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Indirect Measures of Arterial Stiffness and Cognitive Performance in Individuals Without Traditional Vascular Risk Factors or Disease

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Abstract

IMPORTANCE—Whether cognition is influenced by arterial stiffness in the absence of vascular disease remains uncertain.

OBJECTIVE—To test the hypotheses that indirect measures of arterial stiffness are important predictors of cognitive performance and that this relationship varies depending on the presence of vascular disease.

DESIGN, SETTING, AND PARTICIPANTS—Participants included 2573 noninstitutionalized US adults randomly selected from 2 cycles of the National Health and Nutrition Examination Survey (1999–2002). The sample was stratified by groups based on the presence (VASC+) vs the absence (VASC−) of vascular variables negatively associated with cognition to assess the effects of indirect measures of arterial stiffness on cognitive performance. We used logistic regression to obtain odds ratios (ORs) and their 95% CIs. $P < .05$ was considered statistically significant.

MAIN OUTCOMES AND MEASURES—The Digit Symbol Substitution Test score was used as a continuous variable, and the lowest quintile was designated as an indicator of poorer cognitive performance.

RESULTS—In the VASC+ group, poorer cognitive performance was more likely with increasing age (OR, 1.12 [95% CI, 1.08–1.17]; $P < .001$), a sedentary lifestyle (OR, 2.99 [95% CI, 1.62–5.55]; $P = .002$), and the use of dihydropyridine calcium channel blockers (OR, 9.24 [95% CI, 1.35–63.23]; $P = .02$). Poorer cognitive performance in the VASC+ group was less likely in women (OR, 0.37 [95% CI, 0.18–0.72]; $P = .02$), non-Hispanic white individuals (OR, 0.16 [95% CI, 0.09–0.26]; $P < .001$), those with higher educational attainment (OR, 0.23 [95% CI, 0.14–0.38]; $P < .001$), those with higher income levels (OR, 0.56 [95% CI, 0.72–0.76]; $P < .001$), and

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Study concept and design: All authors.

Acquisition, analysis, or interpretation of data: Gutierrez.

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those who used renin-angiotensin system blockers (OR, 0.24 [95% CI, 0.07–0.79]; $P = .02$). In the VASC− group, the most important significant predictors of poorer cognitive performance were an ankle brachial index greater than 1.30 (OR, 18.56 [95% CI, 2.94–117.05]; $P = .002$) and increased blood pressure variability (OR, 3.49 [95% CI, 1.07–11.35]; $P = .04$). Among participants in the VASC− group who had both of these variables, the prevalence of poorer cognitive performance was greater ($\beta = 16.65$; $P < .001$).

CONCLUSIONS AND RELEVANCE—Two indirect measures of arterial stiffness, an ankle brachial index greater than 1.30 and increased blood pressure variability, are associated with poorer cognitive performance among adults 60 years or older without clinical atherosclerotic disease. Among those with vascular disease, factors capable of influencing arterial stiffness, such as exercise and the use of renin-angiotensin system blockers, may be protective against poorer cognitive performance.

A role for vascular disease in cognitive dysfunction and dementia is well established. For example, the prevalence and incidence of Alzheimer disease is greater among individuals with stroke or circle of Willis atherosclerosis.[1–3] Vascular injury, defined as white matter disease and infarcts, is a good predictor of cognitive performance among elderly individuals with cognition ranging from normal findings to mild dementia, and the effects appear to be independent of amyloid deposition in the brain.[4] In addition, other nontraditional markers of arterial disease have been investigated with respect to cognition. For example, aortic stiffness, as measured by central pulse pressure or carotid-femoral pulse-wave velocity (PWV), has been associated with increased markers of vascular disease in the brain, amyloid deposition, and worse cognitive performance.[5,6] Blood pressure variability, an indirect measure of arterial stiffness, has been linked to worse cognition, particularly in the setting of carotid artery disease.[7,8] The current view of how vascular disease influences cognition focuses mainly on traditional vascular risk factors and their treatment as a means of preventing vascular cognitive impairment.[9] Given that aging is associated with arterial stiffness and that arterial stiffness may even precede the development of some of these traditional vascular risk factors,[10] we postulate that easily accessible indirect measures of arterial stiffness are associated with cognition. Facilitating the identification of individuals not otherwise suspected of having vascular disease because they lack traditionally defined vascular risk factors or prior vascular disease may lead to increased awareness among clinicians of the vascular contribution to impaired cognition. In addition, these indirect measures could be used as screening tools for less available but more direct measures of aortic stiffness, such as carotid-femoral PWV. This increased awareness among clinicians could be facilitated if our understanding of risk in those lacking traditionally defined vascular risk factors or prior vascular disease were increased. We therefore tested the hypotheses that indirect measures of arterial stiffness are associated with cognitive performance in a sample of noninstitutionalized US adults and that the association is present even in the absence of overt vascular disease.

