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## Arterial Pulse Wave Velocity and Cognition with Advancing Age

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### Abstract

We hypothesized that carotid-femoral pulse wave velocity, a marker of arterial stiffness, interacts with age such that the magnitude of associations between pulse wave velocity 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. Pulse wave velocity 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 pulse wave velocity, age, and the interaction of pulse wave velocity and age were examined in relation to a Global composite score, the Wechsler Adult Intelligence Scale Similarities test (abstract reasoning) and four cognitive domains indexed by multiple cognitive measures. Adjusting for age, gender, education, height, weight, heart rate, mean arterial pressure, and antihypertensive treatment, pulse wave velocity by age interactions were obtained for the Global, Visual-Spatial Organization and Memory, Scanning and Tracking, and Verbal Episodic Memory composites, and Similarities. The combination of higher pulse wave velocity 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. Pulse wave velocity 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 preservation of cognitive ability.

### Keywords

pulse wave velocity; hypertension; age; cognitive performance; cognitive functioning; cognition; blood pressure

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Hypertension is a risk factor for lowered cognitive performance and dementia.<sup>1,2</sup> 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

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mean arterial BP levels.<sup>3–7</sup> Many hypertension-related changes in the brain have been identified and posited as the mechanisms underlying relations between BP and cognition.<sup>1,2,8</sup> Investigations of BP by age interactions have been driven by a longstanding 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 than younger individuals.<sup>9</sup> Reviews of the literature indicate little in the way of consistent support for this hypothesis.<sup>2,8,10</sup> Cross-sectional studies report either no interactions of age with BP or interactions in the opposite direction, such that systolic, diastolic, and mean arterial BP are more strongly related to cognition in younger than middle-aged adults.<sup>2,8,10</sup>

There is evidence that disproportionately poorer cognitive performance in older than 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 mean arterial BP (MAP) at baseline were the predictor variables.<sup>7</sup> 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.<sup>11</sup> If so, carotid-femoral pulse wave velocity (PWV), which is a more direct measure of arterial stiffness than PP,<sup>11</sup> should also show a higher magnitude of association with cognition in older than younger adult cohorts.

Our hypothesis that arterial stiffness interacts with age gains support from the Baltimore Longitudinal Study<sup>12</sup> in which PWV, adjusted for other cardiovascular risk factors (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,<sup>13</sup> 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<sup>14–16</sup> and, with the exception of a study with the Mini Mental State Examination (MMSE),<sup>17</sup> have not examined PWV by age interactions.

Two major objectives of our study were: (1) to determine whether relations between PWV and cognition are disproportionately larger for older than younger cohorts with adjustment for cardiovascular risk factors, other potential confounds, and MAP; and (2) 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 (MSLS). The MSLS, initiated in 1975, employs a time-lagged sample of men and women in five cohorts defined by time of entry into the study. Recruitment and data collection procedures for the MSLS have been described in detail.<sup>18</sup> 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

>.20 (n=18). Persons with stroke history and dementia were excluded from the study as 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 records, using the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.<sup>19</sup> Prevalent stroke, defined as a focal neurological deficit of acute onset persisting more than 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 (CES-D)<sup>20</sup> and the Spielberger Trait Anxiety scale<sup>21</sup> within a week of neuropsychological testing. They were admitted to the study center on the day of neuropsychological testing following a fast from midnight. A blood sample was drawn, brachial BP measures were obtained, and the pulse wave assessment 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 approved this investigation. Informed consent for data collection was obtained from all participants.

## Blood pressure and pulse wave assessment

Brachial artery pressures were measured using the traditional pressure-cuff method with a Critikon Dinamap ProCare 100 (oscillometric method). All precautions, training and procedures in BP measurement recommended by the Committee Report: Blood Pressure Publication Guidelines<sup>22</sup> were observed. In accordance with the procedure at previous MSLS waves, following 10 minutes of supine rest, five 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, Sydney, Australia) using applanation tonometry. Carotid-femoral path length was measured as the difference between the surface distances joining i) the suprasternal notch, the umbilicus and the femoral pulse and ii) the suprasternal notch and the carotid pulse. Carotid-femoral transit time was estimated in 8–10 sequential electrocardiogram-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.<sup>23</sup> This is a non-invasive and reproducible method to determine arterial stiffness.<sup>11</sup>

