Arterial Pulse Wave Velocity and Cognition With Advancing Age

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Abstract—We hypothesized that carotid-femoral pulse wave velocity (PWV), a marker of arterial stiffness, interacts with age such that the magnitude of associations between PWV and cognitive performance are greater with increasing age and that this interaction is observed despite adjustments for demographic variables, mean arterial pressure, and cardiovascular risk factors. PWV was estimated using applanation tonometry in 409 dementia- and stroke-free participants of the Maine-Syracuse Longitudinal Study (24 to 92 years of age; 62.3% women). Using linear regression analyses in a cross-sectional design, associations between PWV and age and the interaction of PWV and age were examined in relation to a global composite score, the Wechsler Adult Intelligence Scale Similarities test (abstract reasoning), and 4 cognitive domains indexed by multiple cognitive measures. Adjusting for age, gender, education, height, weight, heart rate, mean arterial pressure, and antihypertensive treatment, PWV-by-age interactions were obtained for the global, visual-spatial organization and memory, scanning and tracking, and verbal episodic memory composites, as well as similarities. The combination of higher PWV and age resulted in progressively lower cognitive performance. This finding was the same with an extended model, which also included adjustment for cardiovascular risk factors and other confounds. PWV interacts with age in a multiplicative way to exert a negative influence on cognitive performance level. Early interventions to prevent an increase in arterial stiffness could possibly play an important role in the preservation of cognitive ability. **(*Hypertension*. 2009;53:668-673.)**

Key Words: pulse wave velocity ■ hypertension ■ age ■ cognitive performance ■ cognitive functioning ■ cognition ■ blood pressure

Hypertension is a risk factor for lowered cognitive performance and dementia.[1,2] In cross-sectional, prospective, and longitudinal studies, inverse associations between blood pressure (BP) and cognitive performance level are observed over a wide range of systolic, diastolic, and mean arterial BP (MAP) levels.[3–7] Many hypertension-related changes in the brain have been identified and posited as the mechanisms underlying relations between BP and cognition.[1,2,8]

Investigations of BP-by-age interactions have been driven by a long-standing hypothesis that age- and hypertension-associated changes in brain structure and function interact and, therefore, the magnitude of associations between BP and cognition will be higher in older rather than in younger individuals.[9] Reviews of the literature indicate little in the way of consistent support for this hypothesis.[2,8,10] Cross-sectional studies report either no interactions of age with BP or interactions in the opposite direction, such that systolic, diastolic, and MAP are more strongly related to cognition in younger rather than in middle-aged adults.[2,8,10]

There is evidence that disproportionately poorer cognitive performance in older rather than in younger persons would be observed with measures of arterial stiffness as the independent variable. In a study relating baseline BP to cognitive performance followed over 30 years, the rate of BP-associated longitudinal decline in fluid ability was similar for older and younger adults when systolic, diastolic, and MAP at baseline were the predictor variables.[7] However, higher baseline pulse pressure (PP), an index of arterial stiffness, was associated with longitudinal decline in cognitive performance for older adults but not for younger adults. This finding may reflect the fact that arterial stiffening is strongly related to advancing age.[11] If so, carotid-femoral pulse wave velocity (PWV), which is a more direct measure of arterial stiffness than PP,[11] should also show a higher magnitude of association with cognition in older rather than in younger adult cohorts.

Our hypothesis that arterial stiffness interacts with age gains support from the Baltimore Longitudinal Study[12] in which PWV, adjusted for other cardiovascular risk factors

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(including MAP) and confounds, was associated with more accelerated cognitive decline with advancing age. In the Rotterdam Study, PWV, adjusted for MAP and other cardiovascular risk factors, was not associated with longitudinal cognitive decline or dementia,[13] although higher PWV was related to poorer cognitive performance at baseline. Previous cross-sectional studies have related PWV to cognition for only a few cognitive measures[14–16] and, with the exception of a study with the Mini-Mental State Examination,[17] have not examined PWV by age interactions.

