Nonlinear Relations of Blood Pressure to Cognitive Function
The Baltimore Longitudinal Study of Aging

Shari R. Waldstein, Paul P. Giggey, Julian F. Thayer, Alan B. Zonderman

Abstract—This investigation examined cross-sectional and longitudinal relations, both linear and nonlinear, of blood pressure (BP) and its interaction with demographic and lifestyle variables to a broad spectrum of cognitive functions. Eight hundred forty-seven participants (503 men and 344 women) from the Baltimore Longitudinal Study of Aging completed tests of verbal and nonverbal memory, attention, perceptuo-motor speed, executive functions, and confrontation naming, and clinical assessment of BP on 1 to 7 occasions over 11 years. Mixed-effects regression models, adjusted for age, education, gender, alcohol consumption, smoking status, depression scores, and use of antihypertensive medications, revealed nonlinear relations of systolic BP with longitudinal change on tests of nonverbal memory and confrontation naming; cognitive decline was apparent among older (80 years) individuals with higher systolic BP. Cross-sectional findings, across testing sessions, indicated moderated U- and J-shaped relations between BP and cognitive function. Both high and low diastolic BP were associated with poorer performance on tests of executive function and confrontation naming among less-educated persons; with tests of perceptuo-motor speed and confrontation naming among nonmedicated (antihypertensives) individuals; and with executive function among older individuals. Cross-sectional linear relations included higher systolic BP and poorer nonverbal memory in nondrinkers, and higher diastolic BP and poorer working memory among less-educated individuals. Results indicate that cross-sectional and longitudinal relations of BP to cognitive function are predominantly nonlinear and moderated by age, education, and antihypertensive medications. Careful monitoring and treatment of both high and low BP levels may be critical to the preservation of cognitive function. (Hypertension. 2005;45:374-379.)

Key Words: blood pressure ▪ hypertension ▪ cognitive function ▪ neuropsychology

Hypertension is a major risk factor for stroke, vascular dementia, and possibly Alzheimer’s disease.1–2 Even among stroke-free and dementia-free persons, hypertension or higher blood pressure (BP) levels have been related to lowered levels of cognitive function in numerous cross-sectional and longitudinal investigations.3–5 However, not only high BP but also low BP levels have negative effects on cognitive function. Low BP has been related to risk for Alzheimer’s disease and diminished cognitive function.6 Furthermore, U-shaped relations between BP and cognitive function have been noted such that individuals with high or low BP perform more poorly on cognitive tests and/or display more pronounced cognitive decline than persons with mid-range BP.7–9 With one exception,5 these studies are limited by the assessment of BP, cognitive function, or both on a single occasion.

The purpose of the present investigation was to examine both cross-sectional and longitudinal relations of concurrently measured BP and cognitive function across 1 to 7 testing sessions in a single stroke and dementia-free sample while evaluating potential nonlinear associations, effect modifiers, and a broad spectrum of cognitive functions. To our knowledge, only 1 previous investigation has assessed concurrently measured BP and cognitive function on >2 testing occasions in a small sample (n=140).5 Although several previous studies have examined nonlinear relations of BP to cognition,7–9 few domains of cognitive function were measured (ie, global mental status, verbal memory, perceptuo-motor speed), there was limited assessment of effect modification, and persons with stroke or dementia were included (which may lead to overestimation of BP–cognition relations). Here, we examined measures of verbal and nonverbal memory, attention, perceptuo-motor speed, executive functions, and confrontation naming, and potential interactions of BP with several demographic and lifestyle variables.

