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Neurocognition in treatment-resistant hypertension: profile and associations with cardiovascular biomarkers

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Abstract

Background: Hypertension in midlife has been associated with increased risk of stroke and neurocognitive decline. Few studies, however, have examined neurocognition among individuals with treatment-resistant hypertension or potential mechanisms by which treatment-resistant hypertension may impair neurocognition.

Methods: We examined the pattern of neurocognitive impairment and potential mechanisms in a sample of 96 overweight adults with treatment-resistant hypertension, aged 41–81 years. Neurocognitive function was assessed using a 45-min test battery consisting of executive function and memory. Vascular and metabolic mechanisms examined included cerebrovascular risk factors (CVRFs: Framingham Stroke Risk Profile), insulin sensitivity (homeostatic model assessment of insulin resistance), waist-to-hip ratio, microvascular function (hyperemic response), and peak oxygen consumption from an exercise treadmill test. Simple path analyses were used to assess the association between potential vascular and metabolic mechanisms and neurocognition.

Results: Neurocognitive impairments were common, with 70% of the sample exhibiting impaired performance on at least one executive function subtest and 38% on at least one measure of memory. Higher levels of aerobic fitness, greater insulin sensitivity, and better microvascular function, as well as lower CVRFs and waist-to-hip ratio were associated with better neurocognition. In path analyses, aerobic fitness, microvascular function, and CVRFs all were independently associated with neurocognitive performance. Insulin resistance associated with worse executive function but better memory performance among older participants.

Conclusion: Neurocognitive impairments are common in adults with treatment-resistant hypertension, particularly on tests of executive function. Better neurocognition is independently associated with aerobic fitness, microvascular function, and CVRFs.

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Conflicts of interest

There are no conflicts of interest.

Keywords

cerebrovascular risk factors; cognitive function; resistant hypertension

INTRODUCTION

Hypertension (HTN) remains one of the most common and burdensome cerebrovascular risk factors (CVRFs) and metabolic risk factors in the United States [1], impacting more than half of the older adults [2]. In addition to increasing the risk of cerebrovascular events [3], emerging evidence suggests that HTN is critically important risk factor for the development of Alzheimer's disease and related dementias (ADRD) [4], with some investigators characterizing it as the most modifiable ADRD risk factor [5]. Among individuals with HTN, those with 'resistant hypertension' may have the greatest risk of cerebrovascular complications and ADRD, due to the chronicity and poorly controlled nature of their HTN [6]. Treatment-resistant hypertension is defined as inadequately managed blood pressure (BP) despite adherence to three or more optimally dosed antihypertensive medications (including a diuretic). In addition, because obesity and advancing age are the two strongest risks for treatment-resistant hypertension [6,7], older individuals with metabolic dysfunction are at particularly high risk for treatment-resistant hypertension and associated neurocognitive dysfunction.

Despite the widely acknowledged association between HTN and impaired neurocognition, delineating mechanisms by which HTN may impair neurocognition has proven difficult and is a barrier to targeted preventive treatments [4,8-10]. For example, although insulin resistance and metabolic dysfunction are common among individuals with HTN and known to precipitate neurocognitive decline [11,12], it remains unclear whether these closely related CVRFs act in concert or through parallel pathways [13]. HTN is also a primary risk factor for microvascular dysfunction, which are both a risk factor for neurocognitive impairment, ADRD development, and accelerate functional decline among symptomatic individuals [14-16]. Finally, numerous recent prospective studies have demonstrated that greater aerobic fitness may confer a lower likelihood of neurocognitive impairment, and this may be mediated by underlying metabolic or vascular function [17]. Greater fitness has also been shown to associate with alternative, independent pathways of neurocognitive enhancement [18-20]. No studies have attempted to delineate the potentially overlapping nature of subclinical microvascular disease and insulin resistance, which have a very early impact on neurocognitive impairment.

