conducted for each cognitive domain to determine if vascular functioning was associated with neuropsychological performance independently background characteristics and CVRF. For each model, a hierarchical approach was used in which variables were entered in blocks: 1) background characteristics (age and years of education and baseline arterial diameter (FMD analyses only)) and 2) CVRF (FSRP, lipids, and BMI). After these blocks were entered, we entered IMT, GTN, and FMD alone to examine the contribution of each variable in the presence of the first two blocks. As a final step, IMT and FMD were entered together in addition to the first two blocks. We also conducted two exploratory analyses, as requested by an anonymous reviewer. First, we examined which individual neuropsychological measures were most strongly associated with FMD after controlling for background characteristics, CVRF, and IMT. Second, we examined the pattern of findings when chronological age was entered in the last step of our hierarchical regression model.

Model assumptions of additivity, linearity, and distribution of residuals were evaluated and found to be adequate before analysis. Regression coefficients were scaled using the interquartile range of the predictor variable. This scaling allows the coefficient to be interpreted as comparing a “typical” person in the middle of the upper half of the predictor distribution with a “typical” person in the middle of the lower half of the predictor distribution.

Results

Sample

Participants were generally middle-aged, college-educated, hypertensive, and obese. Nearly two-thirds of the sample was female (64%) and 59% were Caucasian (Table 1). Framingham Stroke Risk Profile scores ranged from 2 to 16 (median = 5). Examination of vascular health indices showed that the vascular health in our sample was relatively lower than levels reported from other population-based studies {Stein, 2008 6742 /id}. Neurocognitive performance levels in our study were generally placed within the average range (i.e. 25^{th}–75^{th} percentile) when compared with age- and demographically-adjusted normative values {Heaton, 2004 6741 /id}.

Neurocognitive Function

Factor analytic results revealed two underlying neurocognitive factors, which we labeled Psychomotor Speed and Executive Function (Table 2). Psychomotor Speed included the Stroop Word, Color, and Color-Word sections, COWAT, Digit Symbol Substitution Test, and the Ruff 2 & 7 Test. The second factor, which we labeled Executive Function, included the Stoop Word and Color-Word sections, Trail Making Test B – A, Verbal Paired Associates, COWAT, Animals, and the Digit Span. Our Psychomotor Speed and Executive Function factors were strongly correlated ($r = .80$, $P < .001$).

Psychomotor Speed—Results from our hierarchical regression analyses of Psychomotor Speed show that both age and education level were significantly associated with Psychomotor Speed and these associations were only modestly attenuated with adjustment

for other cerebrovascular risk factors and vascular functioning (Table 3). Cerebrovascular risk factors were not associated with Psychomotor Speed when added to our model ($F(4,113) = 0.35$, $P = .842$); neither LDL-C ($b = -0.20$, $P = .609$), HDL-C ($b = -0.33$, $P = .487$), FSRP ($b = 0.29$, $P = .388$), nor BMI ($b = -0.25$, $P = .666$) were associated with Psychomotor Speed. We noted a trend for IMT to be associated with Psychomotor Speed when added after cerebrovascular risk factors ($F(1,97) = 2.96$, $b = -0.82$, $P = .084$), with higher levels of IMT tending to predict poorer Psychomotor Speed performance. However, FMD failed to predict better Psychomotor Speed performance ($F(1,93) = 2.39$, $b = 0.72$, $P = .126$), even after controlling for IMT in the final model step ($F(1,86) = 1.28$, $b = 0.54$, $P = .261$). Similarly, IMT was no longer a significant predictor of Psychomotor Speed once FMD was included in our final model step ($b = -0.78$, $P = .127$).

In exploratory analyses, we found that the Stroop Word ($b = 0.25$, $P = .014$) and Stroop Color-Word ($b = 0.19$, $P = .058$) tests were the most strongly related to FMD, whereas the COWAT ($b = 0.10$, $P = .328$), Stroop Color ($b = 0.01$, $P = .901$), Ruff 2 & 7 Test ($b = -0.05$, $P = .617$), and Digit Symbol Substitution Test ($b = 0.01$, $P = .903$) were not significantly associated with FMD. When age was entered in the last step of our hierarchical regression, we noted a significant relationship between measures of vascular health and Psychomotor Speed performance after controlling for education, Framingham index, LDL, and HDL cholesterols (IMT: $b = -1.45$, $P = .002$; FMD: $b = 1.30$, $P = .006$), which were attenuated after controlling for the effects of age.