Methods

The continuous National Health and Nutrition Examination Survey (NHANES) is a biannual periodic survey of noninstitutionalized US adults of all ages selected through a

multistage, clustered-sampling method.[11] Written informed consent was obtained by the NHANES personnel from the individuals participating in the survey or the participants' legal representatives, and the survey was approved by the research ethics review board of the National Center for Health Statistics (http://www.cdc.gov/nchs/nhanes/irba98.htm). Because components of the questionnaires, including physical examination and laboratory data, vary slightly in each 2-year cycle, we used only 2 cycles of the NHANES data (1999–2002). Cognitive performance, specifically psychomotor speed, was the main outcome of this study, and it was assessed with the survey-collected Digit Symbol Substitution Test (DSST) score.[12] The DSST consists of rows of symbols with a blank square underneath. A key appears above these rows showing the numbers 1 through 9, thus pairing each symbol to a number. The respondent is asked to fill in the blank space under each symbol with the corresponding number as quickly as possible. The score is the number of correct symbols drawn in 120 seconds, with a maximum score of 133.[13] Eligibility criteria defined by NHANES for this exercise included being 60 years or older and able to understand and execute the examination.

Age, sex, and race/ethnicity were self-reported. For this analysis, we categorized race and ethnicity between non-Hispanic white or other. Educational attainment was captured as less than high school, no more than high school, or beyond high school and used ordinally. Poverty was assessed with the ratio of poverty to income, which was used continuously or categorized as poverty vs other (ie, ratio of poverty to income, <1.0).[14] Sedentary lifestyle was defined as the absence of moderate or vigorous physical activity in the 30 days before the interview. Obesity was defined as a body mass index greater than 30 (calculated as the weight in kilograms divided by the height in meters squared). Waist circumference was considered increased if it exceeded 102 cm in men or 88 cm in women.[15] Participants who were smokers at the time of the interview were considered current smokers.

Diabetes mellitus was defined by a self-reported diagnosis, use of hypoglycemic drugs or insulin, or a hemoglobin A_{1c} level greater than 6.5% (to convert to a proportion of total hemoglobin, multiply by 0.01). Hypercholesterolemia was a total cholesterol level greater than 230 mg/dL (or >200 mg/dL for patients with diabetes mellitus [to convert to millimoles per liter, multiply by 0.0259]). Levels of C-reactive protein (CRP) were obtained by latex-enhanced nephelometry and were used continuously or categorized into a CRP level greater than 2.0 mg/dL (to convert to nanomoles per liter, multiply by 9.524).[16] Other laboratory measurements used in this analysis included total cholesterol and hemoglobin A_{1c} levels used to characterize the vascular risk factors expressed categorically or continuously. Cardiac ischemic disease (CAD) was defined as self-reported prior myocardial infarction, coronary artery disease, or prior cardiac revascularization. Congestive heart failure (CHF) and stroke (any subtype) were also self-reported. Chronic kidney disease (CKD) was self-reported by participants as a failing kidney or evidenced by a creatinine level greater than 1.2 mg/dL in women or greater than 1.3 mg/dL in men (to convert to micromoles per liter, multiply by 88.4).[17]

Blood Pressure–Derived Variables

The participants were asked to sit in a chair and rest quietly for 5 minutes before blood pressure measurement. Blood pressure was calculated as the mean of 3 measurements obtained in the arm separated by 30-second resting periods on the same day as the administration of the DSST. We excluded from this analysis participants with fewer than 3 blood pressure measurements or any diastolic blood pressure of 0 mm Hg. Central pulse pressure was obtained by subtracting the mean diastolic blood pressure from the mean systolic blood pressure, and it was used continuously or categorized to the upper quartile (for the group with vascular variables negatively associated with cognition present [VASC+ group], a cutoff of 84 mm Hg; for the group with these variables absent [VASC− group], a cutoff of 59 mm Hg). The SDs of the intravisit diastolic and systolic blood pressure values were used as measures of blood pressure variability and were obtained with the following formula:

