Research Article

The Relationship Between Cognitive Functioning and the JNC-8 Guidelines for Hypertension in Older Adults

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Abstract

Background: Guidelines for hypertension treatment by the Eighth Joint National Committee (JNC-8) in 2014 recommended a target systolic blood pressure (BP) of <150/<90 mmHg in persons older than 60 years, in contrast to the 2003 JNC-7 recommendations of systolic BP <140 mmHg. This study evaluated the implications of raising the BP target on cognitive functioning and conversion from normal cognition to mild cognitive impairment (MCI).

Methods: This was a longitudinal study of individuals older than 60 years enrolled in the NIH-NIA Alzheimer’s Disease Centers. All had normal cognition at baseline. 453 participants were taking BP medications and had readings of <140/<90 mmHg at four annual visits (reference group). Two other groups consisted of participants with either systolic BP of 140–149 mmHg (n = 112) or ≥150 mmHg (n = 280) on three or four annual visits.

Results: Compared with the reference and the 140–149 mmHg groups, those with BP ≥150 mmHg exhibited poorer cognitive status by Year 4 on the Mini-Mental State Exam, and they had a higher risk of conversion to MCI. The 140–149 mmHg exhibited poorer performance than the reference group on domains assessing attention and executive functioning. In contrast, their performance was not significantly different from those with BP ≥150 mmHg.

Conclusions: Persons with BP ≥150 mmHg show a faster global cognitive decline and transition to MCI than those with lower BP readings. However, the poor cognitive performance in the attention and executive functioning domains for the 140–149 mmHg group indicates the need for further research evaluating the newer recommended cutoff.

Keywords: Hypertension—Cognitive functioning—Mild cognitive impairment—Older adults—JNC-8 Guidelines

Recently introduced clinical guidelines for the treatment of hypertension proposed by the Eighth Joint National Committee (JNC-8) in 2014 recommended a higher systolic blood pressure (BP) cutoff to initiate antihypertensive treatment than the 2003 JNC-7 recommendations (1,2). These updated guidelines recommended a target BP of <150/<90 mmHg in persons who are 60 years and older, in contrast to the JNC-7 recommendations of BP <140/<90 mmHg for the same age group. After an evidence-based review of randomized clinical trials, the Committee concluded that there was strong (Grade A) evidence that in persons 60 years and older, treatment of BP to a level less than 150/90 mmHg reduced the risk of stroke, heart failure, and coronary disease. In addition, there was low quality evidence demonstrating no additional benefit of setting a goal of systolic BP <140 mmHg versus a goal of 140–160 or 140–149 mmHg.

In reaching their conclusions, the JNC-8 Committee focused on the outcomes of overall mortality (including cardiovascular disease and chronic kidney disease), myocardial infarction, heart failure, stroke, coronary and other revascularization procedures, and end-stage and biomarkers of renal disease. The guidelines did not take into account cognitive and functional outcomes associated with hypertension. These outcomes are also important to consider because hypertension is a risk factor for mild cognitive impairment (MCI) and dementia, including Alzheimer’s disease (3–7). Nearly 70% of persons in the United States who are 60 years or older have hypertension (8), and it is estimated that
13.8 million persons older than 65 years will develop Alzheimer’s disease by 2050 (9).

There have been a number of published commentaries of the JNC-8 guidelines, as well as papers addressing the treatment and economic ramifications (10–15). However, to our knowledge, only one recent study (16) investigated the implications of these recommendations on cognitive outcomes using the Atherosclerosis Risk in Communities sample. Participants were classified as either having or not having a JNC-8 recommendation for treatment when they were initially seen in midlife. Gottesman and colleagues found that individuals who would be candidates for antihypertensive treatment had a greater decline over 20 years on measures of set shifting (Digit Symbol Substitution Test) (17), timed phonemic fluency (18), and overall cognitive status which also included a word list learning task (19).

The above study (16) addressed the impact of midlife hypertension in persons aged 48–67 years at baseline. The present study evaluated the cognitive implications of the JNC-8 guidelines in persons aged 60 years and older using a broader range of cognitive measures as well as an assessment of whether they converted to a diagnosis of MCI.