## Neuropsychological battery

We employed the Similarities test from the Wechsler Adult Intelligence Scale (WAIS I), and four 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<sup>18</sup> 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, Matrix Reasoning); (2) Scanning and Tracking (Trail Making Tests A and B, Digit Symbol Substitution, Symbol Search); (3) Verbal Episodic Memory (Logical Memory Immediate and Delayed, Hopkins Verbal Learning Test) and (4) Working Memory (Digit Span Forward and Backward, Letter-Number Sequence, Controlled Oral Word Associations). Similarities was

treated as a separate test as 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 each score from the mean of the sample distribution and dividing by the sample standard deviation (SD). This linear transformation results in a mean of zero and a 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 the individual tests. All the individual tests making up the composites have the same weights, i.e., 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 (cm), weight (kg), heart rate (beats per minute), antihypertensive drug treatment (yes/no), and MAP (mmHg). Height and weight were employed instead of BMI because it is essential to adjust for height when assessing PWV.<sup>24</sup> MAP was calculated as diastolic BP + 1/3 (systolic BP – diastolic BP). Additional covariates were as follows: race/ethnicity (Caucasian versus not Caucasian), diabetes mellitus, ApoE genotype (one or two ApoE-ε4 alleles versus no ApoE-ε4 alleles), creatinine (μmol/l, reciprocal), total cholesterol (mmol/l), depressed mood, trait anxiety, number of cigarettes per week, history of cardiovascular disease (CVD), total plasma homocysteine (μmol/l), and the number of neuropsychological examinations prior to wave 7. Diabetes mellitus was defined by treatment with insulin, oral anti-diabetic agents, or by fasting glucose level of 7 mmol/l or higher. Eight participants who failed to fast were also classified as diabetic, as their plasma glucose levels were above 11 mmol/l. Standard ApoE genotyping used polymerase chain reaction (PCR) and restriction enzyme digest with HhaI.<sup>25</sup> The reciprocal of serum creatinine (umol/l), used as an index of kidney function,<sup>26</sup> was employed in order to normalize its distribution. Plasma homocysteine (μmol/L), total cholesterol, triglycerides, HDL-cholesterol, and LDL-cholesterol assays were performed as previously described.<sup>18</sup> Smoking was defined by self-report of the number of cigarettes smoked per week.

Using the Framingham Study criteria,<sup>5</sup> the CVD 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 employed as a categorical variable (CES-D ≤16 versus CES-D >16 points) because there was a significant skew in CES-D scores and we wished to use a clinically recognized criterion for depressed mood.<sup>27</sup> To be included as a covariate, variables were required to meet one of two criteria: (1) identified as important based on the PWV or cognitive performance literature; (2) related significantly ( $p < .05$ ) to PWV and/or one or more cognitive performance measures.

### Statistical analysis plan

Two linear regression models were employed. 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.<sup>28</sup>

1. Initial Model: PWV+PWV × Age+age+education+gender+height+weight+ heart rate + MAP+anti-hypertensive medication use.

2. Extended Model: Initial model variables+race/ethnicity+diabetes. mellitus+CVD +reciprocal creatinine+depressed mood+trait anxiety+cigarettes/week+total cholesterol+homocysteine+number of prior exams+ApoE genotype.

Interaction terms involving sex and the quadratic trend component for PWV were tested separately for all 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 analyses relating PWV and PWV and 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/sec) were inversely and significantly related to the Scanning and Tracking Composite score ( $\beta = -.0468$ ;  $SE = .0183$ ,  $p < .01$ ). Thus a 5 m/sec increment in PWV was related to a 0.23 SD decrement in cognitive performance. Age was related to all outcome measures for the Extended model (please see <http://hyper.ahajournals.org>, 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 standard errors for the tests of the  $PWV \times Age$  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  $PWV \times Age$  interaction was not significant ( $p > .05$ ) for the Working Memory composite.

The effect of the  $PWV \times Age$  interactions on cognitive performance is illustrated in three dimensional plots using the Global and Scanning and Tracking composite scores as outcome measures (Figure 1 and Figure 2). Age (older to younger) and PWV (higher 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  $> .20$  ( $n = 18$ ) were included; (3) a second medication covariate which 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; (5) low ( $eGFR < 60$  ml/min/1.73<sup>2</sup>) versus high ( $eGFR \geq 60$  ml/min/1.73m<sup>2</sup>) 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 two primary models.

Finally, two a posteriori analyses were done. First, waist circumference was substituted for weight in order 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 + .40 (pulse pressure)<sup>29</sup> was substituted for the diastolic BP + .33 (pulse pressure) 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 employed in the analyses above. For all of the cognitive variables, quadratic PWV main effect and interaction trends were not significant. No statistically significant Gender  $\times$  PWV or Gender  $\times$  PWV  $\times$  Age interactions were observed for any of the cognitive measures (p-value range across measures and models = .12 to .38).