Two major objectives of our study were to determine whether relations between PWV and cognition are disproportionately larger for older rather than younger cohorts with adjustment for cardiovascular risk factors, other potential confounds, and MAP and to use our large battery of cognitive tests to identify which cognitive domains are associated with PWV. We advanced the following hypotheses with respect to community-based adults free from stroke and dementia: (1) PWV will interact with age-cohort membership such that the magnitude of association between PWV and cognitive performance will be larger as chronological age increases; (2) these associations will be observed for multiple domains of cognitive performance; and (3) these associations will remain despite adjustment for MAP, hypertension-associated cardiovascular risk factors, and other confounds.

Methods

Participants

The community-based sample was composed of participants, ranging in age from 24 to 92 years, in the seventh wave of testing of the Maine-Syracuse Longitudinal Study. The Maine-Syracuse Longitudinal Study, initiated in 1975, uses a time-lagged sample of men and women in 5 cohorts defined by time of entry into the study. Recruitment and data collection procedures for the Maine-Syracuse Longitudinal Study have been described in detail.[18] Of the 436 participants for whom PWV data have been obtained at wave 7, subjects were excluded in the following sequence: (1) dementia (n=3); (2) prevalent stroke (n=5); (3) inability to read test material (n=1); and (4) PWV error of estimate >0.20 (n=18). Persons with stroke history and dementia were excluded from the study, because we were interested in examining PWV and cognitive performance in persons who performed in the normal range of cognitive ability. The clinical diagnosis of dementia was determined from cognitive data, self-report, and medical charts, using the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria.[19] Prevalent stroke, defined as a focal neurological deficit of acute onset persisting for >24 hours, was based on self-report and record review (with permission), confirmed by hospitalization, treatment for stroke, or both. The characteristics of the final sample (N=409) are presented in Table 1.

Procedure

Participants completed the Center for Epidemiological Studies Depression Scale[20] and the Spielberger Trait Anxiety Scale[21] within a week of neuropsychological testing. They were admitted to the study center on the day of neuropsychological testing after a fast from midnight. A blood sample was drawn, brachial BP measures were obtained, and the pulse wave assessment was conducted. A light breakfast, including decaffeinated coffee or tea, was served. Breakfast was followed by a physical examination and neuropsychological testing.

The University of Maine Institutional Review Board approved this investigation. Informed consent for data collection was obtained from all of the participants.

Table 1. Sample Characteristics

Variable	Mean or %	SD	PWV *r**	Age *r**
Age, y	61.3	12.8	0.52†	
Education, y	14.6	2.8	−0.06	0.04
PWV, m/s	10.2	2.8		0.52†
Brachial MAP, mm Hg	94.6	12.0	0.33†	0.01
Brachial systolic pressure, mm Hg	128.9	19.7	0.53†	0.26†
Brachial diastolic pressure, mm Hg	77.5	10.1	0.08	−0.23†
Heart rate, bpm	60.2	9.3	0.19†	−0.07
Alcohol, oz/wk	1.4	2.4	−0.01	−0.02
Cigarettes, per wk	8.3	36.7	−0.01	−0.13†
Height, cm	167.7	9.9	0.04	−0.16†
Weight, kg	82.6	19.3	0.06	−0.31†
Body mass index, kg/m^2	29.3	6.0	0.05	−0.27†
Total cholesterol, mmol/L	4.87	1.02	−0.08	0.08
Creatinine, μmol/L	91.94	19.45	−0.20†	−0.06
Plasma homocysteine, μmol/L	9.9	3.4	0.28†	0.29†
Trait anxiety, total score	20.6	2.7	−0.12‡	−0.15†
Female, %	62.3		−0.13‡	−0.05
White, %	79.5		0.10‡	0.44†
On antihypertensive medications, %	49.9		0.30†	0.24†
Obese, %	36.7		0.08	−0.23†
Depressed mood, %	13.8		−0.12‡	−0.22†
Smoker, %	9.8		−0.03	−0.22†
Cardiovascular disease, %	11.7		0.31†	0.26†
Diabetes mellitus, %	13.9		0.30†	0.03
Apoe-ϵ4, %	29.4		−0.00	−0.03

*Correlation coefficient.
†$P<0.01$.
‡$P<0.05$.

BP and Pulse Wave Assessment

Brachial artery pressures were measured using the traditional pressure-cuff method with a Critikon Dinamap ProCare 100 (oscillometric method). All of the precautions, training, and procedures in BP measurement recommended by the committee report, blood pressure publication guidelines,[22] were observed. In accordance with the procedure at previous Maine-Syracuse Longitudinal Study waves, after 10 minutes of supine rest, 5 brachial BP measurements were taken in the supine, standing, and sitting positions.