Methods
Participants
Study participants were enrolled in the NIH–NIA supported Alzheimer’s Disease Centers (ADCs), a nationwide consortium of academic research sites (http://www.alz.washington.edu/WEB/study-pop.html). We used the information available from 34 past and present ADCs from January 2005 through the December 2014 data freeze. Written consent was obtained for all participants using forms approved by the institutional review boards at each site. Participants included persons aged 60 years or older with a baseline diagnosis of “normal cognition” by their ADC clinicians. Clinical diagnosis of “normal cognition” at each center relies on ADC coding guidelines specifying no MCI, dementia, or other neurological conditions resulting in cognitive impairments. This determination is typically based not only on the neuropsychological test scores but also on the Clinical Dementia Rating (CDR) (20) score which provides an index of cognitive and functional status via a structured interview with the participant and a separate interview with the study inform. Additional inclusion criteria for the present study required that persons had cognitive testing and BP recorded at every visit as part of the standard ADC research protocol, no self-reported strokes, and a minimum follow-up period of 3 years (baseline and three annual visits) in order to examine the longitudinal association of the BP guidelines on cognitive changes.

Procedures
Blood pressure is assessed annually as part of the protocol maintained by the National Alzheimer’s Coordinating Center (NACC) (21). The Uniform Data Set (UDS) guidelines require that BP be measured with the individual seated. Participants were classified into one of three groups. Group 1 consisted of those who were always normotensive (BP <140 mmHg systolic and <90 mmHg diastolic) and were also taking antihypertensive medications at all visits (reference group). The decision to require these participants to be on medications was to have a comparison group that met criteria for a definition of hypertension but yet were well controlled, in contrast to those with elevated readings. Group 2 consisted of participants with systolic BP readings of 140–149 mmHg on three or four visits, and Group 3 included persons with systolic BP readings of ≥150 mmHg on three or four visits. Persons in Group 2 and Group 3 were always classified as being in their respective group at each visit, regardless if one of their BP readings was out of range on one of the four visits. JNC-8 guidelines also specify that diastolic BP readings of ≥90 mmHg warrant treatment. However, there were no isolated cases of individuals obtaining elevated diastolic BP readings (≥90 mmHg) without concurrent elevations in systolic BPs, and therefore no one was classified into the groups based on diastolic readings only.

Outcomes
Annually administered UDS cognitive tests (22) were classified into the four domains that were identified by a previous factor analysis conducted by Hayden and colleagues (23). These domains included attention (Digit Span Forward and Backward Length and Points), executive functioning (completion time for Trails B minus Trails A, Digit Symbol Coding), language (Boston Naming Test, Semantic Fluency), and memory (Logical Memory Immediate and Delayed Recall).

Each center provided an overall clinical diagnosis for each participant of normal cognition, MCI (cognitive impairment but functionally independent), or dementia (cognitive impairment and functionally dependent). In the current study, we examined the clinical diagnoses assigned to the participants at each follow-up occasion in order to determine whether there was a change from the diagnosis of normal cognition at baseline.

Statistical Analyses
One-way analyses of variance and chi-square analyses were conducted to evaluate group differences in demographic and clinical features at baseline. Scores on the tests comprising the domains were converted to z scores based on the performance of the entire group, and these z scores were then averaged to form a composite score reflecting performance in each domain including attention, executive functioning, language, and memory. Separate repeated measures analyses of covariance with group as the between-subject factor and time as the within-subject factor were performed for overall cognitive status (Mini-Mental State Exam [MMSE]) and for each of the cognitive domains, while controlling for potential confounders including demographics (age, gender, education, and race), baseline self-reported vascular comorbidities (heart disease, diabetes, and hypertension), the CDR Sum score, average diastolic BP, and mood (depression). If the main effect and/or interaction were significant for the domain (p < .05), post hoc analyses were conducted to evaluate the individual measures contributing to the overall finding. The relative risk of conversion to a diagnosis of MCI as a function of BP classification group was examined in a separate analysis.

Results
Sample Characteristics
Four visits (baseline and three subsequent annual visits) were chosen as the follow-up period as this represented the largest homogenous analytical data set with complete cognitive and BP data. One thousand twenty-nine participants had BP readings of <140/90 mmHg on all four occasions. Of these, 452 participants were taking BP medications at all visits and thus comprised the reference group. One hundred and twelve participants had systolic readings of 140–149 mmHg on three or four visits. Of these, 90% had elevations...
on three of the four visits, with the remaining individuals having elevations on all four visits. Two hundred and eighty participants had elevations of ≥150 mmHg on three or four visits. Of these, 77% had elevations on three of the four visits, with the remaining individuals having elevations on all four visits.