Tabled results for PWV main effects, age and PWV  $\times$  Age interactions for the individual cognitive tests are shown in Tables S3 and S4 (please see <http://hyper.ahajournals.org>). The PWV  $\times$  Age results for all 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 two longitudinal studies where age was defined as change over time. Scuteri et al.<sup>17</sup> found that higher PWV was related to decline on the MMSE after a median follow-up of 12 months for persons who had memory deficits at baseline. Waldstein et al.<sup>12</sup> reported that persons with higher PWV at baseline exhibited an accelerated decline over time (i.e., 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 employed 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 than younger adults,<sup>9</sup> a prediction that has largely failed to gain consistent support from cross-sectional aging studies employing brachial diastolic and/or systolic BP as a measure of hypertension.<sup>8,10</sup> The consistency of our findings with this hypothesis may be related to the fact that PWV is the gold standard for non-invasive 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,<sup>13</sup> PWV was inversely related with performance on the MMSE, 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 employed 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 as 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. Further, 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 many other changes in the central arteries related to PWV.<sup>30</sup> 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 employed, 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  $\times$  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.<sup>31–33</sup> Arterial stiffness promotes microvascular and macrovascular disease, including impaired cerebral perfusion,<sup>30,34</sup> endothelial dysfunction and nitric oxide deficiency,<sup>30,34–36</sup> lacunar infarctions, and cerebral white matter lesions.<sup>37</sup>

### Study limitations and strengths

Our participants were relatively well-educated, but education is protective of cognitive performance<sup>38</sup> and thus higher education should lead to an underestimation of the relation between PWV and cognition. Our design is cross-sectional with all 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.<sup>39,40</sup> Whether these interventions also lead concomitantly to slower cognitive decline with aging needs further investigation.