PWV was assessed noninvasively in a supine position, using the SphygmoCor system (AtCor Medical) with applanation tonometry. Carotid-femoral path length was measured as the difference between the surface distances joining the suprasternal notch, the umbilicus, and the femoral pulse, as well as the suprasternal notch and the carotid pulse. Carotid-femoral transit time was estimated in 8 to 10 sequential ECG-gated femoral and carotid waveforms as the average time difference between the onset of the femoral and carotid waveforms. The foot of the pulse wave was identified using the intersecting tangent method. PWV was calculated as the carotid-femoral path length divided by the carotid-femoral transit time.[23] This is a noninvasive and reproducible method to determine arterial stiffness.[11]

Neuropsychological Battery

We used the similarities test from the Wechsler Adult Intelligence Scale and 4 composite scores representing relatively independent

cognitive domains identified from previously published principal components and orthogonal rotation analyses of the Maine-Syracuse Neuropsychological Test Battery described previously[18] and in Table S1 (please see http://hyper.ahajournals.org). The composite scores follow with their constituent tests in parentheses: (1) visual-spatial organization and memory (block design, object assembly, visual reproductions immediate and delayed, Hooper Visual Organization Test, and matrix reasoning); (2) scanning and tracking (Trail Making Tests A and B, digit symbol substitution, and symbol search); (3) verbal episodic memory (logical memory immediate and delayed and Hopkins Verbal Learning Test); and (4) working memory (digit span forward and backward, letter-number sequence, and controlled oral word associations). The similarities test was treated as a separate test because it loaded significantly on multiple composite scores in the factor analysis. The results of the previous factor analysis were confirmed for the present sample.

Individual test scores and composite scores were transformed to z scores by subtracting the mean from each score in the sample distribution and dividing by the sample SD. This linear transformation results in a mean of 0 and an SD of 1.00 for each test and enables expression of regression coefficients for the cognitive measures in terms of SD units. In addition to scores derived from factor analysis, a global composite score was calculated by obtaining the average of z scores (standardized scores) for all of the individual tests. All of the individual tests making up the composites have the same weights, ie, each composite is the sum of the z scores for its individual measures divided by the number of tests and then restandardized to z scores.

Independent Variable and Covariates

The independent variable was PWV. The initial set of covariates included age (years), education (years), gender, height (centimeters), weight (kilograms), heart rate (beats per minute), antihypertensive drug treatment (yes/no), and MAP (millimeters of mercury). Height and weight were used instead of body mass index because it is essential to adjust for height when assessing PWV.[24] MAP was calculated as diastolic BP+1/3 (systolic BP−diastolic BP). Additional covariates were as follows: race/ethnicity (white versus not white), diabetes mellitus, apolipoprotein E (ApoE) genotype (1 or 2 ApoE-ε4 alleles versus no ApoE-ε4 alleles), creatinine (micromoles per liter, reciprocal), total cholesterol (millimoles per liter), depressed mood, trait anxiety, number of cigarettes per week, history of cardiovascular disease, total plasma homocysteine (micromoles per liter), and the number of neuropsychological examinations before wave 7. Diabetes mellitus was defined by treatment with insulin, oral antidiabetic agents, or by fasting glucose level of ≥7 mmol/L. Eight participants who failed to fast were also classified as diabetic, because their plasma glucose levels were >11 mmol/L. Standard ApoE genotyping used PCR and restriction enzyme digest with *Hha*I.[25] The reciprocal of serum creatinine (micromoles per liter), used as an index of kidney function,[26] was used to normalize its distribution. Plasma homocysteine (micromoles per liter), total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol assays were performed as described previously.[18] Smoking was defined by self-report of the number of cigarettes smoked per week.

Using the Framingham Study criteria,[5] the cardiovascular disease event variable was defined by the presence of any of the following: myocardial infarction (3.9%), coronary artery disease (7.1%), congestive heart failure (1.2%), angina pectoris (4.9%), or transient ischemic attack (2.0%). Depressed mood was used as a categorical variable (Center for Epidemiological Studies Depression Scale ≤16 versus Center for Epidemiological Studies Depression Scale >16 points), because there was a significant skew in Center for Epidemiological Studies Depression Scale scores, and we wished to use a clinically recognized criterion for depressed mood.[27] To be included as a covariate, variables were required to meet 1 of 2 criteria: identified as important based on the PWV or cognitive performance literature or related significantly ($P<0.05$) to PWV and/or 1 or more cognitive performance measures.