Table 1 shows the demographic and clinical characteristics of the participants as a function of group classification. Individuals with BP ≥150 mmHg were less educated than the other two groups, and they were older than the reference group. The reference group had a higher percentage of men than the other groups. There were significant differences among all three groups in both their systolic and diastolic values (see also Supplementary Table 1). In terms of vascular comorbidities, the reference group had a higher percentage of persons with self-reported cardiac disease than the other groups, and both the reference group and the ≥150 mmHg group had higher self-reports of hypertension compared with the 140–149 mmHg group. There were no significant differences in self-reports of diabetes and depression.

Table 1 also shows the baseline cognitive standard test scores for the MMSE and the domains as a function of group classification. There were no significant differences (p > .05) among the groups in baseline performance.

Overall Cognitive Status
There was a nonsignificant difference among the BP groups in their overall MMSE scores collapsed over time, p = .202. However, the interaction between BP group and time was significant, p = .019 (Figure 1). Post hoc analyses revealed that at Year 4, but not at the other occasions, the mean MMSE score was significantly (p = .002) lower in persons classified in the systolic BP ≥150 mmHg group (mean = 28.36, SE = 0.11) than those classified in either the 140–149 mmHg group (mean = 28.77, SE = 0.16) or the reference group (mean = 28.79, SE = 0.09). These latter groups, in turn, did not differ from each other.

There were no significant differences in MMSE scores among the three groups at the other visits (Time 1: p = .61, Time 2: p = .30, Time 3: p = .31). The groups also differed in their decline on the MMSE from Time 1 versus Time 4, with the mean change in the MMSE score steepest for those persons classified in the ≥150 mmHg group (0.49 points, p < .001) compared with those classified in the 140–149 mmHg group, (0.01 point, p = .83), or the reference group (0.17 points, p = .04).

Cognitive Domains
There was a significant main effect (p = .03) but no significant interaction (p = .99) between group and time for the attention domain (Figure 2). The global performance collapsed across visits (Figure 3) of the 140–149 mmHg group (mean z = −0.13, SE = 0.07) was poorer than the reference group (mean z = 0.07, SE = 0.04) and the

![Figure 1. Mean MMSE scores for each blood pressure group at each annual visit. The systolic BP <140 mmHg and diastolic BP <90 mmHg group includes persons with BP readings in these ranges at every visit. The systolic BP 140–149 mmHg group or the systolic BP ≥150 mmHg group includes persons with BP readings in these ranges on at least three visits. Their group classification stays the same for all occasions. Adjusted for demographics (age, education, race, and gender), vascular comorbidities (self-reported cardiac disease, diabetes, and hypertension), average diastolic BP, depression, and initial cognitive status (CDR Sum score).](image_url)

![Figure 2.](image_url)

![Figure 3.](image_url)

**Table 1. Baseline Characteristics of Participants According to Blood Pressure Classifications**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1: No Elevations (Systolic &lt; 140 mmHg, Diastolic &lt; 90 mmHg)</th>
<th>Group 2: 3 or 4 Elevations (Systolic 140–149 mmHg)</th>
<th>Group 3: 3 or 4 Elevations (Systolic ≥ 150 mmHg)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SE</td>
<td>74.14 ± 0.36a</td>
<td>74.54 ± 0.73</td>
<td>75.75 ± 0.44a</td>
<td>.019*</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>11.0</td>
<td>10.5</td>
<td>11.0</td>
<td>5</td>
</tr>
<tr>
<td>Education, mean ± SE</td>
<td>15.63 ± 0.14a</td>
<td>15.37 ± 0.29b</td>
<td>14.61 ± 0.21a,b</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>190 (42)</td>
<td>36 (32)</td>
<td>96 (34)</td>
<td>.04</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>368 (81)</td>
<td>101 (90)</td>
<td>225 (80)</td>
<td>.06</td>
</tr>
<tr>
<td>Systolic, mean</td>
<td>122.22 ± 0.49a</td>
<td>141.73 ± 0.79a</td>
<td>159.00 ± 1.03a</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Diastolic, mean</td>
<td>69.96 ± 0.42a</td>
<td>77.66 ± 0.90a</td>
<td>81.17 ± 0.70a</td>
<td>&lt;.001*</td>
</tr>
</tbody>
</table>

| Presence of self-reported baseline conditions, n (%) | 88 (20)a,b | 9 (8)a | 29 (10)b | <.001* |
| Cardiac disease | 74 (16) | 13 (12) | 47 (17) | .41 |
| Diabetes mellitus | 334 (74)a | 61 (55)a,b | 208 (75)b | <.001* |
| Hypertension | 80 (18) | 25 (22) | 39 (14) | .12 |
| Depression | 0.04 ± 0.05 | -0.06 ± 0.09 | -0.03 ± 0.07 | .60 |
| MMSE | 0.08 ± 0.05 | -0.10 ± 0.08 | -0.05 ± 0.06 | .12 |
| Attention | 0.06 ± 0.07 | -0.06 ± 0.05 | .004 ± 0.09 | .13 |
| Executive functioning | 0.04 ± 0.07 | -0.07 ± 0.07 | .05 ± 0.05 | .41 |
| Memory | -0.02 ± 0.04 | 0.00 ± 0.07 | 0.05 ± 0.05 | .64 |

Notes: MMSE = Mini-Mental State Exam.