Executive Function—Hierarchical regression analysis of Executive Function revealed that both age and education level were significantly associated with Executive Function performance and this association was only modestly attenuated after controlling for cerebrovascular risk factors and vascular health (Table 4). Cerebrovascular risk factors were not associated with Executive Function when added to our model ($F(4,114) = 1.32$, $P = .267$), and neither LDL-C ($b = -0.29$, $P = .466$), BMI ($b = -0.45$, $P = .457$), nor FSRP ($b = 0.47$, $P = .162$) were significant predictors, although higher levels of HDL-C tended to be associated with poorer Executive Function ($b = -0.83$, $P = .090$). IMT was not a significant predictor of Executive Function ($F(1,98) = 0.50$, $b = -0.33$, $P = .481$. Higher levels of FMD, however, were associated with better Executive Function performance ($F(1,94) = 3.94$, $b = 0.89$, $P = .050$), and this relationship was only partially attenuated after IMT was entered into the model again in the final step ($F(1,87) = 2.69$, $b = 0.75$, $P = .105$).

In exploratory analyses we found that the Trail Making Test B-A ($b = -0.20$, $P = .041$) was strongly related to FMD, in addition to the Stroop Word and Stroop Color-Word tests, as noted above. The Digit Span Test ($b = 0.14$, $P = .189$), Animal Naming ($b = 0.01$, $P = .918$), COWAT ($b = 0.10$, $P = .328$), and Verbal Paired Associates ($b = -0.11$, $P = .270$), were not significantly associated with FMD. When age was entered in the last step of our hierarchical regression model, we noted a significant relationship between measures of vascular health and Executive Function after controlling for education, Framingham index, LDL, and HDL cholesterols (IMT: $b = -0.85$, $P = .054$; FMD: $b = 1.32$, $P = .003$), which were attenuated after controlling for the effects of age.

Discussion

Results from the present analysis suggest that subclinical vascular dysfunction is associated with poorer neurocognitive performance among overweight adults with high blood pressure. Higher levels of FMD were associated with better executive functioning after controlling for demographic factors and CVRF. In addition, greater levels of carotid artery IMT tended to be related to poorer psychomotor speed.

The present study provides support for our previous findings that lower levels of FMD and higher levels of IMT are associated with poorer neurocognitive functioning after controlling for background factors and CVRF {Smith, 2007 6698 /id}. Higher levels of IMT have been shown to predict poorer neurocognitive functioning in numerous population-bases studies, including the Rotterdam {Slooter, 1998 3131 /id} and Atherosclerosis Risk in Communities studies {Cerhan, 1998 1441 /id}, among others {Komulainen, 2007 2030 /id}. IMT appears to be most strongly associated with tests of psychomotor speed, processing efficiency, and executive function {Auperin, 1996 2044 /id;Haley, 2007 2040 /id;Cohen, 2009 6699 /id}, although general measures of orientation {Kaplan, 1996 2045 /id} and memory {Muller, 2007 269 /id} also may be related to IMT. In addition, higher IMT has been associated with both structural white matter changes {de Leeuw, 2000 2493 /id} and functional brain changes during tasks of frontal-lobe functioning among patients with cardiovascular disease {Haley, 2007 6700 /id}. The association between IMT and neurocognitive function in our study was relatively weaker than that observed in previous studies {Komulainen, 2007 2030 /id;Hoth, 2007 20 /id} most likely due to differences in enrollment criteria; previous studies have examined the association between IMT and neurocognition among older adults with cardiovascular disease and higher levels of IMT, whereas our study was conducted among relatively younger individuals and excluded those with a history of cardiovascular events. In addition, our study sample included a substantial number of African-Americans (41%) and women (64%) relative to previous studies, which may also have influenced the pattern of our findings.

Relative to the substantial literature on IMT, endothelial dysfunction and neurocognitive performance have been less well studied. We have previously reported that impaired endothelial function is associated with poorer neurocognitive performance among middle-aged adults with major depressive disorder and that the endothelial function and neurocognition relationship appeared to mediate the observed relationships between CVRF, IMT, and neurocognitive performance {Smith, 2007 6698 /id}. In addition, endothelial dysfunction has been shown to differentiate individuals with Alzheimer's disease (AD) from healthy controls {Dede, 2007 3113 /id}, and a graded relationship has been observed between the progression of AD pathology and FMD. Recent studies have also shown that FMD from the brachial artery is associated with white matter disease burden {Hoth, 2007 20 /id}, particularly in periventricular brain regions {de Leeuw, 2002 2136 /id}. In the present analysis we found that higher levels of FMD were associated with better executive functioning, suggesting that better endothelial function is associated with improved executive abilities. However, we did not observe an association between GTN-D, which measures a more general vascular response, and neurocognitive performance, suggesting that the relationship observed between FMD and executive functioning may be specific to the vascular endothelium. These findings suggest that the association between vascular health and neurocognitive performance may depend on endothelium-derived nitric oxide release and not solely on vascular smooth muscle function.