METHODS

Participants were assessed during baseline assessments from the TRIUMPH study of exercise and diet among individuals with treatment-resistant hypertension [21]. All participants were assessed prior to randomization by assessors blinded to future intervention status. Screening for resistant HTN was carefully conducted and all BP assessments followed JNC 7 guidelines [22]. Clinic SBP and DBP were taken on three separate visits, each 1-week apart. At each screening visit, four BP assessments were taken, with the latter

three from all visits (nine total measurements) being used to determine BP eligibility. Treatment-resistant hypertension was established by a standard protocol for measurement of clinic BP from the three separate clinic visits. Participants had to average a minimum of 130mm SBP or 80mm DBP if they were on three antihypertensive medications or were diagnosed with treatment-resistant hypertension or 120 or 80mmHg if they were on at least four antihypertensive medications. Ambulatory BP assessments were also collected over a 24-h period during baseline assessments [21]. Study assessments are reported in detail below.

Neurocognition

We adopted a 45–60 min neuropsychological battery as recommended by the Neuropsychological Working Group for vascular cognitive disorders [23]. Assessments included multiple subtests of executive function and memory. Participants were grouped into factor scores, as detailed in our results section below and Supplemental Table 1, <http://links.lww.com/HJH/B40>. The neuropsychological test battery was administered in a fixed order with alternative forms and counterbalancing to minimize practice effects. Testing also was streamlined using standard discontinuation rules to reduce participant burden. The battery consisted of the following tests.

Executive function/psychomotor speed

Trail making test—This test is used to measure visuomotor attention and executive function. For Part A of the test, participants draw lines to connect consecutively number circles; for Part B, participants connect consecutively numbered and lettered circles by alternating between the two sequences (1-A-2-B, etc) [24].

Stroop test—This test assesses executive function and set-shifting ability. The standardized version of the Stroop test used in the current study consists of three sections: word, color, and color-word [25].

Animal naming test—This tests semantic fluency and verbal flexibility/executive function as demonstrated by rapidly generating words a specified category (in this case, animals) within a 60 s [26].

Controlled oral word association test—This tests verbal flexibility and executive function as demonstrated by rapidly generating words to a particular letter (C-F-L; P-R-W; F-A-S) in 60 s [27].

Digit span forward and backwards—This test from the Wechsler Adult Memory Scale – IV assesses auditory attention and working memory. Participants repeat digits of increasing length, first in the forward direction as they have heard the numbers and then in reverse order [28].

Digit symbol substitution test—This test from the Wechsler Adult Intelligence Scale measures executive functioning and attention. Participants are asked to draw symbols that

match one of 10 digits copied from a key. Scores on this task are the number of correct symbols drawn in a 120-s time period [28].

Ruff 2 and 7 test—This test assesses sustained attention and executive function. Participants are required to cross out all instances of the numbers ‘2’ and ‘7’ under two conditions: one in which they are embedded among other digits and in the second in which they are embedded among letters. The score is the total number of correct cancellations within a 5-min time period [29].

Memory

California verbal learning test-II—One of two equivalent alternate forms of the California verbal learning test, second edition (CVLT-II) was used to measure verbal learning, recognition, and delayed recall of a 16-item word list. The CVLT-II provides an excellent measure of memory and executive function using a distraction trial [30].

Benton visual retention test-revised—The Benton visual retention test-revised was used to provide a parallel assessment of visual learning and recall abilities. In this test, participants are shown a display with six figures on three separate trials, and given 10 s to study the figures on each trial before being asked to reproduce them from memory. Total learning over all three learning trials and retention following a 30-min delay was used as the outcome indices [31].

Cardiovascular and microvascular biomarker assessments

Clinic and ambulatory blood pressure monitoring—Clinic BP values were assessed on three separate screening visits, each 1-week apart following JNC 7 guidelines [21]. In addition, 24-h ambulatory BP (ABP) was conducted during a typical workday. The AccuTracker II ABP Monitor (Suntech, Raleigh, North Carolina, USA) was worn for approximately 24 h, usually starting between 0800 and 1000 h. until the same time the following morning. The AccuTracker II measures BP noninvasively based on the auscultatory technique and has been previously validated [32-34]. It was programmed to take three BP measurements per hour at random intervals during daytime hours, and two readings per hour during the participant’s anticipated nighttime sleep period. Participants were instructed to follow their normal schedule.

The Framingham stroke risk profile—The Framingham Stroke Risk Profile (FSRP) was used as a marker of stroke risk. The FSRP is a clinical assessment tool used to quantify the risk of incident stroke [35] and has previously been shown to be associated with neurocognitive performance [35,36]. Stroke risk is quantified separately for men and women and includes the following cardiovascular disease (CVD) risk factors: SBP, use of antihypertensive therapy, diabetes mellitus, cigarette smoking, ischemic heart disease, atrial fibrillation, and left ventricular (LV) hypertrophy. We utilized the recently revised FSRP, which was updated to reflect temporal changes in stroke risk following the publication of the original FSRP [37].

