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Selective Impairment of Frontal-Executive Cognitive Function in African Americans with Cardiovascular Risk Factors

Kenneth G. Pugh, MD^{*,†,‡,§}, Dan K. Kiely, MA, MPH[†], William P. Milberg, PhD^{‡,||,¶}, and Lewis A. Lipsitz, MD^{*,†,‡}

*Beth Israel Deaconess Medical Center, Department of Medicine, Gerontology Division, Boston, Massachusetts [†]Hebrew Rehabilitation Center for Aged, Boston, Massachusetts [‡]Division on Aging, Harvard Medical School, Boston, Massachusetts [§]U.S. Navy, Naval School of Health Sciences, Bethesda, Maryland ^{||}Geriatric Neuropsychology Laboratory, Geriatric, Research, Education and Clinical Center (GRECC), Brockton/West Roxbury Department of Veterans Affairs Medical Center, Boston, Massachusetts [¶]Department of Psychiatry, Harvard Medical School, Boston, Massachusetts

Abstract

Objectives—To determine whether a summary cardiovascular risk score is associated with an increased risk of frontal-executive cognitive impairment.

Design—Cross-sectional study.

Setting—Subjects were recruited from senior centers, senior housing complexes, and communities in the Boston metropolitan area.

Participants—Forty-three predominantly female elderly African Americans.

Measurements—Cardiovascular risk factors were assessed during an interview and clinical examination. For each subject, the total number of cardiovascular (CV) risk factors was summed to compute a CV risk score. A battery of neuropsychological tests was administered that examined memory, visuospatial abilities, and frontal-executive functions. Cognitive test scores were transformed into domain-specific (memory, visuospatial, frontal-executive) composite *z* scores. Cognitive impairment for each composite *z* score was defined as performance less than the median for the study group. Multivariate logistic regression was used to examine the relationship between the CV risk score and the risk for cognitive impairment in the three cognitive domains of interest.

Results—After controlling for age and education, the CV risk score was associated only with frontal-executive cognitive impairment (odds ratio (OR) = 2.44, 95% confidence interval (CI) = 1.06–5.65). The CV risk score was not associated with the risk of memory (OR = 1.30, 95% CI =

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Address correspondence to Kenneth G. Pugh, MD, National Naval Medical Center, 8901 Wisconsin Ave, Bethesda, MD 20889. kgpugh@bethesda.med.navy.mil.

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0.64–2.67) or visuospatial impairment (OR = 1.49, 95% CI = 0.66–3.36). Greater CV risk scores were associated with an increased likelihood of having frontal-executive cognitive impairment.

Conclusion—CV risk factors may exert a specific deleterious effect on frontal-executive cognitive abilities as opposed to memory or visuospatial functions. Associated executive dysfunction may compromise the ability of patients with CV risk factors to comply with recommendations for risk reduction.

Keywords

African American; cardiovascular; memory; executive function

Cardiovascular (CV) risk factors are highly prevalent among in older African Americans.¹ Some CV risk factors, including hypertension and diabetes mellitus, are associated with an increased risk of cognitive decline.^{2,3} African Americans may be at greater risk for accelerated cognitive decline than Caucasians, and the adverse effects of CV risk factors on cognitive function may provide a partial explanation.⁴ Yet few studies have specifically sought to examine the influence of CV risk factors on cognitive function in African Americans, and results have been mixed.^{5,6} Improved understanding of the association between CV risk and cognitive function is crucial, because cognitive decline may occur early and more rapidly in patients with CV risk factors such as hypertension or diabetes mellitus.^{5,7}

In high-risk populations, it is important to understand how coexisting CV risk factors might affect cognitive function. Furthermore, whether CV risk factors affect all aspects of cognition equally remains uncertain. Recent studies suggest that cognitive abilities dependent upon the integrity of frontal-subcortical circuits,⁸ especially executive control functions, may be particularly vulnerable to an individual's CV risk status.⁹ If CV risk factors disproportionately affect executive control functions, popular cognitive screening instruments, which typically lack measures of executive control functions, may not adequately identify cognitive dysfunction in patients at high-risk of cardiovascular disease (CVD), including elderly African Americans.¹⁰ Therefore, the authors sought to determine whether nondemented elderly African Americans with risk factors for CVD might suffer from frontal-executive cognitive impairment and asked whether the degree of CV risk was associated with an increased risk of cognitive impairment.

