

# Blood Pressure-Related Cognitive Decline Does Age Make a Difference?

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**Abstract**—Systolic and diastolic blood pressures have been inversely related to cognitive performance in prospective and cross-sectional studies. However, in large, community-based samples, these findings have been limited to older adults. In this 20-year longitudinal study, we examined the relationship between baseline blood pressure and cognitive decline for 529 participants using 2 age groups (18 to 46 years and 47 to 83 years). Cognitive performance was measured over multiple examinations with the Wechsler Adult Intelligence Scale from which 4 scores were derived by factor analysis. A 2-stage growth curve method of analysis was used to model cognitive change. Results indicated that higher levels of baseline systolic blood pressure, diastolic blood pressure, mean arterial pressure, and blood pressure categories as defined by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure were significantly associated with decline in Visualization/Fluid abilities in both younger and older age groups. Young adults are as susceptible to blood pressure-related longitudinal decline in cognitive performance as are older adults. (*Hypertension*. 2004;44:631-636.)

**Key Words:** blood pressure ■ age ■ arterial hypertension ■ cognition ■ prospective studies ■ risk factors

Hypertension is related to poorer cognitive performance in adults,<sup>1,2</sup> and hypertension-related changes in the brain are well-documented.<sup>3-9</sup> Systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels have been inversely related to cognitive performance level.<sup>2,10,11</sup> Moreover, DBP and SBP levels in midlife have been inversely associated with performance levels on cognitive tests administered at later ages.<sup>9,12-14</sup>

It is important to determine whether baseline BP values are associated with accelerated cognitive change with advancing age. Longitudinal designs are methodologically superior to cross-sectional designs because BP level can be related to intra-individual decline in cognitive functioning.<sup>15,16</sup> Most of the longitudinal studies using large, community-based samples have involved only midlife or older individuals.<sup>17-20</sup> Recently, Knopman et al studied persons ranging in age from 47 to 70 years and found that hypertension was related to cognitive decline from baseline to 6-year follow-up, but only for persons aged 58 to 70 years.<sup>21</sup>

In contrast to longitudinal findings, cross-sectional studies indicate that younger adult hypertensive individuals may be more vulnerable to BP-related decrement in cognitive functioning than older hypertensive individuals.<sup>10,22</sup> This phenomenon may be an artifact of cross-sectional designs.<sup>1,2,10</sup> However, the possibility that younger adult hypertensive individuals exhibit greater cognitive decline than older hypertensive individuals has not been tested with a longitudinal

design that included persons younger than 47 years of age. The major objective of the present study was to compare older and younger adults with respect to BP-associated cognitive decline using a prospective longitudinal design with multiple examinations and participants with a wide age range (18 to 83 years). Based on the longitudinal literature, we hypothesized that cognitive decline in relation to baseline BP would be greater for older than for younger adults.

## Methods

### Participants

The subjects were participants of the Maine-Syracuse Longitudinal Study of Hypertension (MLSH) who were administered the Wechsler Adult Intelligence Scale (WAIS)<sup>23</sup> and a hypertension diagnostic examination at baseline and at subsequent examinations (please see <http://hyper.ahajournals.org>).

Individuals with dementia, stroke, alcoholism, drug abuse, or psychiatric illness diagnosed were not eligible for baseline testing. Of the 1019 eligible study participants, 834 were invited to participate in the longitudinal study. Of the 834 invited participants, 305 were lost for the following reasons: died (n=68), refused (n=149), too ill to participate (n=16), too distant to be reached (n=46), and did not reply to contact (n=26). The 529 remaining subjects provided baseline data for the present study.

Participants either had no antihypertensive drug treatment history at baseline (n=296) or, if previously treated (n=233), were requested to withdraw from treatment (under their physician's supervision) 14 to 21 days before baseline testing. The BP profiles used for the present analyses were based on an average of 6 sitting, 6 reclining, and 6 standing BP measurements conducted at baseline.