Homeostatic model assessment of insulin resistance—Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated from fasting serum insulin and fasting plasma glucose using the HOMA-IR method [38] calculated as $\text{HOMA-IR} = [\text{insulin (mg/dl)} \times \text{glucose (uIU/ml)}] / 405$. Insulin sensitivity was examined using the homeostatic model assessment (HOMA-IR) formula, which has previously been associated with ADRD outcomes [39].

Waist-to-hip ratio—Waist-to-hip (WTH) ratio was used as an adiposity marker of metabolic dysfunction. WTH ratio was assessed using the WHO protocol [40]. BMI also was collected using a standard scale.

Microvascular function—Microvascular function was determined using hyperemic velocity change during flow-mediated dilation, which has recently been validated as a peripheral marker of systemic microvascular functioning [41,42]. Pulsed Doppler flow signals in the brachial artery were recorded at baseline and for up to 15 s after cuff release. The velocity–time integral for baseline and reactive hyperemia was based upon the mean of triplicate pulsed-Doppler flow tracings recorded at each of these phases. Hyperemic velocity was derived by dividing the velocity-time integral by the interbeat interval, and hyperemic flow was calculated from hyperemic velocity and brachial artery cross-sectional area.

Aerobic fitness—Participants underwent a maximal graded exercise treadmill test in which workloads were increased at a rate of one metabolic equivalent per minute. Expired air was collected by mouthpiece for quantification of minute ventilation, oxygen consumption, and carbon dioxide production with the Parvo Medics TrueOne measurement system (model 2400; Parvo Medics, Sandy, Utah, USA).

Data reduction and statistical analyses—All analyses were conducted within SAS 9.4 (Cary, North Carolina, USA). To minimize the number of statistical tests in the present analysis, we used principle axis factor analysis with a Promax rotation to combine information from individual neurocognitive subtests into two cognitive domain scores. Following factor analysis, a rank-based global score was created by taking the mean rank of all subtests within each respective domain, which were then used as the outcome measures.

Separate hierarchical multiple regression analyses were conducted for each neurocognitive domain. Because the FSRP quantifies stroke risk based on distinct algorithms for men and women, we did not include sex as an additional demographic predictor. In addition, because of the substantial overlap between cardiometabolic predictors, results are presented using simple path analyses available within PROC CALIS, which allows for modeling interrelated predictors while minimizing bias in the marginal distribution. Results were similar using standard regression modeling techniques (see Supplemental Analyses, <http://links.lww.com/HJH/B40>). Prior to conducting our hierarchical regression, we first examined the association between our predictors of interest and performance in each neurocognitive domain after controlling for age only. Assumptions regarding linearity, independence, and model residuals were evaluated in all analyses, with particular attention paid to potential moderation of our predictors of interest by participant age, given the known variation for SBP and insulin with ADRD risk dependent on age of assessment.

RESULTS

Sample characteristics

Background and demographic features of the sample are shown in Table 1. As shown, sample participants tended to be middle-aged, highly educated, and were evenly distributed in terms of sex and racial background. Participants tended to have been diagnosed with HTN for more than a decade [median = 18 years (interquartile range = 16)] and were being treated with the equivalent of approximately five standard doses of antihypertensive medications at the time of enrollment. Target organ damage was uncommon, with only a small subset of participants exhibiting LV hypertrophy (7%). In addition, participants demonstrated moderately high CVD risk, as indicated by elevated Framingham Stroke Risk Scores and atherosclerotic cardiovascular disease risk profiles, with a subset of participants having a history of CVD events, including either cardiac (11%) or cerebrovascular (9%).