Methods

Participants
Participants from the Baltimore Longitudinal Study of Aging (BLSA), a prospective study of community-dwelling volunteers initiated by the National Institute on Aging in 1958, return to the Gerontology Research Center in Baltimore every ~2 years for medical, psychological, and cognitive testing.10 Beginning in 1986, participants 60 years and older were administered a more extensive...
At each study visit, standard neuropsychological tests were administered to 928 participants (ages 39 to 96) available for potential inclusion. We excluded persons with dementia (n=34;11), cerebrovascular diseases including stroke (n=55), and renal failure (n=1) across all assessment visits. Eight hundred forty-seven participants (503 men and 344 women) met study criteria. Baseline sample characteristics are presented in Table 1. The total number of participants per visit is listed in Table 2. Because the BLSA uses continuous enrollment procedures, participants have different numbers of visits, in part, because of differential start times in the project. Follow times are also variable. Participants had an average of 2.7 (SD=1.5) visits, and the average time between visits was 2.32 (SD=0.8) years. Number of follow-up visits (mean, SD, range) by 10-year increments in age are as follows: 50 to 60 years (2.80, 1.79, 1 to 6); 60 to 70 years (2.82, 1.44, 1 to 6); 70 to 80 years (2.93, 1.54, 1 to 7); 80 to 90 years (2.18, 1.31, 1 to 6); and 90 to 100 years (1.33, 0.71, 1 to 3). Over the course of the investigation, 11 participants died and 7 formally withdrew from the investigation; therefore, rate of attrition was 2%. Institutional Review Board approval was obtained from the Johns Hopkins Bayview Medical Center for the investigation and the University of Maryland, Baltimore County for the current data analyses. All participants provided written informed consent.

### Neuropsychological Tests

At each study visit, standard neuropsychological tests were administered by extensively trained psychometricians.12 The sample sizes that follow each test indicate respective reductions in sample size because of test-specific missing data. The Digits Forward and Backward portions of the Wechsler Adult Intelligence Scale–Revised (n=733) assessed attention and working memory. The California Verbal Learning Test (n=689) measured verbal learning and memory (ie, List A total, learning slope, short and long free recall), and the Benton Visual Retention Test (BVRT) (n=796) evaluated nonverbal memory. Trail Making Test Parts A and B (n=847) assessed attention, perceptuo-motor speed, visuomotor scanning, and mental flexibility (an executive function). Letter Fluency (n=847) and Category Fluency (n=847) examined phonetic and semantic association fluency, respectively, and executive function. The Boston Naming Test (n=847) assessed confrontation naming (ie, word finding).

### Blood Pressure

At each study visit, BP was measured in the morning by trained nursing staff at least 90 minutes after a light breakfast. After a 5-minute rest period, a mercury sphygmomanometer with an appropriate-sized occluding cuff was used to measure BP once from each arm while patients sat in an upright position. Systolic BP and diastolic BP were determined by Kortokoff phase I and phase V, respectively. The 2 measurements were averaged for data analysis.

### Covariates

Age and education were assessed in years. Alcohol use was quantified categorically according to types and numbers of drinks (one drink=12 ounces beer, to 5 ounces of wine, or 2 ounces of spirits) consumed per week. Categorical ratings obtained at each visit were added to yield a single score. Smoking status was defined as “never/ever.” Use of antihypertensive medications was collapsed into a single “yes/no” category. Depressive symptomatology was examined using the Center for Epidemiological Studies Depression Scale (CES-D).13

### Data Analyses

Mixed-effects regression analyses were conducted to examine cross-sectional (collapsed across all testing sessions) and longitudinal relations of BP to cognitive function. Mixed-effects models are the preferred method of analyzing data with different numbers of repeated outcome measurements that are obtained at nonuniform intervals.14,15 These analyses model change over time by computing rate of change for each participant based on all data for that individual. The model computes rate of change for the entire group and then computes each individual’s deviation from the group rate. Mixed-effects models evaluate the unique effects of individual predictors adjusted for all other predictors in the model, includes both fixed and random effects, accounts for the correlation among repeated measurements on the same participant, and is unaffected by randomly missing data. In the present instance, it permits analysis of the rate of change in cognitive performance as a function of rate of change in BP (and all relevant covariates).

To maximize the unique information provided by each neuropsychological test, separate models were examined for each test as a dependent measure. Separate models were constructed for systolic BP and for diastolic BP. Both linear and quadratic (squared) effects were included in each model. Baseline age, years of education, alcohol consumption, depression scores, and time interval between assessments were treated as continuous covariates, and gender, antihypertensive medications, and smoking status were treated as categorical covariates. Baseline age indexes cross-sectional age differences, whereas time interval (ie, years since baseline testing for each administration of the dependent measure) indexes longitudinal age change.

All main effects and 2-way interactions were entered into each model in addition to the 3-way interactions of baseline age, linear BP, and time interval, and baseline age, quadratic BP, and time interval. A backward elimination procedure was used in which nonsignificant interaction terms (P>0.05) were eliminated from each model until a final solution was reached. Significant effects of BP on longitudinal rate of cognitive change are indicated by significant interactions of BP and time interval (or the 3-way interaction of age, BP, and time interval). Cross-sectional relations of BP and cognition (mean cognitive test scores collapsed across all testing sessions) are revealed by BP main effects or interactions of BP with demographic or lifestyle covariates.