Methods

Study Population

A cross-sectional study was conducted of elderly community-dwelling African Americans from the Boston metropolitan area. The investigators recruited subjects through local newspaper and radio advertisements or from presentations on stroke prevention at senior centers with a predominantly African-American population. During July 2000 to May 2001, 58 potential participants contacted the investigators and underwent a brief telephone interview. Potential participants were excluded if they reported use of psychotropic medications that might affect neuropsychological testing, prior stroke, Parkinson's disease, schizophrenia, major depression, past psychiatric illness requiring hospitalization, head

trauma that resulted in unconsciousness, or a previous diagnosis of dementia. After screening, five participants were excluded for the following reasons: three for use of psychotropic medications that included barbiturates or benzodiazepines, one for past head trauma, and one for treatment of major depression. After the interviews, 10 subjects were no longer interested or were not available for participation, leaving 43 participants for inclusion in this study. The institutional review board of the Hebrew Rehabilitation Center for Aged approved this study. Each subject provided informed consent.

Cardiovascular Measures

The primary objective was to examine the relationship between an overall measure of well-established CV risk factors that can easily be obtained in clinical practice and cognitive function. The presence of CV risk factors or established CVD was determined during a clinical interview with a board-certified geriatrician (KGP). Interviews were conducted at senior centers, the subject's home, or the research laboratory. Each person was asked whether a physician or healthcare provider had previously diagnosed him or her with hypertension, diabetes mellitus, congestive heart failure (CHF), coronary artery disease (CAD), myocardial infarction (MI), or peripheral vascular disease. Smoking status was coded as current versus never or past smoker. Height and weight were measured and body mass index (BMI) calculated (weight (kg)/height (m²)). Subjects were classified as obese if their BMI was 30 kg/m² or higher. Supine blood pressure was measured with a mercury sphygmomanometer after 5 minutes of rest. After 2 additional minutes of rest, this was repeated and the average systolic and diastolic blood pressure calculated. Because self-report of hypertension may not correlate with measured blood pressure, and treated hypertensive patients often remain poorly controlled, the subjects were classified according to their current measurements. Therefore, subjects were classified as hypertensive if the average systolic blood pressure was 140 mmHg or greater or average diastolic blood pressure was 90 mmHg or greater, regardless of treatment status. Subjects receiving treatment for hypertension but who were well controlled (average blood pressure < 140/90 mmHg) were classified as normotensive. A 12-lead electrocardiogram (EKG) was obtained and examined for the presence of atrial fibrillation and left ventricular hypertrophy (LVH). LVH was assessed using sex-specific Cornell voltage criteria, which provide excellent sensitivity and specificity compared with other voltage criteria in African Americans.¹¹ To detect undiagnosed diabetes mellitus, a random (nonfasting) blood glucose was obtained using a portable glucometer (Precision QID, Abbott Laboratories, Abbott Park, IL). No subject was found to have unsuspected diabetes mellitus, defined by a glucose greater than 200 mg/dL. For each subject, a composite CV risk score was computed by summing the presence (score = 1) or absence (score = 0) of all the individual risk factors (diabetes mellitus, CHF, MI, CAD, current smoker, obese, hypertension, LVH). Because no person was found to have atrial fibrillation or reported peripheral vascular disease, these variables were not included in the CV risk score.

Neuropsychological Tests

The same investigator (KGP) administered a brief battery of neuropsychological tests to each subject under the guidance of a board-certified neuropsychologist (WPM). The primary

cognitive domains of interest included episodic memory, visuospatial abilities, and frontal-executive functions.

Memory Measures

Memory, including measures of verbal and visual memory, was evaluated using the Wechsler Memory Scale, Third Edition (WMS-III).¹² Verbal memory was assessed using the Logical Memory component of the WMS-III. In Logical Memory, subjects are read two short stories, each embedded with 25 unit items for recall. After each story, subjects were asked to immediately recall as many items as possible. After an approximately 25-minute delay, subjects were asked to recall as many of the original items as possible from both stories. Visual memory was assessed using the Visual Reproductions test from the WMS-III. In this test, subjects were shown five line drawings, one at a time, for a 10-second study period. After each study period, subjects were asked to reproduce each line drawing from immediate memory. After a 25-minute delay, they were asked to reproduce as many of the original drawings as possible from memory. Administration and scoring followed the WMS-III procedure manual.¹²

Visuospatial and Visuo-perceptual Measures

Visuospatial skills were assessed using the copy portion of the Visual Reproductions test in which subjects were asked to simply copy the line drawings with no imposed time limit. In the visuo-perceptual test, they had to correctly match a figure from five competing and similar figures. Administration and scoring followed the WMS-III procedure manual.¹²