$$\sqrt{\left\{\left[\sum (x-\mu)^2\right]/[n-1]\right\}}$$

Increased blood pressure variability was considered to have occurred when the SDs of the systolic and diastolic blood pressure values were in the upper quartile regardless of the VASC group (ie, systolic SD, >6.4 mm Hg; diastolic SD, >4.2 mm Hg). Hypertension was defined by self-reported diagnosis, the use of antihypertensives, or a mean systolic blood pressure of greater than 140 mm Hg or a mean diastolic blood pressure of greater than 90 mm Hg. Participants with diabetes mellitus used a mean systolic blood pressure of greater than 120 mm Hg or a diastolic blood pressure of greater than 80 mm Hg as cut-offs. Among participants who were taking any medications and who agreed to show the medication bottles to the interviewers, we also extracted the total numbers and classes of drugs used to lower blood pressure (diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, and so forth) per participant.

We included the ankle-brachial pulse index (ABI) only in participants 60 years or older. The left or right ABI was obtained automatically by dividing the mean systolic blood pressure in each ankle by the brachial mean systolic blood pressure. We assigned the diagnosis of peripheral arterial disease (PAD) when the ABI in either leg was less than 0.9 or when participants reported much difficulty in walking one-fourth of a mile or an inability to do it all in the absence of stroke or CHF. An ABI greater than 1.3 in either leg, blood pressure variability, central pulse pressure, and a posterior tibial systolic blood pressure value in the upper quartile were used as measures of arterial stiffness, as previously reported.[18–22]

Statistical Analysis

The analysis adjusted for oversampling and clustering of the sample. The first analysis focused on determining the differences between NHANES participants 60 years or older and who had all data available for the analysis, and those who had incomplete information and were thus ineligible for the current study. The normality of the DSST score distribution was tested with the Kolmogorov-Smirnov test and visual inspection of the histogram. The raw score deviated slightly to the left. The square root transformation normalized the

distribution of the DSST score and was used as the outcome variable in a linear regression to identify vascular variables negatively associated with cognitive performance. This linear regression included all the demographic and clinical variables described in Table 1 as the predicting variables. We then stratified the sample into the VASC+ group for participants with any vascular variable negatively associated with the transformed DSST score and the VASC− group for participants with none of these variables. We then used logistic linear regressions to obtain odds ratios (ORs) and their 95% CIs of poorer cognitive performance (defined as the lowest quintile in the DSST performance for each subgroup). $P < .05$ was considered statistically significant using a χ^2 distribution. The analysis was performed with commercially available software (SAS, version 9.3; SAS Institute Inc).

Results

Sample Characteristics

We included 2573 eligible participants 60 years or older with complete data; 56.7% were women and 83.8% were non-Hispanic white. Participants in this study were younger and had a higher educational attainment and a higher prevalence of hypercholesterolemia compared with those not included. The ineligible group tended to be poorer and less physically active and more likely to have diabetes mellitus and a history of stroke or CHF (Table 1).

Global Predictors of Cognitive Performance

In the univariate analysis, cognitive performance was worse with increasing age, a sedentary lifestyle, a proinflammatory state, hypertension, diabetes mellitus, stroke, CKD, CAD, CHF, and PAD. Cognitive performance was better in non-Hispanic white participants and those with greater educational attainment, greater household income, and hypercholesterolemia. We found no statistically significant differences in cognitive performance by sex, obesity status, waist circumference, or current smoking. In our multivariate analysis, being female, having a higher educational attainment and greater household income, and being of non-Hispanic white ethnicity were associated with better cognitive performance, whereas increasing age, hypertension, diabetes mellitus, stroke, and CAD were associated with worse cognitive performance (Table 2). Of note, CHF, CKD, and PAD were negative predictors of cognitive performance only in the univariate analysis but were used to select participants into the VASC+ group because they represent forms of vascular disease. Although smoking, hypercholesterolemia, and CRP levels were not used to stratify the sample, we controlled for these variables in all models.