### TABLE 1. Characteristics of Study Sample at First BLSA Visit (n=847)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70.6</td>
<td>(8.5)</td>
<td>39</td>
<td>96</td>
</tr>
<tr>
<td>Education, y</td>
<td>16.6</td>
<td>(2.7)</td>
<td>4</td>
<td>24</td>
</tr>
<tr>
<td>Gender, % male</td>
<td>59</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race, % white</td>
<td>84.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol use*</td>
<td>0</td>
<td>(2)</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Ever smoker, %</td>
<td>59</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensive medication, %</td>
<td>33.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CES-D</td>
<td>6.5</td>
<td>(6.3)</td>
<td>0</td>
<td>45</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>138.7</td>
<td>(20.0)</td>
<td>90</td>
<td>220</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>82.0</td>
<td>(10.9)</td>
<td>50</td>
<td>115</td>
</tr>
</tbody>
</table>

*1 unit of alcohol use corresponds to ~1.4 drinks per week. Data presented for alcohol use are the median and interquartile range.

CES-D indicates Center for Epidemiological Studies Depression Scale; DBP, diastolic blood pressure; SBP, systolic blood pressure.

### TABLE 2. Sample Size by Number of Repeat Administrations

<table>
<thead>
<tr>
<th>No. of Repeat Administrations</th>
<th>No. (% of Sample)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>595 (70.2)</td>
</tr>
<tr>
<td>3</td>
<td>438 (51.7)</td>
</tr>
<tr>
<td>4</td>
<td>296 (34.9)</td>
</tr>
<tr>
<td>5</td>
<td>106 (12.5)</td>
</tr>
<tr>
<td>6</td>
<td>26 (3.1)</td>
</tr>
<tr>
<td>7</td>
<td>3 (0.004)</td>
</tr>
</tbody>
</table>
Significant main and interactive effects of systolic and diastolic BP with respect to the cognitive outcomes are listed in Tables 3 and 4, respectively. Longitudinal findings were as follows. First, a significant 3-way interaction of baseline age, time interval, and quadratic systolic BP was noted for the BVRT and the Boston Naming Test. Graphic depiction of predicted parameters associated with these interactions (Figure) indicates, for the BVRT, that among younger individuals (age 60 at baseline), those with higher systolic BP made more errors on the BVRT than those with normal BP but improved over time (ie, practice effects). In contrast, among older individuals (age 80 at baseline), those with higher systolic BP declined in BVRT performance over time. On the Boston Naming Test, younger individuals (age 60 at baseline) with higher systolic BP performed more poorly than those with lower systolic BP across testing sessions. For older individuals (age 80 at baseline), those with higher systolic BP declined in performance over time.

Next, several cross-sectional findings (across all testing sessions) were noted. Significant linear relations of BP to cognitive function were almost always qualified by nonlinear (ie, quadratic) effects (please see http://hyper.ahajournals.org for Figure I depicting all quadratic associations). Specifically, significant nonlinear relations of diastolic BP and education were found for the Boston Naming Test and Trail Making B. For Boston Naming, individuals with lower levels of education and either high or low BP performed more poorly than those with mid-range BP (a U-shaped relation). For Trail Making B, a J-shaped relation revealed that among less educated persons, those with high or low BP performed more poorly than those with mid-range BP, but particularly among those with high BP. On both tests, individuals with higher levels of education performed similarly irrespective of BP level.

Significant interactive effects of quadratic diastolic BP and use of antihypertensive medication were noted for the Boston Naming Test and Trail Making A. For Boston Naming, individuals who were not medicated displayed poorer performance at both high and low BP levels (as compared with mid-range); medicated individuals performed similarly at all levels of BP. For Trail Making A, a J-shaped relation was noted such that among nonmedicated persons, those with higher BP displayed poorer performance than those with mid-range BP; those with lower BP also displayed poorer performance than those with mid-range BP, although to a lesser extent than persons with high BP.