Frontal-Executive Measures

Several neuropsychological tests of executive control functions were administered. Although not specific to any anatomical region, performance on such tests is considered to depend heavily upon the integrity of frontal-subcortical networks, which subserve executive control functions.⁸ The tests included parts A and B of the Trail Making Test, letter fluency, and category fluency and were administered according to standard instructions.¹³ In the letter fluency tests, subjects were asked to name as many items as possible starting with the individual letters F, A, and S in 1 minute. In category fluency, subjects were asked to name as many animals as possible in 1 minute. The score consisted of all unique items named in 1 minute. Letter-number sequencing, was included as a measure of working memory.¹² Subjects were required to listen to an auditory presentation of alternating numbers and letters and then repeat back the numbers in ascending order, followed by the letters alphabetically. For example, 5-J-3-C-8 would be correctly reported as 3-5-8-C-J. Together these tests assess a range of cognitive abilities associated with frontal-executive control, including sustained attention, working memory, set shifting, mental flexibility, effective retrieval, and perseverance.^{12,13}

Cognitive Impairment

Three cognitive-domain-specific composite scores (memory, visuospatial and frontal-executive function) were developed for each subject by transforming the individual raw test scores within each cognitive domain into *z* scores and summing the *z* scores. The three

composite z score distributions were examined and subjects were considered impaired in the specific cognitive domain if their composite z score fell below the median for the study group.

Covariates

Information regarding education, alcohol consumption, and self-perceived health status was obtained during the interviews. Subjects were asked to rate their health as excellent, good, fair, or poor and to compare their health with others their age and rate their health as better, about the same, or worse. A short version of the Center for Epidemiologic Studies—Depression Scale (CES-D), previously shown to correlate with the longer version, was used to detect the presence of depression.¹⁴

Statistical Analysis

Descriptive statistics were calculated for each independent variable and covariate. Mean scores and standard deviations were determined for each component of the cognitive battery and for covariates. The associations between the CV risk score and domain specific cognitive impairment (memory, visuospatial, and frontal-executive function) were assessed using bivariate logistic regression. Multi-variate logistic regression was used to examine the association between the CV risk score and domain-specific cognitive impairment while controlling for the influence of several covariates. Results are reported as odds ratios (ORs) and 95% confidence intervals (CIs). All data manipulation and analyses were performed using SAS for Windows, Version 8.2 (SAS Institute Inc., Cary, NC).

Results

Information on the subjects' demographic characteristics and cognitive test scores are displayed in Table 1. All subjects were community-dwelling African Americans whose mean age $\pm$ standard deviation was 71.8 $\pm$ 5.7. Most described their health as excellent or good (72%). The majority (84%) were women. The mean score on an instrumental activity of daily living (IADL)¹⁵ scale was 2.6 $\pm$ 0.17, indicating that most were completely independent in 10 essential IADLs. The prevalence of preexisting CVD was surprisingly low. Only one person reported a history of MI or CHF, yet many subjects had identifiable CV risk factors. Fifty-eight percent reported a diagnosis of hypertension and all but one person who reported being diagnosed with hypertension were receiving treatment. The average systolic and diastolic blood pressures of the group were 148.7 $\pm$ 21.3 mmHg and 83.2 $\pm$ 9.1 mmHg, respectively. By direct measurement of blood pressure, the investigators classified 63% as hypertensive. EKGs revealed LVH in 40% of the subjects. The mean BMI (30.7 $\pm$ 6.4 kg/m²) confirmed that obesity was a frequent (40%) risk factor. Twelve percent reported a prior diagnosis of diabetes mellitus. Three persons (7.0%) were current smokers. The mean number of CV risk factors for each subject was 1.70 and ranged from 0 to 4.

A low prevalence of alcohol abuse and depression, which may confound cognitive performance, was found. Most (56%) reported no alcohol use, and more than 90% reported using alcohol fewer than 2 days per week. The mean score on the short CES-D was 1.93; a score of 4 or greater provides excellent sensitivity and specificity for the clinical diagnosis

of depression.¹⁴ Performance on verbal and visual memory tests (Table 1) demonstrated that the percentage of material retained over a 25-minute delay, as a proportion of material initially learned (savings score), was excellent. The average savings score was 88% for verbal memory and 72% for visual memory.