Neurocognitive performance

Neurocognitive subtest scores and frequency of impairment based on demographically normative data [43] are presented in Table 2. For the purposes of characterizing neurocognition in the present sample, mean values are presented as well as the frequency of low average, borderline, and impaired performance based on comparison with population norms for individuals of the same age, education, and sex, consistent with clinical practice. Factor analytic results yielded a two-factor solution, with subtest loadings suggesting an executive function factor and a memory factor (Supplemental Table 1, <http://links.lww.com/HJH/B40>). As shown, impairments were most commonly observed on tests of executive function, with 70% of individuals exhibiting at least one impairment and 27% of two or more impairments on tests from the executive function factor. Similarly, a substantial minority of participants also exhibiting impairments in memory, with 37% exhibiting at least one impairment and 20% exhibiting two or more impairments.

Predictors of neurocognitive performance

Examination of individual associations between the executive function factor and vascular function, metabolic function, and aerobic fitness were first examined after adjusting for age. Results revealed that lesser WTH ratio ($\beta = -0.19$, $P = 0.025$), CVRFs ($\beta = -0.21$, $P = 0.030$), and insulin resistance ($\beta = -0.19$, $P = 0.030$), as well as greater microvascular function ($\beta = 0.20$, $P = 0.026$) and aerobic fitness ($\beta = 0.23$, $P = 0.022$) were all associated with better executive function. Similarly, examination of associations with the memory factor revealed that lesser WTH ratio ($\beta = -0.21$, $P = 0.025$) and CVRFs ($\beta = -0.21$, $P = 0.030$), as well as greater microvascular function ($\beta = 0.20$, $P = 0.026$) and aerobic fitness ($\beta = 0.23$, $P = 0.022$) were all associated with better memory performance. Notably, we observed a significant age by insulin resistance interaction ($P = 0.028$) such that greater insulin resistance was unrelated to memory among middle-aged participants ($r = -0.19$, $P = 0.194$ for participants <65 years) but was associated with better memory performance among older participants ($r = 0.36$, $P = 0.016$ for participants ≥ 65 years).

Results from our simple path analyses of executive function and memory are presented in Table 3. As shown, after accounting for all predictors, results suggested that the most robust

associations with executive function were observed for greater aerobic fitness ($\beta = 0.41$, $P < 0.001$), microvascular function ($\beta = 0.17$, $P = 0.030$), and lower CVRFs ($\beta = -0.27$, $P = 0.004$), with a similar nonsignificant trend for insulin resistance ($\beta = -0.16$, $P = 0.074$). Notably, the associations between CVD biomarkers and executive function were comparable or stronger than that observed for age.

Results for memory also are presented in Table 3. As shown, after accounting for all predictors, results suggested that the most robust associations with memory were observed for greater aerobic fitness ($\beta = 0.23$, $P = 0.013$) and better microvascular function ($\beta = 0.22$, $P = 0.011$). Notably, insulin resistance tended to be associated with greater memory performance after accounting for other predictors ($\beta = 0.19$, $P = 0.059$). The associations between CVD biomarkers and memory were comparable or stronger than that observed for both age and family history of dementia. Similar results were found using standard regression approaches (Supplemental Table 1, <http://links.lww.com/HJH/B40>).

DISCUSSION

Results from the current study suggest that neurocognitive impairments are common among individuals with treatment-resistant hypertension, particularly on tests of frontal lobe function, and are associated with multiple markers of CVD and metabolic function. The present findings add to a burgeoning body of evidence suggesting that metabolic dysfunction [44-46] and microvascular disease [47-49] are associated with adverse neurocognitive outcomes among individuals with HTN. In addition, our findings suggest that these early, functional precursors of systemic dysfunction may associate most closely with behavioral indicators of preclinical dysfunction.

The current study adds several important findings to a growing literature linking HTN and neurocognitive impairment. First, this is the first study, to our knowledge, to carefully characterize the pattern and severity of neurocognitive impairments among individuals with treatment-resistant hypertension, despite previous studies suggesting this may be a patient group with elevated risk of neurocognitive impairment [50,51]. Our results indicated that impairments were common, particularly on executive function subtests with greater processing speed requirements. Moreover, more than a third of our participants exhibited at least mild evidence of memory impairment and the average Montreal Cognitive Assessment Battery score fell below the conventionally used cutoff of 26 [52], suggesting that impairments were not solely on more vulnerable executive tests despite a wide age range of participants and more than half of participants (52%) enrolling before age 65.