Table 2. Regression Coefficients (β) and SEs (seβ) for the PWV×Age Interactions

	Extended Model*	
Composite/Test	β	seβ
Global composite	−0.0037†	0.0012
Visual-spatial organization and memory	−0.0038†	0.0013
Verbal episodic memory	−0.0037†	0.0014
Working memory	−0.0009	0.0015
Scanning and tracking	−0.0035‡	0.0012
Similarities	−0.0034‡	0.0014

*Extended model indicates age, education, sex, height, weight, heart rate, brachial MAP, antihypertensive medications, reciprocal creatinine, trait anxiety, depressed mood, diabetes mellitus, cardiovascular disease, number of previous exams, race/ethnicity, total cholesterol, cigarettes per week, ApoE genotype, homocysteine, PWV, and PWV×age.

†$P<0.01$.

‡$P<0.05$.

Statistical Analysis Plan

Two linear regression models were used. The PWV main effect term and the PWV-by-age interaction term were used in each model. Age and PWV were continuously distributed variables and, thus, the interaction term was the PWV-by-age product vector.[28] The initial model was as follows: PWV+(PWV×age)+age+education+sex+height+weight+heart rate+MAP+antihypertensive medication use. The extended model was as follows: initial model variables+race/ethnicity+diabetes mellitus+cardiovascular disease+reciprocal creatinine+depressed mood+trait anxiety+cigarettes per week+total cholesterol+homocysteine+number of previous exams+ApoE genotype. Interaction terms involving sex and the quadratic trend component for PWV were tested separately for all of the models.

Results

Table 1 summarizes the demographic and health characteristics of the sample and their correlations with PWV and age in years. With a few exceptions, these variables correlated significantly either with PWV or age.

The pattern of significant results for all of the analyses relating PWV and PWV×age to cognitive performance was exactly the same for the initial and extended regression models, and, thus, we report findings for the extended model only. Increments of PWV (1 m/s) were inversely and significantly related to the scanning and tracking composite score ($\beta=-.0468$; SE=0.0183; $P<0.01$). Thus, a 5-m/s increment in PWV was related to a 0.23-SD decrement in cognitive performance. Age was related to all of the outcome measures for the extended model (please see Table S2). However, main-effect findings must be qualified, given the finding of numerous PWV-by-age interactions.

Table 2 displays the regression coefficients and SEs for the tests of the PWV×age interaction. A statistically significant interaction was observed for the global composite, the visual-spatial memory and organization composite, the scanning and tracking composite, the verbal episodic memory composite, and the similarities test. The PWV×age interaction was not significant ($P>0.05$) for the working memory composite.

The effect of the PWV×age interactions on cognitive performance is illustrated in 3D plots using the global and scanning and tracking composite scores as outcome measures (Figures 1 and 2). Age (older to younger) and PWV (higher

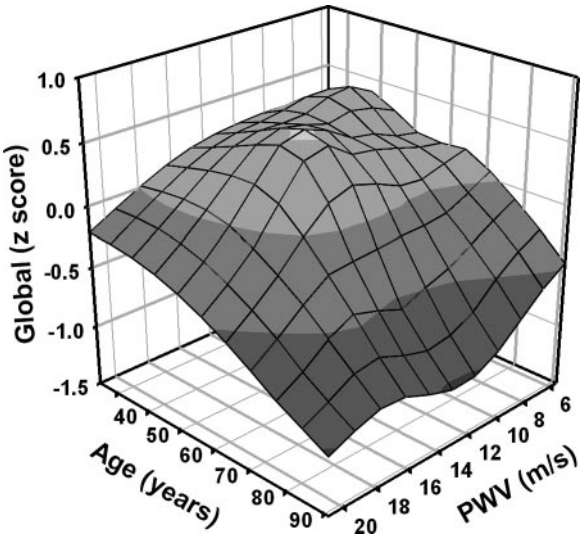

Figure 1. 3D plot showing the interaction of PWV and age in relation to the global composite cognitive score for the extended regression model.