Significant interactive effects of quadratic diastolic BP and baseline age were identified for Letter Fluency. At younger ages, higher diastolic BP levels conferred a slight performance advantage. At older ages, those with high and low diastolic BP performed more poorly than those with mid-range BP. The effect was more pronounced for those with higher BP.

Finally, results revealed 2 significant, cross-sectional, and linear relations of BP to cognitive function that were not qualified by quadratic effects (Figure II). An interaction of systolic BP and alcohol consumption was found for the BVRT. Higher systolic BP was associated with more BVRT errors among nondrinkers than individuals who reported drinking alcohol. An interaction of diastolic BP and education for Digits Backward revealed that less-educated individuals with higher BP performed worse on this test than their more educated counterparts.

### Table 3. Summary of Significant Systolic Blood Pressure Effects From Mixed-Effects Regression Analyses

<table>
<thead>
<tr>
<th>Neuropsychological Test*</th>
<th>Significant SBP Effects</th>
<th>Coefficient†</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benton Visual Retention Test</td>
<td>Interval*SBP linear</td>
<td>0.03381</td>
<td>7.33</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>Alcohol*SBP linear</td>
<td>0.00412</td>
<td>4.32</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Age0<em>Interval</em>SBP linear</td>
<td>-0.00049</td>
<td>8.01</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>Interval*SBP quadratic</td>
<td>-0.04332</td>
<td>7.79</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>Age0<em>Interval</em>SBP quadratic</td>
<td>0.00062</td>
<td>7.84</td>
<td>0.005</td>
</tr>
<tr>
<td>Boston Naming Test</td>
<td>SBP linear</td>
<td>0.03284</td>
<td>5.74</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Age0*SBP linear</td>
<td>-0.00046</td>
<td>5.95</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Interval*SBP linear</td>
<td>-0.01003</td>
<td>9.30</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Age0<em>Interval</em>SBP linear</td>
<td>0.00015</td>
<td>9.89</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>SBP quadratic</td>
<td>-0.04416</td>
<td>7.62</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>Age0*SBP quadratic</td>
<td>0.00064</td>
<td>8.25</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>Interval*SBP quadratic</td>
<td>-0.00837</td>
<td>4.00</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Age0<em>Interval</em>SBP quadratic</td>
<td>-0.00012</td>
<td>4.44</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Separate regression models were computed for each neuropsychological test. Each model contained all relevant main effects and interaction terms as detailed in text. However, for space-saving purposes, we only report significant findings for each model in this table. Complete data for each model are available from the authors.

†Regression coefficients, although indicative of effect sizes may be misleading because of correlations among main effects and interactions.
Discussion

This study examined both cross-sectional and longitudinal relations of concurrently measured BP and cognitive function across 1 to 7 testing sessions in a moderately large stroke-free and dementia-free sample while evaluating potential nonlinear associations, multiple relevant effect modifiers, and a fairly extensive range of neuropsychological tests. In almost all instances, significant linear relations of BP to cognitive function were qualified by nonlinear associations. This is, to our knowledge, the first report of age-moderated, nonlinear relations of systolic BP to longitudinal change in cognitive performance, in addition to cross-sectional (across testing sessions), nonlinear relations of BP to cognitive function that are moderated by age, education, and antihypertensive medication. Measurement of concurrent BP and cognitive function on testing occasions greatly strengthens measurement reliability and ability to track longitudinal covariation in these 2 variables.

With respect to longitudinal change in cognitive function, we found that among individuals age 60 years at baseline, those with higher systolic BP performed more poorly than those with lower systolic BP across all sessions on a test of confrontation naming. This cohort also performed more poorly on a test of nonverbal memory but showed improvement over time (likely reflecting practice effects). In contrast, among persons age 80 at baseline, those with higher systolic BP showed longitudinal decline on tests of nonverbal memory and confrontation naming. Thus, elderly persons may be most vulnerable to the cognitive consequences of higher systolic BP over time. Interesting, these same tests of nonverbal memory and confrontation naming have shown predictive usefulness with respect to later development of dementia in the larger BLSA sample and other studies. Previous longitudinal investigations have not noted interactive relations of age and BP to cognitive decline in cohorts of similar (although not identical) age range. However, nonlinear effects were not always examined, there were fewer follow-up visits, and dissimilar cognitive tests were used.