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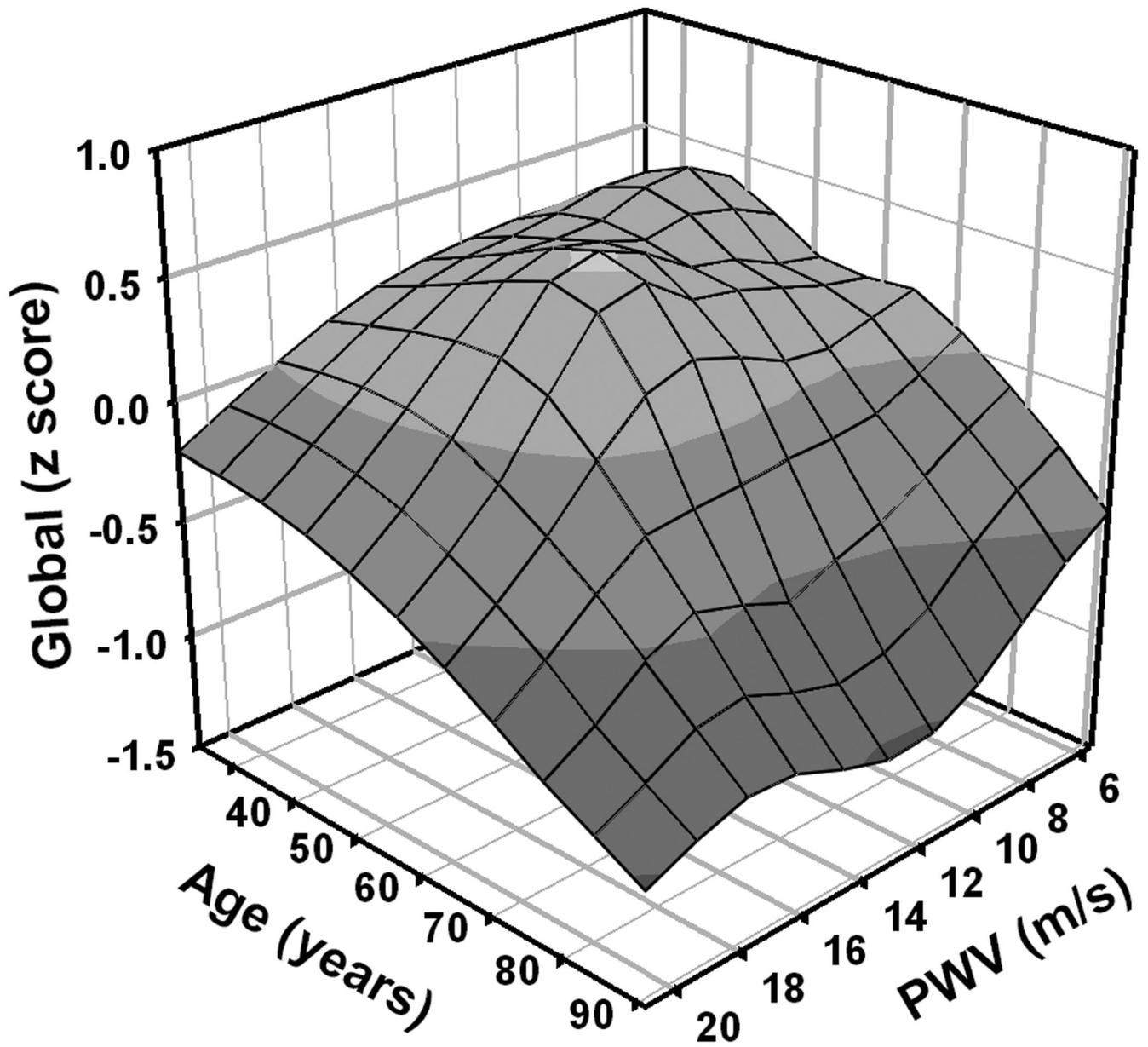
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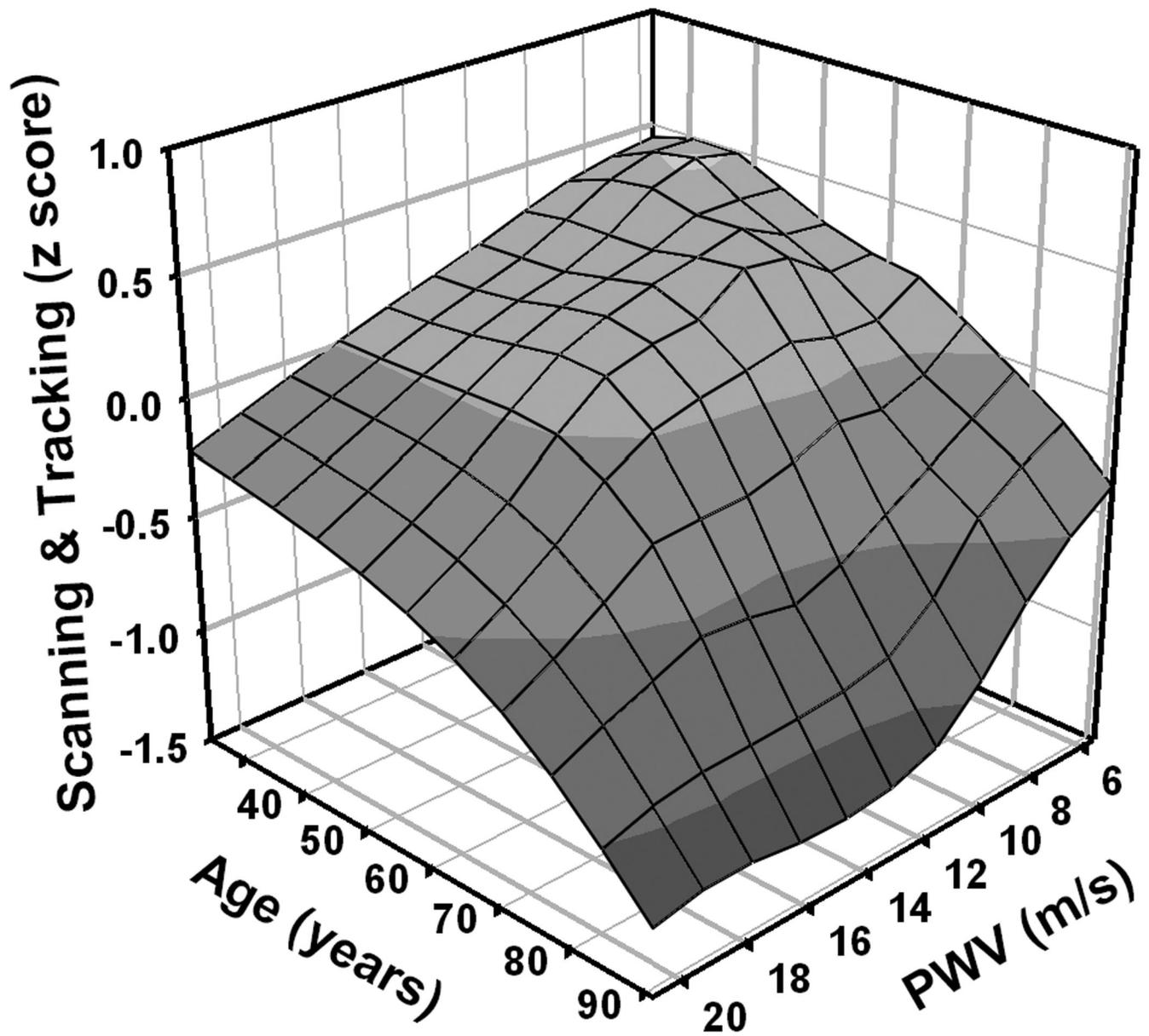
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**Figure 1.**  
Three-dimensional plot showing the interaction of PWV and age in relation to the Global Composite cognitive score for the Extended regression model.