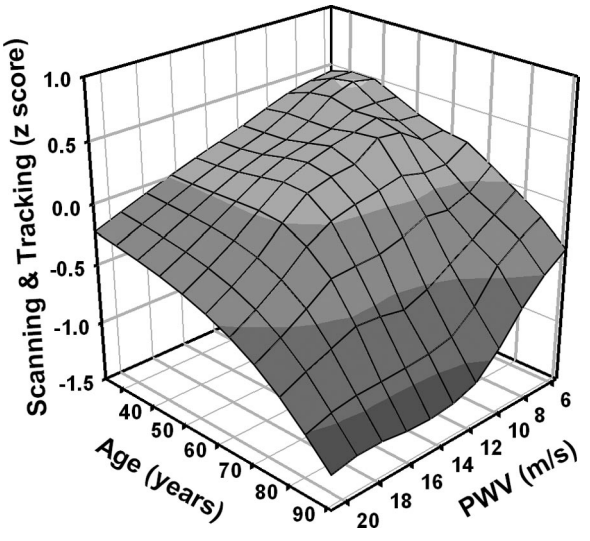

Figure 2. 3D plot showing the interaction of PWV and age in relation to the scanning and tracking composite score for the extended regression model.

to lower) are represented on the horizontal axes, and the residual *z* scores for cognitive performance (lower to higher) are shown on the vertical axis. The combination of older age and higher PWV, shown in the foreground, is associated with the lowest level of cognitive performance, whereas lower age and PWV are associated with better performance.

Five additional planned analyses were performed: (1) MAP and antihypertensive medications were dropped as covariates from the initial model; (2) participants who were excluded from the primary analyses because their PWV error of estimate was >0.20 (n=18) were included; (3) a second medication covariate that contrasted persons taking medications with vasodilating properties (n=160) with persons not taking any of these medications (n=249) was included in the models; (4) lipid measures were substituted for total cholesterol; and (5) low (estimated glomerular filtration rate <60 mil/min per 1.73^2) versus high (estimated glomerular filtration rate ≥60 mil/min per 1.73 m^2) estimated glomerular filtration rate was substituted for the reciprocal of creatinine as the index of renal function. Results for each of these additional analyses were the same as those obtained with the 2 primary models.

Finally, 2 a posteriori analyses were done. First, waist circumference was substituted for weight to evaluate the potential effect of bias related to overweight and central obesity, which may result in a systematic overestimation of a carotid-femoral transit length and, consequently, PWV. Results were the same, indicating that no systematic bias was introduced by differences in central adiposity. Second, a formula recommended for avoiding underestimation of mean pressure at the upper arm, diastolic BP+0.40 (PP),[29] was substituted for the diastolic BP+0.33 (PP) formula used in the primary analysis. Results were unaltered by this substitution.

Plots of the residuals, inspection of the data, and tests of quadratic trend (with adjustment for the linear component) indicated that the best fit was obtained with the linear regression terms used in the analyses above. For all of the cognitive variables, quadratic PWV main effect and interaction trends were not significant. No statistically significant gender×PWV or gender×PWV×age interactions were observed for any of the cognitive measures (*P* value range across measures and models=0.12 to 0.38).

Tabled results for PWV main effects, age, and PWV×age interactions for the individual cognitive tests are shown in Tables S3 and S4. The PWV×age results for all of the individual measures composing the spanning and tracking, visual-spatial organization and memory, and verbal episodic memory composites were consistent in that the interactions were either statistically significant or showed regression coefficients consistent in sign with those obtained for the composite score.

Discussion

As hypothesized, the inverse association between PWV and cognition increased in magnitude as a function of age. This was true despite adjustment for the extended-model covariate set, which included age, height, weight, education, heart rate, antihypertensive drug treatment, cardiovascular risk factors, MAP, and other confounds, including anxiety and depressed mood.