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TABLE 1. Patient Flow for the Maine–Syracuse Study

Cohort	Baseline Dates	N Available at Baseline Who Met Study Criteria	Contacted and Invited		Participated in at Least 2 Examinations	
			N	%	N	%
1	1976–1977	102	101	99	79	78
2	1981–1985	379	291	77	171	59
3	1986–1990	369	277	75	179	61
4	1991–1995	169	165	98	109	66
Totals		1019	834	82	529	63

Blood pressure was measured with a Critikon Dinamap 1846SX automated BP monitor. Hypertension was defined as SBP $\geq$ 140 mm Hg and/or DBP $\geq$ 90 mm Hg.

A time-lagged, cohort-sequential design was used, ie, 4 cohorts defined on the basis of the year that baseline testing was accomplished were followed longitudinally for 4 (cohort 1), 3 (cohort 2), 2 (cohort 3), and 1 (cohort 4) examinations beyond baseline. Data on number of participants throughout the course of the study are shown in Table 1.

After baseline testing, the 529 longitudinal participants were tested as follows: 283 were tested once, 132 tested 2 times, 58 tested 3 times, and 56 tested 4 times within the 20-year study period (mean time between examinations=5.2 years, SD=0.63 years).

Mean age was 46 years. To maximize the balance in numbers of subjects in the older and younger groups, we established an age of 46 as the upper limit for our younger group and 47 as the lower limit for our older group. Thus, the ages of all individuals in our young group were younger than 47 years, the lower age limit of the subjects in the Knopman et al<sup>21</sup> study. Consequently, we were able to examine longitudinal BP–cognitive relationships for younger adults in a relatively unexplored age range. There was no statistically significant difference in number of times tested for the younger and older participants ( $P>0.05$ ).

The study was approved by the University of Maine and The State University of New York (SUNY) Upstate Medical University Institutional Review Boards. Informed consent for participation was obtained in writing before data collection.

### Dependent Variables

The WAIS<sup>23</sup> was administered at each longitudinal examination and included the following subtests in a verbal scale (Information, Vocabulary, Comprehension, Arithmetic, Digit Span, and Similarities) and a performance scale (Picture Completion, Object Assembly, Block Design, Picture Arrangement, and Digit Symbol Substitution). To achieve variable reduction and theoretically meaningful summary scores of abilities measured by the WAIS, we used 4 scores based on extensive factor analytic studies in previous investigations.<sup>24,25</sup> These scores were as follows: (1) Crystallized/Verbal (Comprehension, Similarities, Vocabulary, and Information); (2) Visualization/Fluid (V/F) (Picture Completion, Picture Arrangement, Block Design and Object Assembly); (3) Memory (Arithmetic, Digit Span Forward and Digit Span Backward); and (4) Speed (Digit Symbol Substitution).

Each WAIS subtest score was expressed as a percent correct score, ie, the number of points correct was divided by the total possible number of points. The 4 composite scores were derived by adding the subtest scores (percent correct) within a composite and dividing by the number of subtests in that composite.<sup>26</sup>

### Predictor Variables

Five mean BP variables were calculated from the 18 measurements obtained at baseline: (1) DBP; (2) SBP; (3) pulse pressure (PP), calculated as SBP–DBP; (4) mean arterial pressure (MAP), calculated as MAP=DBP+PP/3; and (5) BP classification based on the criteria of the Seventh Report of the Joint National Committee (JNC)

on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure,<sup>27</sup> ie, 4 ordinal categories: Normal, defined as SBP <120 mm Hg and DBP <80 mm Hg; Prehypertension, defined as SBP=120 to 139 or DBP=80 to 89; Stage I Hypertension, defined as SBP=140 to 159 or DBP=90 to 99; and Stage II Hypertension, defined as SBP $\geq$ 160 or DBP $\geq$ 100.

### Covariates

Regression models included the following covariates: (1) age (years at baseline); (2) education (years at baseline); (3) occupation (highest level); (4) gender; (5) alcohol use (drinks/d, averaged over all examinations); (6) cigarettes/d (averaged over all examinations); (7) psychotropic medication use during the study (yes=1 or no=0); (8) body mass index (averaged over all examinations); and (9) Zung depression scale scores (averaged over all examinations). Age (in years) at baseline was included among the covariates because it might be expected to have a confounding effect via both BP levels and cognitive performance regardless of age range of the sample.