**Figure 2.** Three-dimensional plot showing the interaction of PWV and age in relation to the Scanning and Tracking composite score for the Extended regression model.

**Table 1**

## Sample characteristics

Variable	Mean or Percent	SD	PWV r <sup>*</sup>	Age r <sup>*</sup>
Age (years)	61.3	12.8	.52 <sup>†</sup>	
Education (years)	14.6	2.8	-.06	.04
Pulse wave velocity (PWV, m/sec)	10.2	2.8		.52 <sup>†</sup>
Brachial mean arterial pressure (mmHg)	94.6	12.0	.33 <sup>†</sup>	.01
Brachial systolic pressure (mmHg)	128.9	19.7	.53 <sup>†</sup>	.26 <sup>†</sup>
Brachial diastolic pressure (mmHg)	77.5	10.1	.08	-.23 <sup>†</sup>
Heart rate (beats/min)	60.2	9.3	.19 <sup>†</sup>	-.07
Alcohol (oz/wk)	1.4	2.4	-.01	-.02
Cigarettes (per wk)	8.3	36.7	-.01	-.13 <sup>†</sup>
Height (cm)	167.7	9.9	.04	-.16 <sup>†</sup>
Weight (kg)	82.6	19.3	.06	-.31 <sup>†</sup>
Body mass index (kg/m <sup>2</sup> )	29.3	6.0	.05	-.27 <sup>†</sup>
Total cholesterol (mmol/l)	4.87	1.02	-.08	.08
Creatinine (μmol/l)	91.94	19.45	-.20 <sup>†</sup>	-.06
Plasma homocysteine (μmol/l)	9.9	3.4	.28 <sup>†</sup>	.29 <sup>†</sup>
Trait anxiety (total score)	20.6	2.7	-.12 <sup>‡</sup>	-.15 <sup>†</sup>
Female (%)	62.3		-.13 <sup>‡</sup>	-.05
Caucasian (%)	79.5		.10 <sup>‡</sup>	.44 <sup>†</sup>
On anti-hypertensive medications (%)	49.9		.30 <sup>†</sup>	.24 <sup>†</sup>
Obese (%)	36.7		.08	-.23 <sup>†</sup>
Depressed mood (%)	13.8		-.12 <sup>‡</sup>	-.22 <sup>†</sup>
Smoker (%)	9.8		-.03	-.22 <sup>†</sup>
Cardiovascular disease (%)	11.7		.31 <sup>†</sup>	.26 <sup>†</sup>
Diabetes mellitus (%)	13.9		.30 <sup>†</sup>	.03
Apoe-ε4 (%)	29.4		-.00	-.03

\* Correlation coefficient

† p &lt; .01

‡ p &lt; .05

**Table 2**Regression coefficients ( $\beta$ ) and standard errors ( $se\beta$ ) for the PWV  $\times$  Age interactions.

Composite/Test	Extended Model*	
	$\beta$	$se\beta$
Global Composite	-.0037 <sup>†</sup>	.0012
Visual-Spatial Organization and Memory	-.0038 <sup>†</sup>	.0013
Verbal Episodic Memory	-.0037 <sup>†</sup>	.0014
Working Memory	-.0009	.0015
Scanning and Tracking	-.0035 <sup>‡</sup>	.0012
Similarities	-.0034 <sup>‡</sup>	.0014

\* Extended Model = Age, Education, Gender, Height, Weight, Heart Rate, Brachial MAP, Antihypertensive medications, Reciprocal Creatinine, Trait Anxiety, Depressed Mood, Diabetes Mellitus, CVD, Number of Prior Exams, Race/Ethnicity, Total Cholesterol, Cigarettes/Week, ApoE genotype, homocysteine, PWV, PWV  $\times$  Age.

<sup>†</sup>  
p < .01

<sup>‡</sup>  
p < .05