The relations among PWV, age, and cognition in our cross-sectional study support results in 2 longitudinal studies where age was defined as change over time. Scuteri et al[17] found that higher PWV was related to decline on the Mini-Mental State Examination after a median follow-up of 12 months for persons who had memory deficits at baseline. Waldstein et al[12] reported that persons with higher PWV at baseline exhibited an accelerated decline over time (ie, with aging) on tests of verbal and nonverbal learning, memory, and concentration. Findings in our cross-sectional study are consistent with findings in these longitudinal studies in so far as the decrement in performance associated with PWV increases with increasing chronological age. It is important to see this consistency between cross-sectional findings and longitudinal findings when measures of arterial stiffness are used

as the predictor variable. Moreover, our data are consistent with the classic hypothesis that age- and hypertension-associated changes in brain structure and function interact, and, therefore, the magnitude of associations between BP and cognition will be higher in older rather than in younger adults,[9] a prediction that has largely failed to gain consistent support from cross-sectional aging studies using brachial diastolic and/or systolic BP as a measure of hypertension.[8,10] The consistency of our findings with this hypothesis may be related to the fact that PWV is the gold standard for noninvasive estimation of arterial stiffness, an integrative marker of arterial function, and that arterial stiffness contributes significantly to the progressive decline in cognitive performance with advancing age.

In the Rotterdam Study,[13] PWV was inversely related to performance on the Mini-Mental State Examination, Word Fluency Test, and Stroop Color Test at baseline with adjustment for demographic factors. These associations were attenuated by adjustment, first, for MAP and heart rate, and with further adjustment for additional cardiovascular risk factors, remaining significant only for the Stroop Color Test. However, PWV was not associated with change over time on any of the cognitive measures used between baseline and a second measurement. As suggested by the Rotterdam investigators, regression to the mean and selection bias through participant attrition could explain the negative longitudinal findings, because the individuals who underwent serial cognitive measurements manifested less cardiovascular disease and had lower levels of arterial stiffness than those who did not participate in follow-up measurements. In addition, it is possible that statistical control for carotid intima-media thickness, a marker of subclinical atherosclerosis, in the Rotterdam Study may explain the negative findings, although this is unlikely given the many other changes in the central arteries related to PWV.[30] Despite limitations of our cross-sectional analyses, regression to the mean and loss to follow-up are not issues affecting cross-sectional results.

Our composite scores may be viewed as theoretically relevant constructs representing domains of cognitive performance, as indexed by multiple individual clinical cognitive tests. Regardless of the statistical model used, we found that the combination of higher age and higher PWV was associated with poorer performance on the global, visual spatial organization and memory, verbal episodic memory, and scanning and tracking composites and for the similarities (abstract reasoning) test. It is not clear why working memory was not associated with the interaction term (PWV×age) other than the possibility that the clinical tests chosen to index working memory were low in task difficulty for our relatively highly educated sample.

Taken as a whole, the pattern of results suggests that arterial stiffness influences multiple brain areas. This hypothesis can only be tested adequately in a study involving cognitive assessment in conjunction with neuroimaging and/or cerebral blood flow studies. However, the hypothesis of a diffuse effect of central arterial stiffness on brain structure and function and, hence, a broad range of cognitive abilities, is consistent with functional and structural changes associated with arterial stiffness. Arterial stiffness plays an important role in atherosclerosis in large and small vessels.[31–33] Arterial stiffness promotes microvascular and macrovascular disease, including impaired cerebral perfusion,[30,34] endothelial dysfunction and NO deficiency,[30,34–36] lacunar infarctions, and cerebral white matter lesions.[37]

Study Limitations and Strengths

Our participants were relatively well-educated, but education is protective of cognitive performance,[38] and, thus, higher education should lead to an underestimation of the relation between PWV and cognition. Our design is cross-sectional, with all of the inherent limitations of conclusions about causality of associations.

Strengths of the study include the use of a community-based sample, the inclusion of theoretically relevant cognitive domains indexed by multiple clinical tests, and adjustment of PWV-cognition relations for multiple cardiovascular risk factors, including MAP.

Perspectives

Arterial stiffness becomes more prevalent with advancing age, and increasing numbers of adults are surviving into old age. These dynamics make arterial stiffness–related attributable risk for lowered cognitive performance an important health concern. Evidence suggests that antihypertensive drug treatment, aerobic exercise, dietary modification, caloric restriction, weight loss, and sodium restriction may be particularly effective interventions with regard to preventing or slowing the progression of arterial stiffening.[39,40] Whether these interventions also lead concomitantly to slower cognitive decline with aging needs further investigation.

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Disclosures

None.