In secondary analyses, subjects with a history of, treated for, or diagnosed with 1 or more coexisting diseases at any point in the study were excluded. These included subjects with type I or type II diabetes ( $n=53$ ), other major diseases such as cancer ( $n=9$ ), and hypertension-related complications, ie, coronary artery disease, myocardial infarction, transient ischemic attack, stroke, kidney disease ( $n=52$ ).

### Statistical Analyses: Measurement of Cognitive Change

A 2-stage growth curve method was used.<sup>28</sup> This method does not require equal numbers of participants at each examination or equal time intervals between serial examinations. Data for all subjects who completed at least 2 longitudinal examinations, including the baseline examination, are used to estimate missing longitudinal data.<sup>28–30</sup> Longitudinal attrition is controlled statistically because all the longitudinal data are used in the estimates of cognitive change over time.

For stage 1, a linear model was fit to the each of the WAIS composite scores for each individual using the method of least squares:  $Y_{it} = a_i + b_i t_i + e_{it}$ . For each individual ( $i$ ) at occasion of testing ( $t$ ),  $Y$  is the observed test score,  $a$  is the intercept, and  $b$  is the raw regression coefficient for test scores regressed on time ( $t$ ). Because each individual's test scores over time are regressed on number of years from point of entry into the study (defined as 0), the intercept value ( $a$ ) is each individual's estimated test score at entry into the study (examination 1) and the slope value ( $b$ ) is each individual's estimated longitudinal change over time. Change over time was expressed in 1-year intervals of longitudinal study participation. Thus, every study participant received 2 scores in stage 1 analyses: (1) an intercept score representing estimated baseline performance; and (2) a slope score representing estimated change in performance over 1 year of study participation.

The slope values (*cognitive change scores*) were the dependent variables for stage 2 of the analysis. However, intercepts were included in all stage 2 regression models to control for estimated baseline performance.

### Regression Analyses

For stage 2, multiple linear regression analyses were performed with the BP variables as the predictors and the estimated slopes as the dependent variables. Separate analyses were conducted for each combination of predictor (SBP, DBP, MAP, and PP in 10 mm Hg increments; JNC BP classification expressed as 1, 2, 3, 4 ordinal scale) and dependent variables (Crystallized/Verbal, V/F, Memory, and Speed scores).

These multiple regression analyses resulted in raw regression coefficients ( $\beta$ ) expressing independent statistical associations between each of the covariables and the slope values for the WAIS composite scores. A weighted least-squares analysis was used to allow slope values estimated with more precision to be weighted more than those with larger standard errors.<sup>30</sup>

**TABLE 2. Characteristics of the Younger and the Older Study Participants**

Descriptive Variable	Younger (Age <47) (n=285)			Older (Age ≥47) (n=244)			P<
	Mean	SD	Range	Mean	SD	Range	
Age, y	34.9	7.6	18–46	58.1	8.4	47–83	0.001
Occupation level	5.4	1.0	1–6	4.7	1.2	1–6	0.001
Education, y	14.3	2.3	8–20	14.3	2.7	7–20	NS
Baseline SBP, mm Hg	134.2	22.6	86–209	152.0	30.1	91–216	0.001
Baseline DBP, mm Hg	86.4	15.5	49–130	91.3	16.7	54–127	0.001
All examination SBP, mm Hg	130.4	18.5	86–197	146.2	22.5	85–240	0.001
All examination DBP, mm Hg	80.2	11.4	49–115	83.4	12.2	49–146	0.01
Zung depression	42.9	10.4	26–84	42.1	9.9	25–84	NS
BMI, kg/m <sup>2</sup>	27.8	6.1	17.4–58.1	27.9	4.8	17.6–48.1	NS
			%			%	
Female			51.6			51.2	NS
Smoker (ever)			14.7			11.9	NS
Alcohol use (ever)			51.6			49.2	NS
Hypertensive at baseline			55.8			73.8	0.001
Ever hypertensive			59.6			78.7	0.001
Treated at baseline*			66.7			70.5	NS
Ever treated†			92.9			86.5	0.05
Comorbid disease‡			14.7			29.5	0.001

\*Percentage of individuals hypertensive who were treated with antihypertensive medications at baseline.