Our findings also provide the first evidence suggesting that aerobic fitness, microvascular function, and CVRFs may independently contribute to neurocognitive impairments among individuals with treatment-resistant hypertension. Microvascular disease is one of the most commonly observed pathophysiological features among individuals with AD/ADRD [48,49], and has been widely reported among individuals with both Alzheimer's disease and vascular dementia, as well as at-risk adults with either MCI [53] and vascular cognitive impairment, no dementia [54]. CVRFs and HTN in particular have been characterized as the most modifiable risk factor(s) for AD/ADRD [5] and is thought to have

particularly deleterious effects in the presence of obesity [55,56]. Greater aerobic fitness has been widely associated with better neurocognition [17], and has been the primary intervention target of nonpharmacologic prevention trials [57,58]. Although greater fitness associates with lower ADRD risk, surprisingly, increases in fitness from randomized exercise trials show little association with neurocognitive improvements [59,60], leading some to postulate improvements may be better explained by improved insulin sensitivity [44,61,62].

There are several mechanisms linking treatment-resistant hypertension and cognitive impairment. Treatment-resistant hypertension is believed to associate with worse neurocognition through several mechanisms, including arterial stiffening [63-66], hypotensive episodes [67], comorbid left ventricular hypertrophy [68], comorbid chronic kidney disease [69], and even depression [70,71]. Chronic HTN has been shown to worsen arterial function, leading to both central [51] and peripheral target organ damage [69]. In addition, it has been posited that greater BP variability in treatment-resistant hypertension may increase the frequency and severity of hypotension and perfusion deficits, which have been associated with adverse neurocognitive outcomes [72]. Although treatment-resistant hypertension may also associate with neurocognitive impairment through its impact on insulin resistance, this association appears to vary by age and neurocognitive status [13,45,46,73]. Available evidence suggests that while insulin resistance in middle-age confers greater risk of ADRD, peripheral markers of insulin resistance in older adults have been associated with preserved memory performance in some studies, particularly among symptomatic individuals (e.g. MCI) [73]. These seemingly inconsistent findings have been hypothesized to result from central insulin resistance, such that increased peripheral markers of insulin associate with preserve performance in the earlier stages of Alzheimer's disease-related neurocognitive decline.

The current study must be viewed with several limitations in mind. First, our study was cross-sectional and therefore our inference regarding the causal associations between CVD biomarkers and neurocognition is limited. Future intervention studies are necessary to more rigorously examine the potential combined benefits of improving multiple treatment-resistant hypertension mechanisms to preserve neurocognitive function. Second, our study is limited in that our assessments of microvascular and metabolic function were peripheral and would have been improved by complementary neuroimaging assessment. Although our study relied on a relatively novel marker of microvascular endothelial function, this measure has recently gained favor as a peripheral measure of systemic, microvascular function [41,42,74]. In addition, it should be noted that our sample had a higher BMI compared with previously reported cohorts, most likely because of the relatively higher number of African-American participants [75]. Third, our sample size was relatively small, although it is the largest to examine these associations in treatment-resistant hypertension, to our knowledge. Future prospective studies should therefore attempt to replicate the observed pattern of findings in larger patient cohorts.

In conclusion, our study demonstrates that neurocognitive impairments in treatment-resistant hypertension are common and may be associated with multiple CVD biomarkers of vascular, metabolic, and aerobic fitness. If replicated, results may suggest that multicomponent

interventions targeting multiple cerebrovascular risk pathways may be necessary to effectively improve neurocognition and mitigate ADRD risk [76-79]. Future mechanistic studies utilizing more sensitive neuroimaging assessments are also warranted to better delineate potential variations between peripheral and centrally assessed vascular and metabolic mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

AD	Alzheimer's disease
ADDA	Alzheimer's disease and related dementias
CVD	cardiovascular disease
CVLT-II	California verbal learning test, second edition
CVRF	cerebrovascular risk factors
HOMA-IR	homeostatic model assessment of insulin resistance
HTN	hypertension
WTH	wait-to-hip ratio

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TABLE 1.