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Short Title: Pulse Wave Velocity, Age, and Cognition

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S1. Descriptions of the cognitive tests used to define (index) the composite scores*

Composite / Tests	Cognitive Ability Measured
Visual-Spatial Organization/Memory	
Visual Reproductions-Immediate Recall†	Immediate recall, visual memory, and visual-spatial problem solving
Visual Reproductions-Delayed Recall†	Delayed recall, visual memory and visual-spatial problem solving
Matrix Reasoning†	Abstract reasoning and pattern recognition
Block Design§	Visual-spatial perception, organization and construction
Object Assembly§	Speed of visual-spatial organization
Hooper Visual Organization	Visual-spatial organization; some demands on executive function
Verbal Episodic Memory	.
Logical Memory-Immediate Recall†	Immediate memory, verbal
Logical Memory-Delayed Recall†	Delayed memory, verbal
Hopkins Verbal Learning Test	Verbal learning and memory
Working Memory	
Digit Span Forward§	Attention and concentration
Digit Span Backward§	Attention, concentration, and working memory
Letter-Number Sequence‡	Information processing while holding information in memory
Controlled Oral Word Associations	Verbal fluency and executive functioning
Scanning and Tracking	
Trail Making A‖	Visual scanning and tracking; concentration and attention
Trail Making B‖	Trails A plus demands on executive function abilities
Digit Symbol Substitution§	Psychomotor performance
Symbol Search‡	Visual processing speed
Similarities	Verbal intelligence and abstract reasoning

*The tests employed in each composite score/domain define the abilities measured by that domain. All tests within the composite are assigned equal weights based on z scores. Test composites are obtained by adding the z scores, dividing by the number of tests, and then re-standardizing to z scores, mean= 0; SD= 1.
†Origin Wechsler Memory Scale-Revised
‡Origin Wechsler Adult Intelligence Scale III
§Origin Wechsler Adult Intelligence Scale
‖Origin Halstead-Reitan Neuropsychological Test Battery

S2. Regression coefficients and standard errors describing associations between age and cognitive performance.

Composite/Test	Initial Model*		Extended Model†‡	
	β	seβ	β	seβ
Global Composite	-.0237‡	.0043	-.0416‡	.0042
Visual-Spatial Organization and Memory	-.0223‡	.0045	-.0385‡	.0045
Verbal Episodic Memory	-.0223‡	.0047	-.0385‡	.0051
Working Memory	-.0102§	.0049	-.0217‡	.0055
Scanning and Tracking	-.0273‡	.0042	-.0416‡	.0044
Similarities	-.0000	.0049	-.0179‡	.0052

*Initial Model = Age, Education, Gender, Height, Weight, Heart Rate, MAP, Antihypertensive medications, PWV, PWV X Age.
†Extended Model = Age, Education, Gender, Height, Weight, Heart Rate, MAP, Antihypertensive medications, Reciprocal Creatinine, Trait Anxiety, Depressed Mood, Diabetes Mellitus, CVD, Number of Prior Exams, Race/Ethnicity, Total Cholesterol, Cigarette/Week, ApoE genotype, Homocysteine, PWV, PWV X Age.
‡$p < .001$
§$p < .05$

S3. Individual Tests. Regression coefficients (β) and standard errors (seβ) for PWV and Age main effects and PWV x Age interactions for individual test scores (z-scores) organized by the composite scores that they index (Initial regression model*)