Vascular Variables Negatively Associated With Cognitive Performance

Vascular risk factors and disease with negative β estimates for cognition were used to stratify the sample. The VASC− group included 555 participants (21.6%) of the total sample who were free of vascular variables negatively associated with cognition (ie, hypertension, diabetes mellitus, stroke, CAD, CHF, PAD, or CKD). The remaining 2018 participants who were assigned to the VASC+ group had a worse socioeconomic and clinical profile overall compared with those in the VASC− group (Table 3). In multivariate analysis, poorer cognitive performance in the VASC+ group was more likely with increasing age (OR, 1.12

[95% CI, 1.08–1.17]; $P < .001$) and a sedentary lifestyle (OR, 2.99 [95% CI, 1.62–5.55]; $P = .002$) and was associated with the use of dihydropyridine calcium channel blockers (OR, 9.24 [95% CI, 1.35–63.23]; $P = .02$) (Table 4). Poorer cognitive performance in the VASC+ group was less likely in women (OR, 0.37 [95% CI, 0.18–0.72]; $P = .02$), non-Hispanic white individuals (OR, 0.16 [95% CI, 0.09–0.26]; $P < .001$), those with a higher educational attainment (OR, 0.23 [95% CI, 0.14–0.38]; $P < .001$), those with higher income levels (OR, 0.56 [95% CI, 0.07–0.76]; $P < .001$), and those who used renin-angiotensin system blockers compared with other antihypertensives (OR, 0.24 [95% CI, 0.07–0.79]; $P = .02$). These estimates were independent of the degree of hypertension control.

In participants in the VASC− group, age, sex, ethnicity, and income were not significant predictors of cognition (Table 4). A higher educational attainment (OR, 0.19 [95% CI, 0.10–0.38]; $P \leq .001$) and non-Hispanic white ethnicity (OR, 0.22 [95% CI, 0.06–0.86]; $P = .03$) were the only sociodemographic variables protective against poorer cognitive performance in this group. The most important significant predictors for poorer cognitive performance in the VASC− group were an ABI greater than 1.30 (OR, 18.56 [95% CI, 2.94–117.05]; $P = .002$) and increased blood pressure variability (OR, 3.49 [95% CI, 1.07–11.35]; $P = .04$). In the post hoc analysis, we explored statistical interactions between the upper terciles of pulse pressure and blood pressure variability with an ABI greater than 1.30; the only significant interaction was the joint presence of an ABI greater than 1.30 and blood pressure variability in the upper terciles as a predictor of poorer cognitive performance in the VASC− group ($\beta = 16.65$; $P < .001$). Although some participants presumably free of vascular cognitive burden had listed drugs that could be considered antihypertensives, we did not adjust for them owing to the small size of these subgroups and the potential bias for indications other than hypertension.

Discussion

The predictors of cognitive performance were different among study participants with and without vascular disease in this nationwide sample of US adults who were administered the DSST. We found that demographics, traditional vascular risk factors, and vascular disease were the most important predictors of cognitive performance. Nevertheless, we confirmed our hypothesis that indirect measures of arterial stiffness, defined here as an ABI greater than 1.30 and increased blood pressure variability, were important predictors of cognition among those without vascular disease. In addition, an ABI greater than 1.30 has additive effects with increased blood pressure variability. Although both measures have been indirectly correlated with more precise measures of aortic stiffness, a high ABI is more highly correlated with more precise measures of arterial stiffness, such as the central augmentation index, whereas increased blood pressure variability is more highly correlated with aortic PWV.[8,22] Individuals who have a high ABI and increased blood pressure variability might have more extreme cases of arterial stiffness and thus might be exposing brain parenchyma to increased pulsatility energy and endothelial damage.

In NHANES participants with vascular disease (defined by traditional risk factors or prior vascular disease), the following 3 modifiable factors were protective against poorer cognitive performance: increased physical activity, the use of renin-angiotensin system