Background and demographic features of the sample

Variable	
Age (years)	62.7 (8.8)
Female sex	49 (51%)
Race	
Black	56 (57%)
White	36 (37%)
Other	6 (6%)
Years of education	16.1 (2.4)
Fitness/CVD risk factors/vascular function	
Clinic SBP (mmHg)	139.8 (11.0)
Clinic DBP (mmHg)	79.1 (9.7)
Ambulatory SBP (mmHg)	133.7 (12.5)
Ambulatory DBP (mmHg)	71.1 (11.1)
Duration of hypertension, median years (IQR)	18 (16)
Hypertension daily defined dose (unit)	4.4 (2.2)
Left ventricular hypertrophy, <i>n</i> (%)	6 (6%)
Creatinine (mg/dl)	1.1 (0.3)
eGFR (ml/min per 1.73 m ²)	76.5 (18.5)
Insulin (IU/ml)	16.0 (8.3)
Glucose (mg/dl)	108.4 (20.0)
Framingham stroke risk profile	10.1 (3.5)
HOMA-IR	4.4 (2.7)
BMI (kg/m ²)	35.7 (5.6)
Waist-to-hip ratio	0.98 (0.06)
Peak VO ₂ (ml/kg per min)	17.5 (4.4)
Flow-mediated dilation (%)	2.16 (2.5)
Hyperemic reactivity (%)	226 (156)

CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HOMA-IR, homeostatic model assessment of insulin resistance; IQR, interquartile range; VO₂, peak oxygen consumption from exercise treadmill test

TABLE 2.

Neurocognitive performance on individual subtests

Neurocognitive subtest	Mean (SD)	Low average	Borderline	Impaired
Montreal cognitive assessment battery	25.1 (2.5)	-	-	54 (57%)
Stroop color-word (executive function)	32.6 (9.0)	26 (27%)	21 (22%)	1 (1%)
Trail making B, seconds (executive function)	94.2 (51.3)	14 (15%)	4 (4%)	1 (1%)
COWA (executive function)	37.9 (11.0)	12 (13%)	8 (8%)	2 (2%)
Animal naming (executive function)	19.9 (5.4)	7 (7%)	3 (3%)	3 (3%)
Ruff 2 & 7 test (executive function)	225.8 (43.2)	33 (34%)	18 (19%)	1 (1%)
Stroop color (executive function)	61.8 (14.1)	22 (23%)	21 (22%)	18 (19%)
Stroop word (executive function)	87.6 (15.3)	26 (27%)	21 (22%)	21 (22%)
Trail making A, seconds (executive function)	39.6 (15.2)	21 (22%)	5 (5%)	5 (5%)
Digit symbol substitution test (executive function)	58.0 (14.1)	14 (15%)	10 (10%)	9 (9%)
Digit span (executive function)	16.4 (3.8)	10 (10%)	10 (10%)	5 (5%)
CVLT total learning (memory)	43.9 (9.1)	10 (10%)	7 (7%)	1 (1%)
CVLT immediate recall (memory)	8.8 (3.1)	15 (16%)	5 (5%)	3 (3%)
CVLT delayed recall (memory)	9.7 (3.2)	8 (8%)	8 (8%)	3 (3%)
BVMT total learning (memory)	23.7 (7.1)	6 (6%)	9 (9%)	5 (5%)
BVMT total recall (memory)	9.0 (2.7)	5 (5%)	7 (7%)	6 (6%)

Low average (9–23%), borderline (2–8%), or impaired (<1%) performance is defined as test performance compared with demographically-corrected normative data, based on age, education, sex, and race. BVMT, Benton Visual Memory Test; COWA, controlled oral word association test; CVLT, California verbal learning test.

TABLE 3.

Results from individual path analyses for executive function and memory

Predictor	Executive function	Memory
Age	−0.28 *	−0.19 **
Education	0.15 **	0.04
Race	−0.19 *	−0.30 ***
Family history of AD	−0.07	−0.21 *
Waist-to-hip ratio	−0.04	−0.13
BMI	0.07	0.04
Framingham stroke risk profile	−0.27 ***	−0.15 **
HOMA-IR	−0.16 **	0.19 **
Hyperemic response (%)	0.17 *	0.22 *
Peak oxygen consumption	0.41 ***	0.23 *

Predictors of interest included waist-to-hip ratio (WTH), stroke risk factors (FSRP), insulin sensitivity (HOMA), microvascular function, and aerobic fitness. Both analyses accounted for age, education, race, gender, and family history of dementia. AD, Alzheimer's disease; HOMA-IR, homeostatic model assessment of insulin resistance.

* $P < 0.05$.

** $P < 0.10$.

*** $P < 0.01$.