Composite/Test		PWV	Age	PWV x Age
Visual-Spatial Organization and Memory				
Block Design	β	-.0173	-.0168†	-.0039†
	seβ	.0211	.0048	.0014
Object Assembly	β	.0202	-.0201‡	-.0054‡
	seβ	.0220	.0050	.0015
Visual Reproductions – Immediate	β	-.0381	-.0176‡	-.0035§
	seβ	.0206	.0047	.0014
Visual Reproductions – Delayed	β	-.0519§	-.0247‡	-.0038†
	seβ	.0198	.0045	.0014
Hooper Visual Organization Test	β	-.0378	-.0174†	-.0049†
	seβ	.0212	.0048	.0014
Matrix Reasoning	β	-.0296	-.0107§	-.0054†
	seβ	.0120	.0048	.0014
Verbal Episodic Memory				
Logical Memory – Immediate	β	-.0044	-.0169†	-.0045†
	seβ	.0214	.0049	.0015
Logical Memory – Delayed	β	-.0104	-.0195‡	-.0033§
	seβ	.0212	.0048	.0015
Hopkins Verbal Learning Test	β	-.0004	-.0233‡	-.0040†
	seβ	.0210	.0048	.0015
Working Memory				
Digit Span Forward	β	.0048	-.0028	.0004
	seβ	.0230	.0053	.0016
Digit Span Backward	β	-.0089	.0012	.0003
	seβ	.0225	.0052	.0016
Controlled Oral Word Associations	β	-.0170	-.0087	-.0026
	seβ	.0218	.0050	.0015
Number-Letter Sequencing	β	-.0168	.0206‡	-.0034§
	seβ	.0212	.0048	.0015
Scanning and Tracking				
Digit Symbol	β	-.0348	-.0264‡	-.0029§
	seβ	.0189	.0043	.0013
Trail Making A	β	-.0650†	-.0170‡	-.0051‡
	seβ	.0208	.0048	.0014
Trail Making B	β	-.0758‡	-.0154†	-.0060‡
	seβ	.0207	.0047	.0014
Symbol Search	β	-.0353	-.0260‡	-.0044†
	seβ	.0202	.0046	.0014

*Initial Model = Age, Education, Gender, Height, Weight, Heart Rate, MAP, Anti-hypertensive Medications, PWV, PWV x Age
†$p < .01$
‡$p < .001$
§$p < .05$

S4. Individual Tests. Regression coefficients (β) and standard errors (seβ) for PWV and Age main effects and PWV x Age interactions for individual test scores (z-scores) organized by the composite scores that they index (Extended regression model*)

Composite/Test		PWV	Age	PWV x Age
Visual-Spatial Organization and Memory				
Block Design	β	-.0080	-.0291†	-.0019
	seβ	.0220	.0052	.0015
Object Assembly	β	.0245	-.0039†	-.0031‡
	seβ	.0223	.0053	.0015
Visual Reproductions – Immediate	β	-.0190	-.0321†	-.0019
	seβ	.0215	.0051	.0014
Visual Reproductions – Delayed	β	-.0447‡	-.0329†	-.0030‡
	seβ	.0212	.0051	.0014
Hooper Visual Organization Test	β	-.0122	-.0311†	-.0036‡
	seβ	.0223	.0053	.0015
Matrix Reasoning	β	-.0320	-.0268†	-.0039§
	seβ	.0210	.0050	.0014
Verbal Episodic Memory				
Logical Memory – Immediate	β	.0160	-.0308†	-.0041§
	seβ	.0258	.0055	.0015
Logical Memory – Delayed	β	.0174	-.0345†	-.0024
	seβ	.0227	.0054	.0015
Hopkins Verbal Learning Test	β	.0054	-.0375†	-.0032‡
	seβ	.0219	.0052	.0015
Working Memory				
Digit Span Forward	β	.0127	-.0086	.0011
	seβ	.0254	.0061	.0017
Digit Span Backward	β	.0092	-.0057	.0006
	seβ	.0244	.0058	.0017
Controlled Oral Word Associations	β	-.0051	-.0176§	-.0021
	seβ	.0246	.0059	.0016
Number-Letter Sequencing	β	-.0153	-.0337†	-.0024
	seβ	.0221	.0053	.0015
Scanning and Tracking				
Digit Symbol	β	-.0284	-.0395†	-.0019
	seβ	.0198	.0047	.0013
Trail Making A	β	-.0578§	-.0340†	-.0028‡
	seβ	-.0210	.0050	.0014
Trail Making B	β	-.0541§	-.0342†	-.0035‡
	seβ	.0207	.0049	.0014
Symbol Search	β	-.0343	-.0374†	-.0029‡
	seβ	.0205	.0049	.0014

*Extended Model = Age, Education, Gender, Height, Weight, Heart Rate, MAP, Anti-hypertensive Medications, Creatinine (reciprocal), Depressed Mood, Trait Anxiety, Diabetes Mellitus, CVD, Number of Prior Exams, Race/Ethnicity, Total Cholesterol, Cigarettes/Day, APOE Genotype, Homocysteine, PWV, PWV x Age

†$p < .001$

‡$p < .05$

§$p < .01$