The bivariate logistic regression (Table 2) demonstrated a significant relationship between the CV risk score and the likelihood of frontal-executive cognitive impairment (OR = 2.66, 95% CI = 1.22–5.82). Total CV risk scores had no effect on the risk of memory (OR = 1.57, 95% CI = 0.81–3.03) or visuospatial impairment (OR = 1.90, 95% CI = 0.94–3.86). Controlling for age and education, the relationship between CV risk score and frontal-executive impairment was only slightly attenuated (OR = 2.44, 95% CI = 1.06–5.65) and remained the only cognitive domain associated with the CV risk score (Table 2). Including the CES-D scores in the multivariate model did not significantly change the results (data not presented). Subjects with greater CV risk scores were substantially more likely to have frontal-executive cognitive impairment (Figure 1).

Discussion

The results of this study suggest that, in elderly community-dwelling African Americans, CV risk factors exert a specific deleterious effect on frontal-executive cognitive abilities but not on episodic memory or visuospatial function. Furthermore, the total burden of CV risk correlates with the risk for poor frontal-executive performance.

Although the study was cross-sectional, these findings are consistent with two recent longitudinal studies that demonstrated a relationship between CV risk factors and an increased likelihood of frontal-executive dysfunction.^{5,7} In the Atherosclerosis Risk in Communities Study, 10,963 subjects aged 47 to 70 underwent cognitive testing and were followed for 6 years. Hypertension and diabetes mellitus were associated with significant decline in measures of frontal-subcortical function (Digit Symbol Substitution Test and word fluency) but not memory.⁵ In a second study of elderly women, subjects with diabetes mellitus were twice as likely to suffer severe cognitive decline, defined as the greatest 10th percentile decline, on tests of frontal-subcortical abilities (Digit Symbol Substitution Test and Trails B) but not general cognition or memory.⁷ Further evidence of a selective effect of CV risk on frontal-executive cognition comes from the Normative Aging Study, in which a measure of CV risk, the Framingham stroke risk score, accounted for significant decline on tests of executive function over 3 years but not memory or spatial abilities.¹⁶ The magnitude of the effect of CV risk on executive function rivaled that of age, a known confounder of executive function.¹⁶

Unfortunately, these studies included few African Americans or did not consider the effects of multiple CV risk factors on specific domains of cognitive function. Considerable evidence indicates that normal aging is most likely to result in changes in cognitive abilities dependent upon the prefrontal cortex and its subcortical connections.¹⁷ The data from the present study imply that age-acquired CV risk factors might be equally important. The effect of the CV risk score on frontal-executive cognition remained essentially unchanged after adjustment for age, education, and depression. Several studies suggest that hypertension is a

risk factor for cognitive decline.¹⁸ African Americans have not only a high prevalence of hypertension but also of obesity, diabetes mellitus, and smoking.¹ The cumulative burden of CV risk on frontal-executive functions is particularly relevant for high-risk groups and must be considered when examining normal age-related changes in cognitive abilities.

Most instruments used to assess cognitive function, such as the Mini-Mental State Examination, do not include frontal-executive measures and therefore might overlook cognitive impairment associated with CV risk factors.¹⁰ Moreover, frontal-executive cognitive abilities, including goal formulation, planning, and self-monitoring are precisely the cognitive skills required to reduce CV risk through dietary, lifestyle, and pharmacological measures. Instead of being recognized as having frontal-executive cognitive impairment, patients who fail to follow recommendations or achieve therapeutic goals may be labeled as noncompliant, stubborn, or unmotivated. Recognition of frontal-executive cognitive impairment is crucial, because these cognitive skills are an excellent predictor of an elderly persons' ability to maintain independence.¹⁹

Several limitations of this present study deserve comment. Some information on CV factors was gathered by self-report and may not be completely accurate. Because this study was cross-sectional, it cannot be determined whether the current level of cognitive function represented a change from previous levels. Because executive control functions represent the highest level of cognitive integration, brief neuropsychological batteries are unlikely to capture all aspects of executive control. Difficulty differentiating between executive and nonexecutive components of any given cognitive task further complicates measurement of executive control functions. Some subjects might have had early dementia, such as Alzheimer's disease (AD), that accounted for their poor performance. This seems unlikely, because savings scores for verbal and visual material were generally within normal limits and are a sensitive indicator of early AD.²⁰ The sample size and the low prevalence of certain CV risk factors did not provide the power to independently assess the association between individual CV risk factors and frontal-executive impairment, but the primary objective was to examine the relationship between a clinically relevant level of overall risk and individual cognitive domains. These subjects might not have been entirely representative of a population-based sample of elderly African Americans, limiting the generalizability of the results. This study might not have had the statistical power to detect an association between the CV risk score and memory or visuospatial impairment. Nevertheless, the magnitude of the effect measures suggests that, if a relationship exists, it is likely weaker than that for frontal-executive impairment.