†Percentage of ever hypertensive individuals who were ever treated with antihypertensive medications.

‡Comorbid disease is an aggregate category including the following: coronary artery disease, myocardial infarction, transient ischemic attack, stroke, noninsulin-dependent diabetes, insulin-dependent diabetes, cancer, kidney disease.

## Results

Table 2 displays the demographic and health characteristics of the participants. Baseline and mean (all examinations) SBP and DBP, the prevalence of hypertension at baseline, hypertension at any examination, and number of comorbid diseases were higher for the older individuals. A modestly larger percentage of young hypertensive persons than older hypertensive persons received treatment when referred back to their physicians.

Subjects lost before examination 2 were lower in occupation (4.5 versus 5.1,  $P<0.001$ ), younger (41.2 versus 45.6 years,  $P<0.001$ ), and exhibited lower Crystallized/Verbal (69.2 versus 71.5,  $P<0.01$ ) and Memory (69.5 versus 71.3,  $P<0.05$ ) scores, but dropouts and those successfully recruited did not differ with respect to V/F or Speed scores.

### Age Group Analyses

Baseline BP values were unrelated to cognitive change (slope scores) over time for the composites indexing Crystallized/Verbal Ability, Memory, and Speed. Consequently, we present results only for the V/F composite (Table 3).

The covariate-adjusted regression coefficients shown in Table 3 are the product of regressing individual cognitive change (slope) values on the baseline BP measures. Thus, the regression coefficients representing change in performance longitudinally are actually regression coefficients for the intra-individual slope values and can be interpreted in the following manner. The magnitude of the regression coefficient reflects the average intraindividual change in cognitive

performance over time per increment in BP and the negative sign indicates the direction of the change (decrement).<sup>28</sup>

For V/F slopes, higher SBP, DBP, MAP, and JNC categories were associated with longitudinal decrement in performance for the younger and older groups. These relationships were observed when all study participants were included in the analyses and when persons with coexisting diseases were excluded.

PP also showed a significant association with the V/F composite for older participants only. The interaction of PP with age approached significance ( $P=0.09$ ). However, when persons with coexisting disease were excluded from the analysis, the effect of PP was nonsignificant for both age groups.

To illustrate the linear trends in cognitive change, using MAP as an example, we dichotomized the continuous MAP values into 2 groups: MAP <105 mm Hg and MAP ≥105 mm Hg.<sup>31</sup> The estimated regression lines (adjusted for all covariates) for the younger and older age groups are shown in the Figure. Each regression line represents the estimated amount of change that would be expected over 20 years for the 2 age groups and MAP categories. Both younger and older age groups in the higher MAP category showed substantially more cognitive decline relative to their counterparts in the lower MAP category. When the dichotomous MAP variable was used in the full regression model, results for both the younger ( $\beta=-0.307$ ,  $P<0.05$ ) and the older ( $\beta=-0.423$ ,  $P<0.03$ ) groups were significant.

Interactions of age with the blood pressure measures were tested in 2 ways: age treated as a group variable (as in Table

**TABLE 3. Regression Coefficients ( $\beta$ ) and Standard Errors ( $SE\beta$ ) Expressing the Relationship of Blood Pressure to Change Over Time for Each Year of Participation in the Longitudinal Study\* for the Visualization/Fluid Composite†**

BP Variable	All Participants		Disease Excluded‡	
	Younger	Older	Younger	Older
Baseline SBP (10 mm Hg)				
$\beta$	-0.047	-0.086§	-0.066¶	-0.094§
$SE\beta$	0.031	0.028	0.036	0.036
Baseline DBP (10 mm Hg)				
$\beta$	-0.092	-0.152§	-0.104	-0.160§
$SE\beta$	0.045	0.050	0.051	0.059
Baseline PP (10 mm Hg)				
$\beta$	-0.001	-0.099	-0.035	-0.100
$SE\beta$	0.048	0.044	0.058	0.061
Baseline MAP (10 mm Hg)				
$\beta$	-0.081	-0.134§	-0.098	-0.141
$SE\beta$	0.041	0.041	0.047	0.050
Baseline JNC category				
$\beta$	-0.160	-0.236§	-0.184	-0.244§
$SE\beta$	0.065	0.078	0.073	0.092

\*Change can be expressed in other units of longitudinal study participation, eg, 10-year increments ( $10\times$  the regression coefficient).