blockers independent of blood pressure control, and an increased pulse pressure. Physical activity and the use of renin-angiotensin system blockers are indirectly related to arterial stiffness.[23–25] For example, multiple studies have reported the detrimental effects of a sedentary lifestyle or, conversely, the benefits of exercise in reducing the risk for dementia, even after taking into account white matter disease and medial temporal atrophy.[26] In addition, physical exercise can lead to decreased arterial stiffness and improved use of oxygen, which might counteract the effects of arterial aging.[23,24] We also found that the use of renin-angiotensin system blockers was protective against poorer cognitive performance among those with established vascular disease independent of the degree of control of hypertension. One plausible mechanism to explain this association is that renin-angiotensin system blockers are capable of reducing the carotid-femoral PWV, a marker of aortic stiffness.[25] Increasing aortic stiffness might lead to greater transmission of pulsatility to distal organs, particularly those with low-resistance flow (eg, brain and kidneys).[27] Increasing carotid-femoral PWV has been associated with lower scores of verbal memory and evidence of microvascular disease in brain parenchyma in a community-based study.[5] In addition, a small study among dementia-free patients[6] found that greater degrees of arterial stiffness, as measured by increased PWV, were associated with greater odds of amyloid plaques in the brain parenchyma. This finding suggests that by decreasing PWV, this class of antihypertensives might dampen the deleterious effects of aortic stiffness in participants with vascular cognitive burden. Such a hypothesis is supported by other observational studies,[28–30] but a clinical trial is needed to address this notion. Although we expected that an increased pulse pressure would be associated with poorer cognitive performance, we found a counterintuitive association between increased pulse pressure and better cognitive performance. Multiple explanations can be invoked for this finding. For example, because pulse pressure is heavily influenced by cardiac output, an increased pulse pressure per se might be indicative of better cardiac function, which is known to be associated with better cognitive performance.[31,32]

To better understand the discrepant results among the subgroups, it is important to determine the most likely underlying arterial pathologic features in each group. Almost 40% of participants in the VASC+ group had some form of cardiovascular disease. The underlying cause of CAD and PAD is overwhelmingly atherosclerotic.[33,34] Although stroke is a more heterogeneous disease than CAD and PAD, atherosclerosis of the precerebral and cerebral arteries can be found in about half the cases.[35–37] A high systolic blood pressure is a marker of subclinical atherosclerosis, even among individuals considered to be at low risk.[38] Although evidence suggests that a high ABI can also be indicative of PAD as determined by angiography or the toe-brachial index, this evidence is more applicable for patients with diabetes mellitus, CKD, and CAD who have PAD symptoms.[39–41] Having segregated participants with diabetes mellitus, CKD, and CAD who have PAD symptoms into the VASC+ group, we further increased the chances that a high ABI in the VASC− group is not indicative of PAD. Based on these considerations, we believe that the most likely underlying arterial pathologic feature in the VASC+ group is atherosclerosis. In addition, although lesser degrees of atherosclerosis or asymptomatic atherosclerosis may have been included in the VASC− group, our findings argue against atherosclerosis being the predominant arterial phenotype in this group. Therefore, we propose that cognitive performance is poorer among

participants with evidence suggestive of greater aortic stiffness in the absence of clinical atherosclerotic disease. Our findings suggest that further research is needed to confirm the notion that individuals with relatively healthier aging may be at risk for cognitive deterioration despite the absence of traditional vascular risks or scores.

An advantage of using the NHANES data to explore a mechanistic hypothesis is that the results are applicable to the US population as a whole. In this study, however, participants who were willing to participate in the administration of the DSST were more often white and were wealthier, healthier, and better educated than those who refused to participate. This bias might have underestimated even further the degree to which socioeconomic and clinical variables related to vascular disease affect cognition in the poorest and sickest segments of the US population and in ethnic minorities. Our analysis was cross-sectional, and causality can only be suggested. The lack of more direct measurement of aortic stiffness or brain subclinical vascular disease is a limitation in the NHANES data, and it might introduce error and bias in the associations we detected. Nevertheless, these relatively easy-to-obtain measures of arterial stiffness broaden the applicability of our findings in the identification of individuals more likely to have poorer cognitive performance.

Conclusions

Markers of aortic arterial stiffness are associated with poorer cognitive performance among US adults older than 60 years without clinical atherosclerotic disease. Among those with vascular disease, the association between markers of arterial stiffness and cognition was less robust, possibly owing to the greater influence of other risk factors. We suggest, however, that factors capable of influencing aortic stiffness, such as the use of renin-angiotensin system blockers and physical activity, may be protective against poorer cognitive performance among participants with established vascular disease.

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Table 1.