*Indicates a significant difference among groups as shown by the p value.

A shared letter indicates a significant difference between paired comparisons (LSD, p < .05).

'Trait' atrial fibrillation, heart attack, and congestive heart failure.

Analyses control for potential confounders including demographics (age, gender, education, and race), baseline self-reported vascular comorbidities (heart disease, diabetes, and hypertension), the CDR Sum score, average diastolic BP, and depression in the past 2 years.
(mean $z = -0.06, SE = 0.05$). Post hoc analysis of the subtests comprising the domain indicated that overall digit span length was significantly different among the groups ($p = .019$), with both the 140–149 mmHg group (mean $z = -0.12, SE = 0.07$) and the ≥150 mmHg group (mean $z = -0.08, SE = 0.05$) exhibiting shorter span lengths than the reference group (mean $z = 0.08, SE = 0.04$), but not from each other. A similar trend ($p = .05$) was observed for the number of correct trials on digit span. The 140–149 mmHg group had significantly ($p = .018$) fewer correct trials (mean $z = -0.14, SE = 0.07$) than the reference group (mean $z = 0.06, SE = 0.04$), with the performance of the ≥150 mmHg group intermediate (mean $z = -0.05, SE = 0.05$).

Analysis of the executive functioning domain consisting of coding and trail making demonstrated a significant main effect of group, $p = .013$ but no significant interaction of group and time, $p = .31$ (Figure 4). Post hoc analyses revealed poorer overall performance collapsed across visits (Figure 5) in both the 140–149 mmHg group (mean $z = -0.10, SE = 0.05$) and the ≥150 mmHg group (mean $z = -0.05, SE = 0.03$) versus the reference group (mean $z = 0.05, SE = 0.03$). The two elevated BP groups’ performance did not significantly differ from each other. Although the performances of the 140–149 mmHg and ≥150 mmHg groups were lower than the reference group on the individual measures comprising the overall domain, these group differences were not statistically significant (coding: $p = .07$; trail making: $p = .19$).

Performance on the memory and language domains did not statistically differ by group ($p = .12$ and $p = .83$) respectively.

Conversion From Normal Cognition to MCI

We examined the risk of conversion to a diagnosis of MCI as a function of whether persons were classified in the reference group, the
140–149 mmHg group, and the >150 mmHg group throughout the study. The analysis revealed that 9.1% of the reference group, 8.9% of persons classified in the 140–149 mmHg group, and 15.7% of persons classified in the ≥150 mmHg group had converted to a diagnosis of MCI at Visit 4 compared with their diagnosis of normal cognition at baseline. Logistic regression analyses, controlling for the same potential confounders as in the prior analyses, including the baseline CDR Sum score, revealed that individuals classified in the BP ≥150 mmHg group were more likely to convert to MCI compared to those classified in the BP <140 mmHg group (odds ratio [OR] = 1.76 (1.08–2.87); p = .015). In contrast, the risk of conversion to MCI was not significant for those classified in the BP 140–149 group compared with the reference group (OR = 0.85 (0.39–1.86); p = .24).

Analysis of Dropout Rate
We examined the possibility that the proportion of persons who did not return for an additional follow-up visit at Year 5 differed from those who did return as a function of their BP classification status. Twenty seven percent of those in the reference group, 37% in the 140–149 mmHg group, and 30% of those in the ≥150 mmHg group were not seen at a subsequent fifth annual visit. This difference was not significant, chi-square = 3.87, p = .15.