Several mechanisms may underlie the association between CV risk factors and frontal-executive cognitive impairment. White matter lesions and silent lacunar infarctions, both strongly associated with CV risk factors, are likely to play a role, because these lesions tend to localize in frontal-subcortical regions that govern executive control functions.²¹ Small vessel cerebrovascular disease appears to preferentially affect prefrontal metabolism and the related cognitive domains of working memory and executive control of cognition.²² Epidemiological studies suggest that African Americans are at greater risk for small vessel cerebrovascular disease, including lacunar infarction and severe diffuse white matter lesions.^{23,24}

An important public health question is whether aggressive CV risk reduction can prevent cognitive decline or improve cognition. Preliminary evidence suggests that aerobic exercise,²⁵ aspirin,²⁶ lipid-lowering agents,²⁷ anti-hypertensive therapy,²⁸ and postmenopausal estrogen replacement²⁹ may help to preserve cognitive function. The beneficial effects are most prominent for measures of frontal-executive function, but caution is warranted before considering these therapies solely for cognitive benefits, as recently illustrated by a study that showed an increased risk of stroke associated with hormone replacement therapy.³⁰ Results from studies examining aggressive CV risk-factor reduction in elderly patients that include cognitive function as an outcome are eagerly awaited.³¹

In conclusion, this study found that a summary measure of CV risk was associated with an increased risk for poor cognitive performance on measures of frontal-executive cognitive function in otherwise highly functional African Americans. These findings have importance for identification and prevention of cognitive decline, particularly in high-risk populations. Associated executive dysfunction might compromise the ability of patients with CV risk factors to comply with recommendations for risk reduction.

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Figure 1. Percentage of subjects classified by cardiovascular (CV) risk score as having frontal-executive impairment.

Table 1
Characteristics and Cognitive Test Scores of African-American Subjects (N = 43)

Characteristic	With Characteristic
Age, mean±SD	71.8±5.7
Female, n (%)	36 (84.0)
Education, years, mean±SD	13.7±2.2
Medical conditions	
Body mass index, kg/m ² , mean±SD	30.7±6.4
Obese, n (%)	17 (40.0)
Prior diagnosis hypertension, n (%)	25 (58.0)
Systolic BP, mmHg, mean±SD	148.7±21.3
Diastolic BP, mmHg, mean±SD	83.2±9.1
Hypertensive, n (%)	27 (63.0)
Diabetes mellitus, n (%)	5 (12.0)
Left ventricular hypertrophy, n (%)	17 (40.0)
Congestive heart failure, n (%)	1 (2.3)
Myocardial infarction, n (%)	1 (2.3)
Current smoker, n (%)	3 (7.0)
Cardiovascular risk sum, mean±SD (range)	1.7±1.0 (0–4)
Cognitive test scores, mean±SD	
Frontal-executive tests	
Trails A (39.5–163.0 sec)*	72.1±36.0
Trails B (59.4–364.0 sec)*	163.1±0.1
Verbal fluency (8–53)	32.5±2.0
Category fluency (3–23)	15.3 ±4.5
Letter number sequence (3–14)	8.3±3.1
Memory tests	
Logical memory I (17–49)	32.4±7.6
Logical memory II (6–33)	18.8±6.1
Verbal savings score %	88±20
Visual reproduction I (18–102)*	63.6±22.0
Visual reproduction II (8–102)*	47.1±23.0
Visual savings score, % *	72±18
Visuospatial tests	
Copy (82–106)*	100.3±5.9
Visual discrimination (4–7)*	6.7±0.7

* (N = 42) These tests were not performed for one subject due to the possible confounding effects of poor vision.

SD = standard deviation; BP = blood pressure.

Table 2
Bivariate and Multivariate Logistic Regression Association Between Cardiovascular Risk Score and Risk of Cognitive Impairment

Cognitive Domain	Bivariate	Multivariate
	Odds Ratio (95% Confidence Interval)	
Frontal-executive function	2.66 (1.22–5.82)	2.44 (1.06–5.65)
Memory function	1.57 (0.81–3.03)	1.30 (0.64–2.67)
Visuospatial function	1.90 (0.94–3.86)	1.49 (0.66–3.36)

Note: Multivariate model was adjusted for age and education. Model was also run including Center for Epidemiological Studies—Depression Scale scores, with similar results.