†Regression coefficients are adjusted for age, education, occupation, gender, alcohol consumption, cigarettes/day, psychotropic medication, body mass index, depression, and estimated baseline performance (stage I intercepts).

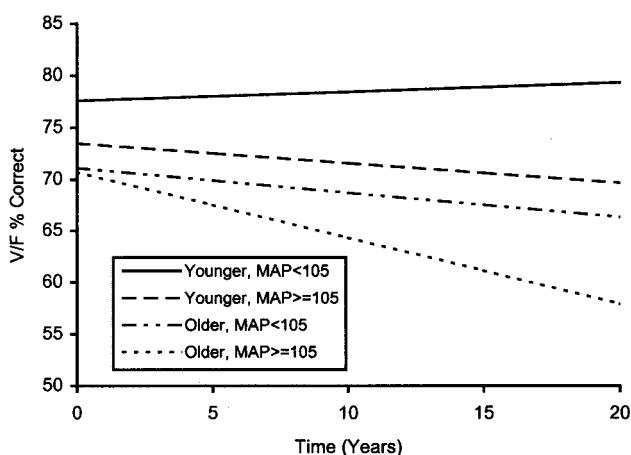
‡Participants with diabetes, major diseases such as cancer, coronary artery disease, myocardial infarction, transient ischemic attack, stroke, and kidney disease were excluded from the analysis.

§ $P<0.01$ .

|| $P<0.05$ .

¶ $P<0.07$ .

3) and age treated as a continuous variable. All interactions were nonsignificant ( $P=0.09$  to  $0.99$ ) and thus indicate that relations between BP variables and cognitive performance were substantially the same for younger and older study participants. However, SBP-related cognitive decline was



Linear regression lines for older and younger age groups by MAP category.

**TABLE 4. Main Effect Regression Coefficients ( $\beta$ ) and Standard Errors ( $SE\beta$ ) Expressing the Relationship of Baseline BP to Change Over Time for Each Year of Participation in the Longitudinal Study\* for the Visualization/Fluid Composite†**

BP Variable	$\beta$	$SE\beta$
Baseline SBP (10 mm Hg)	-0.074‡	0.024
Baseline DBP (10 mm Hg)	-0.123‡	0.037
Baseline PP (10 mm Hg)	-0.059	0.041
Baseline MAP (10 mm Hg)	-0.111‡	0.033
Baseline JNC category	-0.203‡	0.056

\*Change can be expressed in other units of longitudinal study participation, eg, 10-year increments ( $10\times$  the regression coefficient).

†Regression coefficients are adjusted for age, education, occupation, gender, alcohol consumption, cigarettes/day, psychotropic medication, body mass index, depression, and estimated baseline performance (stage I intercepts). Persons with co-existing disease were excluded from the analysis.

‡ $P<0.01$ .

modestly greater for the older than for the younger group (Table 3) and statistically significant only for the older group.

In summary, baseline BP and JNC classifications were associated with longitudinal decrement in performance on the V/F composite score. No significant BP $\times$ age interactions were observed for any of the cognitive measures.

### Main Effects of Blood Pressure on Cognition

Because there was no significant age $\times$ BP interaction for the V/F composite, it is important to examine main effects. Table 4 presents the results for the association between BP variables and change in cognitive function for the sample with exclusions for coexisting disease. All baseline BP variables were associated with decline in cognitive performance with the exception of PP. There was no indication of poorer performance at the lower BP levels. Results were the same when participants with coexisting disease were included, except that now PP was significantly related to the V/F composite ( $\beta=0.067$ ;  $SE\beta=0.032$ ,  $P<0.05$ ). Neither days on antihypertensive drug holiday at baseline nor ever-treated versus never-treated with antihypertensive drugs during the longitudinal study was related to the cognitive outcome measures with the full set of covariates ( $P>0.05$ ).