Secondary Analysis of Diabetes on Outcomes
The JNC-8 guidelines state that persons with BP ≥140 mmHg who also have diabetes have an “indication for treatment.” In a secondary analysis, we combined participants who had a self-reported recent history of diabetes and BP readings of 140–149 mmHg with participants having BP readings ≥150 mmHg. We continued to find a significant difference among the groups for the executive functioning domain (p = .010), but no significant interaction of group and time. The 140–149 and ≥150 mmHg BP groups performed more poorly than the reference group. The interaction of group and time was not significant; as before, digit span length was significantly poorer in the former two groups relative to the reference group. The adjusted relative risk of conversion, compared with the reference group, remained significant for those with an “indication for treatment” (OR = 2.39 (1.46–3.91); p = .001) and was nonsignificant for the <140 mmHg group without diabetes (OR = 0.73 (0.29–1.87); p = .10).

Discussion
These findings extend studies (13,14) on the treatment and economic ramifications of the new JNC-8 guidelines to encompass whether they are associated with an increased risk for cognitive impairment. In support of the newer treatment guidelines, it was found that persons 60 years and older in the systolic BPs ≥150 mmHg group exhibited a faster decline on the MMSE and a higher risk of conversion to MCI than the groups with BPs of 140–149 or <140 mmHg. Our results are consistent with those of Gottesman and colleagues (16) who reported that persons having a baseline JNC-8 indication for treatment exhibited a more rapid cognitive decline over the course of 20 years than those without a treatment indication. The higher rate of conversion to MCI was replicated in a secondary evaluation of the JNC-8 recommendation to initiate treatment if systolic BP is ≥140 mmHg and diabetes is present. It is reasonable to jointly consider hypertension and diabetes given evidence for their synergistic relationship in increasing the risk of cognitive decline and dementia (24). The NACC database relies on self-report of medical comorbidities as opposed to objective measures such as fasting glucose levels.

This may have resulted in misclassification of individuals. The presence of chronic kidney disease, another guideline for treatment, is not recorded in the NACC database.

These results, however, offer only partial support for the newer guidelines given the evidence of poor performance in attention and executive functioning for the 140–149 mmHg group. These individuals performed more poorly than the reference group on the digit span indices, and their overall executive functioning domain scores were also lower than the reference group. These findings suggest that it is premature to dismiss the importance of achieving a lower systolic cutoff than 140 mmHg in older adults. The Systolic Blood Pressure Intervention Trial (SPRINT) was recently terminated due to the unequivocal conclusion in persons 50 years and older that a target BP of 120 mmHg results in a significant reduction in cardiovascular events and death compared with a target systolic pressure of 140 mmHg (http://www.nhlbi.nih.gov/health/dci/Topics/hbp). This reduction in poor outcome was found to be comparable between persons younger than 75 years and persons 75 years or older (25). Parallel studies to identify optimal BP cutoffs to protect against cognitive decline are needed, including a consideration not only of a person’s age but also of their functional status (26). Future research with longer follow-ups could examine whether there are differences in trajectories of cognitive decline as a function of different BP cutoffs.

A limitation of our study is the small sample size in some BP categories as well as a short duration of follow-up which prevents the ability to determine at what age individuals began to experience cognitive decline. BP levels in midlife may have been responsible for cognitive decline (27–29). In addition, it is not known whether all centers followed published recommendations to obtain at least two measures of BP. Measurement at only one time point may have resulted in some spuriously elevated values due to factors such as the “white coat syndrome.” In addition, we cannot be certain that the three groups were matched in terms of their control of hypertension. For example, 55% of persons in the 140–149 mmHg group self-reported that they had hypertension, compared with 75% in the other two groups. This could mean that the mid-range group had better control. A sensitive and objective measure of subclinical vascular disease such as arterial stiffness, which predicts cognitive decline in older adults (30,31), is not available in the NACC database and could have been useful in validating the BP group classifications. Another limitation is the absence of structural and functional neuroimaging data to delineate potential mechanisms. Although we excluded individuals with a baseline report of strokes, the possibility remains that group differences could be due to intervening strokes at the follow-up occasions. We did not find significant differences in the percentage of persons in each group who reported a stroke at each time point (Follow-Up Time 1: p = .97; Time 2: p = .75, Time 3: p = .41). However, silent strokes, that is, radiologically evident lesions that lack clinically overt stroke-like symptoms, and increased microvascular disease could have been the driving mechanisms. Our study had a relatively short time frame (baseline and three subsequent annual visits) because this comprised the largest sample with complete cognitive and BP data. Finally, our analyses did not take into account at which visit a deviation in BP may have occurred or the extent of that deviation. As a result, the findings are not visit specific and this in turn may have affected the ability to detect interactions for the domain-specific scores.

Supplementary Material
Please visit the article online at http://biomedgerontology.oxfordjournals.org/ to view supplementary material.
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Conflict of Interest
None

References