Neurocognitive deficits are common among individuals with high blood pressure {Robbins, 2005 284 /id;Elias, 2003 37 /id}, which is associated with an increased risk of stroke and AD {Birkenhager, 2001 2532 /id}. In addition, the deleterious effects of high blood pressure on neurocognition appear to be particularly strong among individuals with central obesity {Waldstein, 2006 6687 /id;Elias, 2003 37 /id}. Recent evidence suggests that among middle-aged adults only those with both hypertension and obesity exhibit neurocognitive dysfunction, while neither hypertension nor obesity are independent predictors {Wolf, 2007 6685 /id}. In the present study, our findings were unchanged when analyses were restricted to those individuals with clinically-defined levels of hypertension (data not shown). Although this study may be the first to examine the relationship between neurocognitive functioning and vascular health among individuals with high blood pressure, elevated blood

pressure is a well-known risk factor for increasing levels of IMT {Zanchetti, 1998 6735 /id} and endothelial dysfunction {Taddei, 2000 90 /id} and both are associated with incident cardiovascular events in this population {Gokce, 2003 9 /id;Lorenz, 2007 6697 /id;Lorenz, 2006 6736 /id}. In addition, high blood pressure has been shown to predict greater burden of white matter disease {de Leeuw, 2002 2489 /id}, cerebral infarctions {Uehara, 1999 45 /id}, gray matter volume loss {Gianaros, 2006 6505 /id}, and poorer regional perfusion {Beason-Held, 2007 6528 /id}.

The present study has several limitations. First, the ENCORE inclusion criteria precluded older individuals with neurocognitive dysfunction from participating and it is therefore unclear if the same pattern of findings would have been observed in a sample of older and more cognitively disabled adults. Second, our neurocognitive test battery was designed primarily to assess executive functions and the majority of measures had significant speed requirements. It is therefore unclear to what extent endothelial dysfunction and vascular health might be associated with memory or tasks of executive function without speed components. Finally, because our study was cross-sectional we are unable to examine how the present pattern of findings might change over extended follow-up periods.

In summary, higher levels of IMT and lower FMD were associated with poorer neurocognitive function among overweight and obese adults with high blood pressure. Notably, these relationships were observed above and beyond the influence of background characteristics and CVRF. Future studies should examine the longitudinal relationship between endothelial dysfunction and neurocognition among older adults to assess the role of declining FMD in predicting neurocognitive decline. In addition, additional intervention trials are needed to determine whether improving endothelial function and vascular health might result in better neurocognitive performance.

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Abbreviations

BMI	body mass index
COWAT	controlled oral word association test
CVRF	cerebrovascular risk factors
DBP	diastolic blood pressure
FMD	flow mediated dilation
FSRP	Framingham Stroke Risk Profile
GTN-D	nitroglycerin mediated dilation
HDL	high density lipoprotein
IMT	intima medial thickness
KGS	kilograms
SBP	systolic blood pressure
VPA	verbal paired associates

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Table 1

Background characteristics of sample. Data are given as mean (SD) unless otherwise indicated. SBP indicates systolic blood pressure; DBP indicates diastolic blood pressure; FSRP = Framingham Stroke Risk Profile; IMT = intima medial thickness; mm Hg indicates millimeters of mercury; KGS indicates kilograms.