Next, the present findings revealed a series of significant cross-sectional, U-shaped, and J-shaped relations of diastolic BP to cognitive function that were moderated by age, education, and antihypertensive medication. Measurement of concurrent BP and cognitive function on >2 testing occasions greatly strengthens measurement reliability and ability to track longitudinal covariation in these 2 variables.

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implications for quality of life and daily functioning, and therefore may be clinically meaningful.

Finally, effect modification was also noted with respect to linear BP. Higher levels of systolic BP were associated with poorer performance on a test of nonverbal memory among nondrinkers. Less alcohol consumption has previously been associated with poorer cognitive function, a risk that may be exacerbated in the presence of higher BP. In addition, and similar to previous work, we noted that higher diastolic BP was associated with poorer performance on a test of working memory among less educated individuals.

Younger age, higher levels of education, use of antihypertensive medications, and some alcohol use may protect against the neurobiological consequences of high BP, and
thereby cognitive performance. Relevant mechanisms include enhanced white matter disease, small silent infarctions, brain atrophy, and atherosclerosis in the large cerebral and cerebrovascular arteries, and reduced cerebral blood flow or metabolism. Lower BP may negatively affect cognitive function by similar means via insufficient cerebral perfusion and associated neuro-pathology. Individuals with lower BP may also have comorbid cardiovascular conditions, perhaps involving left ventricular dysfunction, which may also negatively affect cognitive function. It is possible that over time, the cognitive and neurobiological correlates of hypotension and hypertension may progress to mild cognitive impairment and/or dementia. Cerebral hypoperfusion may be particularly relevant to the future development of vascular dementia and Alzheimer’s disease.

Limitations to this investigation include the sample of convenience, which was generally highly educated and predominantly white, thus limiting the study’s generalizability. Next, because the sample was followed frequently for medical comorbidities, hypertensive participants were most often medicated. Although critical for ethical reasons, it is apparent from previous investigations that BP effects on cognition are more pronounced among untreated individuals. It is unclear why systolic and diastolic BP displayed differential relations to cognitive outcomes. It is possible that, in part, reflects the known heterogeneity of hypertension and differential underlying factors (eg, genetic, hormonal, hemodynamic) that contribute to systolic versus diastolic BP elevation. Finally, the rate of attrition in the present study is unusually low. This may be attributable to that fact that study participants are contacted regularly and retain close ties with study staff. In addition, participants receive extensive medical evaluation and treatment as part of the study that may affect overall mortality rates.

To conclude, the present findings largely indicate U-shaped and J-shaped relations of BP to both cross-sectional and longitudinal cognitive performance that are moderated by age, education, or use of antihypertensive medications. Minimal linear longitudinal cognitive performance that are moderated by age, education and alcohol use. These findings indicate that studies of relations of BP to cognition were also noted as a function of education and alcohol consumption and cognitive performance in the Framingham Heart Study. Further, persons who display cognitive dysfunction or decline in association with hypertension or hypotension should be followed-up for future incidence of mild cognitive impairment and dementia. Increased awareness is needed that the brain is an early target organ of both high and low BP before stroke or dementia. Future research should address whether the biological underpinnings of BP—cognition relations differ among subgroups of individuals and further determine whether the normalization of BP level by antihypertensive treatment can prevent cognitive decline and dementia. In that regard, results of further clinical trials will be critical.

References
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Hypertension. 2005;45:374-379; originally published online February 7, 2005;
doi: 10.1161/01.HYP.0000156744.44218.74
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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Data Supplement (unedited) at:
http://hyper.ahajournals.org/content/suppl/2005/02/17/45.3.374.DC1
Figure I: Interaction of nonlinear (quadratic) diastolic BP and education for the Boston Naming Test and Trail Making B; quadratic diastolic BP and antihypertensive medication use for the Boston Naming Test and Trail Making A; quadratic diastolic BP and age for Letter Fluency. Higher scores indicate worse performance on Trail Making A and B. All results are cross-sectional (collapsed across all testing sessions).

Figure II: Interaction of linear systolic BP and alcohol consumption for the Benton Visual Retention Test, and linear diastolic BP and education for Digits Backward. Results are cross-sectional (collapsed across all testing sessions).
Systolic blood pressure

Predicted Benton Visual Retention Test errors

No drinking
Moderate drinking

Diastolic blood pressure

Predicted Digits Backward score

12 years education
16 years education