Characteristics of the Sample of NHANES Participants 60 Years or Older by Eligibility for This Analysis

Characteristic	Participants, % (SE)[a]		*P* Value
	Eligible (n = 2573)	Ineligible (n = 661)	
Age, mean (SE), y	70.5 (0.3)	74.1 (0.5)	<.001
Female sex	56.7 (0.1)	56.0 (2.5)	.81
Non-Hispanic white	83.8 (1.9)	64.6 (3.8)	<.001
Educational attainment beyond high school	40.6 (1.6)	32.1 (2.6)	<.001
Living in poverty	11.9 (1.2)	19.7 (3.3)	<.001
Sedentary lifestyle	48.9 (1.9)	73.7 (2.2)	<.001
Increased waist circumference	63.7 (1.2)	63.0 (3.0)	.78
Obesity	31.9 (1.1)	34.2 (3.5)	.51
Hypertension	64.6 (1.7)	62.4 (2.7)	.49
Diabetes mellitus	17.5 (0.1)	24.4 (2.5)	.003
Hypercholesterolemia	75.4 (1.1)	67.7 (2.8)	.005
Current smoking	12.2 (0.8)	11.6 (1.6)	.68
CKD	7.1 (1.6)	6.1 (0.4)	.001
Stroke	5.4 (0.05)	12.4 (2.4)	<.001
CAD	17.6 (1.0)	21.6 (2.9)	.18
CHF	5.8 (0.5)	10.2 (1.5)	.007
PAD	25.5 (2.6)	16.1 (0.9)	.85

Abbreviations: CAD, cardiac ischemic disease; CHF, congestive heart failure; CKD, chronic kidney disease; NHANES, National Health and Nutrition Examination Survey; PAD, peripheral arterial disease.

[a]Unless otherwise indicated, data are expressed as percentage of participants.

Table 2.

Adjusted Global Predictors for Cognitive Performance[a]

Predictor	β Estimate (SE)	*P* Value
Age, y	−0.06 (0.01)	<.001
Female sex, yes/no	0.36 (0.06)	<.001
Non-Hispanic white, yes/no	0.93 (0.09)	<.001
Educational attainment, No. of school years	0.45 (0.04)	<.001
Ratio of poverty to income	0.17 (0.02)	<.001
Sedentary lifestyle, yes/no	−0.18 (0.06)	.003
Increased waist circumference, yes/no	0.02 (0.05)	.65
Obesity, yes/no	−0.05 (0.06)	.43
C-reactive protein level >2.0 mg/dL	−0.35 (0.21)	.11
Hypertension, yes/no	−0.12 (0.06)	.050
Diabetes mellitus, yes/no	−0.23 (0.09)	.02
Hypercholesterolemia, yes/no	0.09 (0.06)	.11
Current smoking, yes/no	0.04 (0.10)	.67
Stroke, yes/no	−0.35 (0.10)	.002
CAD, yes/no	−0.16 (0.06)	.02
CHF, yes/no	−0.09 (0.10)	.37
CKD, yes/no	−0.08 (0.09)	.10
PAD, yes/no	−0.25 (0.09)	.055

Abbreviations: CAD, cardiac ischemic disease; CHF, congestive heart failure; CKD, chronic kidney disease; PAD, peripheral arterial disease.

SI conversion factor: To convert C-reactive protein to nanomoles per liter, multiply by 9.524.

[a]The β estimates were obtained with a multivariate linear regression, with all the variables listed here used concomitantly.

Table 3.

Characteristics of the Sample by Vascular Cognitive Burden Status[a]

Characteristic	Risk Group, Mean (SE)	
	VASC+ (n = 2018)	VASC− (n = 555)
Age, y	71.2 (0.3)	68.1 (0.4)
Female sex, %	57.5 (1.3)	54.5 (2.4)
Non-Hispanic white, %	83.2 (2.1)	85.9 (2.2)
DSST score, No. of correct substitutions	44.9 (0.6)	52.5 (1.2)
Educational attainment beyond high school, %	38.8 (1.5)	46.5 (2.7)
Ratio of poverty to income	2.66 (0.08)	3.19 (0.15)
Sedentary lifestyle, %	50.9 (2.0)	42.3 (3.3)
Obesity, %	35.3 (1.3)	21.0 (2.0)
C-reactive protein level, mg/dL	0.55 (0.02)	0.43 (0.05)
Current smoking, %	11.7 (0.1)	14.1 (1.9)
Pulse pressure, mm Hg	70.8 (0.7)	52.5 (0.6)
Mean systolic blood pressure, mm Hg	142.8 (0.9)	123.2 (0.6)
Mean diastolic blood pressure, mm Hg	72.0 (0.5)	70.1 (0.7)
Systolic blood pressure variability, mean (SD)	4.9 (0.1)	4.1 (0.1)
Diastolic blood pressure variability, mean (SD)	3.1 (0.1)	3.2 (0.2)
Total cholesterol level, mg/dL	210.4 (1.4)	221.8 (1.8)
Diabetes mellitus, %	22.8 (0.9)	NA
Stroke, %	7.1 (0.1)	NA
CAD, %	22.9 (1.4)	NA
CHF, %	7.6 (0.1)	NA
PAD, %	21.1 (1.1)	NA
CKD, %	7.9 (0.6)	NA
Any cardiovascular disease, %	44.8 (1.7)	NA