Variable	Mean (SD)	Range
Age, y	52.3 (9.6)	36 – 77
Males, n (%)	45 (36)	N/A
Whites, n (%)	68 (59)	N/A
Years of education	15.3 (2.6)	8 – 20
College Degree, n (%)	68 (55)	N/A
IMT, mm	0.70 (0.14)	0.46 – 1.25
Non-Endothelial Dependent Arterial Diameter	17.3 (7.2)	3.7 – 40.6
Flow Mediated Dilation	2.6 (3.6)	−3.8 — 17.4
Framingham Stroke Risk Profile	6.0 (2.8)	2 – 16
Current Smoker, n (%)	11 (8.9)	N/A
Clinic SBP, mm Hg	138.3 (8.4)	122 – 162
Clinic DBP, mm Hg	86.1 (6.5)	69 – 100
Hypertensive*, n (%)	55 (44.4)	N/A
High Density Lipoprotein	53.8 (14.4)	26 – 108
Low Density Lipoprotein	125.1 (35.6)	66 – 285
Weight, kgs	93.5 (14.3)	67 – 130
BMI, kgs / m2	32.8 (3.8)	25.6 – 39.9
Trail Making Test B-A, seconds	42.7 (33.2)	−29 — 176
Stroop Word	96.8 (14.3)	49 – 134
Stroop Color	69.7 (12.6)	39 – 103
Stroop Color/Word	38.5 (9.9)	13–63
Verbal Paired Associates	17.2 (3.9)	5 – 24
COWAT	38.3 (11.2)	7 – 64
Animals	21.2 (5.4)	7 – 38
Ruff 2 & 7 Test	236.9 (50.2)	101 – 423
Digit Symbol Substitution Test	57.4 (10.9)	30 – 80
Digit Span	15.1 (3.6)	8 – 24

*Hypertensive defined as either SBP > 140 or DBP > 90.

Table 2

Neurocognitive factor analytic results. Results revealed two underlying factors, which we have labeled Psychomotor Speed and Executive Function.

Test	Psychomotor Speed	Executive Function
Stroop Word	**71**	**44**
Stroop Color	**83**	38
Stroop Color-Word	**67**	**54**
Trail Making Test B-A	−25	**−60**
VPA	19	**53**
COWAT	**42**	**49**
Animals	5	**65**
Digit Span	29	**67**
Digit Symbol Substitution Test	**76**	13
Ruff 2 & 7 Test	**71**	10

Table 3

Results from regression analyses of Psychomotor Speed, cerebrovascular risk factors (CVRF), and vascular health. The values presented are regression coefficients standardized using the interquartile range. Step 1 = background characteristics; step 2 = background characteristics and CVRF; step 3 = background characteristics, CVRF, and intima medial thickness; step 4 = background characteristics, CVRF, and nitroglycerine-mediated dilation; step 5 = background characteristics, CVRF, and flow-mediated dilation; step 6 = background characteristics, CVRF, intima medial thickness, and flow-mediated dilation.

Set	Variable	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
Background Characteristics	Age	−2.50**	−2.55**	−2.16**	−2.76**	−2.27**	−2.02**
	Education	1.97**	2.06**	2.43**	2.21**	2.26**	2.42**
Cerebrovascular Risk Factors	Framingham Stroke Risk Profile		.29	.45	.22	.34	.55
	LDL		−.20	−.05	−.07	−.11	−.17
	HDL		−.33	−.41	−.24	−.11	−.26
	BMI		−.25	−.13	−.32	−.08	−.15
Vascular Health	Intima Medial Thickness			−.82†	----	----	−.78
	GTN-D				−.77	----	----
	FMD					.72	.54

** P < .01;

* P < .05;

† P < .10

Table 4

Results from regression analyses of Executive Function, cerebrovascular risk factors (CVRF), and vascular health. The values presented are regression coefficients standardized using the interquartile range. Step 1 = background characteristics; step 2 = background characteristics and CVRF; step 3 = background characteristics, CVRF, and intima medial thickness; step 4 = background characteristics, CVRF, and nitroglycerine-mediated dilation; step 5 = background characteristics, CVRF, and flow-mediated dilation; step 6 = background characteristics, CVRF, intima medial thickness, and flow-mediated dilation.

Set	Variable	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
Background Characteristics	Age	−2.00**	−2.11**	−1.89**	−2.15**	−1.70**	−1.84**
	Education	2.49**	2.65**	2.76**	2.94**	2.89**	2.60**
Cerebrovascular Risk Factors	Framingham Stroke Risk Profile		.47	.64†	.41	.45	.75*
	LDL		−.29	−.16	−.23	−.20	−.31
	HDL		−.83†	−.89†	−.84	−.66	−.71
	BMI		−.45	−.58	−.29	−.18	−.44
Vascular Health	Intimal Media Thickness			−.33	----	----	−.15
	GTN-D				.11	----	----
	FMD					.89*	.75

** P < .01;

* P < .05;

† P < .10