When individual components of the V/F composite were examined, it was found that Picture Completion (MAP,  $\beta=-0.170$ ,  $SE\beta=0.050$ ;  $P<0.001$ ), Block Design (MAP,  $\beta=-0.133$ ,  $SE\beta=0.048$ ;  $P<0.01$ ), and Object Assembly (MAP,  $\beta=-0.111$ ,  $SE\beta=0.059$ ;  $P<0.05$ ) were the primary tests accounting for the significant main effects. Results for SBP, DBP, and JNC categories showed similar significant relationships.

### Discussion

We tested the hypothesis that older adults would show greater BP-related cognitive decline than younger adults. The hypothesis was not confirmed by tests of the age $\times$ BP interactions. Further, with the exception of PP, the amounts of cognitive decline in V/F abilities associated with baseline BP shown by adults aged 18 to 47 and 48 to 83 were similar. Our data support the association between blood pressure and cognition for older study participants as shown by Knopman

et al,<sup>21</sup> and we have extended these findings to much younger adults. Our results were observed for adults exhibiting the normal range of cognitive functioning. No participants had dementia diagnosed throughout the course of the study and all participants were able to complete the test protocol.

Many cognitive abilities are affected by hypertension.<sup>1,2</sup> However, findings of longitudinal BP–cognition relationships are often limited to tasks that index fluid abilities and executive function,<sup>10,32</sup> as does our V/F composite. Our study indicates that higher baseline BP levels and JNC classifications are predictive of cognitive decline in V/F abilities, whereas Crystallized/Verbal, Memory, and Speed abilities are spared.

Our data and the findings by Knopman et al<sup>21</sup> are consistent with the general conclusion that BP-associated performance deficits in nondemented, stroke-free individuals are relatively minor and manageable in terms of everyday functioning. For example, from the regression coefficient for the ordinal JNC scale (based on 1 year of change; Table 3), we see that moving from the “Normal” BP classification to the “Stage I Hypertension” classification (2 ordinal steps) would result in an estimated 8.12% decrement in correct responses on the V/F composite over 20 years. Commenting on findings from the ARIC study, Knopman et al<sup>21</sup> observed that hypertension-related cognitive decline over 6 years was relatively small, and that its importance is with respect to marking potential pathophysiological changes in brain structure and function.

### Study Limitations

Several study limitations most likely served to attenuate the estimated rate of longitudinal decline. Our subjects were relatively well-educated and concerned about treatment and their cognition. Further, persons lost to the study after baseline exhibited lower Crystallized/Verbal and Memory composite scores than those who provided longitudinal data. However, longitudinal change is generally not reported for the Crystallized/Verbal tests used in the present study<sup>10</sup> and, whereas BP-related change in memory has been reported, tests used in these studies placed considerably more demands on working and episodic memory than tests that index the Memory component of the WAIS.<sup>1,2</sup>

### Perspectives

The longitudinal changes that we see in young adults are consistent with a literature that indicates that the BP-related pathophysiological processes adversely affecting the brain may begin earlier in the adult lifespan than previously thought.<sup>1,2,10</sup> The main importance of our findings lies at the population level. Blood pressure lowered by just 20 mm Hg SBP or 10 mm Hg DBP, or from “Hypertensive” to “Normal” JNC classification, would have a considerable beneficial effect on the preservation of cognitive abilities in the population as a whole. Given that younger adults appear at least as vulnerable to BP-related cognitive decline as are older adults, these benefits would be seen among young as well as middle-aged and older adults. It is important to continue and expand clinical trials relating the lowering of BP to cognitive performance. To the extent that BP effects on cognition are

not reversible, it is important to prevent an increase in BP levels as early as possible in the life cycle.

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