Abbreviations: CAD, cardiac ischemic disease; CHF, congestive heart failure; CKD, chronic kidney disease; DSST, Digit Symbol Substitution Test; NA, not applicable; OR, odds ratio; PAD, peripheral arterial disease; VASC−, absence of vascular variables negatively associated with cognition; VASC+, presence of vascular variables negatively associated with cognition.

SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; C-reactive protein to nanomoles per liter, multiply by 9.524.

[a]In the VASC+ regression, we adjusted for the degree of blood pressure control. Optimally controlled hypertension was defined as evidence of a systolic blood pressure of less than 140 mm Hg and a diastolic blood pressure of less than 90 mm Hg (or <130 mm Hg and <80 mm Hg, respectively, in participants with diabetes mellitus).

Table 4.

Adjusted Predictors of Poorer Cognitive Performance by Group[a]

Predictor	Risk Group, OR (95% CI)	
	VASC+ (n = 2018)	VASC− (n = 555)
Age, y	1.12 (1.08–1.17)	1.02 (0.87–1.17)
Female sex, yes/no	0.37 (0.18–0.72)	0.85 (0.36–2.05)
Non-Hispanic white, yes/no	0.16 (0.09–0.26)	0.22 (0.06–0.86)
Educational attainment, No. of school years	0.23 (0.14–0.38)	0.19 (0.10–0.38)
Ratio of poverty to income, yes/no	0.56 (0.07–0.76)	0.85 (0.50–1.44)
Sedentary lifestyle, yes/no	2.99 (1.62–5.55)	0.52 (0.12–2.22)
Obesity, yes/no	1.33 (0.72–2.44)	0.56 (0.10–3.10)
C-reactive protein level, mg/dL	1.13 (0.80–1.59)	0.99 (0.52–1.89)
Current smoking, yes/no	0.50 (0.19–1.35)	0.35 (0.05–2.54)
Increased blood pressure variability, yes/no	1.46 (0.74–2.80)	3.49 (1.07–11.35)
Ankle-brachial index >1.30, yes/no	0.65 (0.12–3.44)	18.56 (2.94–117.05)
Tibial systolic blood pressure	0.99 (0.99–1.01)	0.99 (0.96–1.01)
Total cholesterol level, per every 10 mg/dL	0.99 (0.94–1.05)	1.09 (0.93–1.01)
Hemoglobin A_{1c} level	1.14 (0.85–1.54)	7.78 (0.95–63.71)
Stroke, yes/no	1.63 (0.60–4.44)	NA
Cardiac disease, yes/no[b]	1.15 (0.70–3.01)	NA
PAD, yes/no	1.56 (0.66–3.72)	NA
Use of renin-angiotensin system blockers, yes/no	0.24 (0.07–0.79)	NA
Use of dihydropyridine calcium channel blockers, yes/no	9.24 (1.35–63.23)	NA

Abbreviations: DSST, Digit Symbol Substitution Test; NA, not applicable; OR, odds ratio; PAD, peripheral arterial disease; VASC−, absence of vascular variables negatively associated with cognition; VASC+, presence of vascular variables negatively associated with cognition.

SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; C-reactive protein to nanomoles per liter, multiply by 9.524; hemoglobin A_{1c} to proportion of total hemoglobin, multiply by 0.01.

[a]In the VASC+ regression, we adjusted for the degree of blood pressure control. Optimally controlled hypertension was defined as evidence of a systolic blood pressure of less than 140 mm Hg and a diastolic blood pressure of less than 90 mm Hg (or <130 mm Hg and <80 mm Hg, respectively, in participants with diabetes mellitus).

[b]Given that more than 50% of participants with congestive heart failure had cardiac ischemic disease, we merged both categories into cardiac disease to solve the collinearity.