High-Normal Blood Pressure Is Associated With Poor Cognitive Performance

Stefan Knecht, Heike Wersching, Hubertus Lohmann, Maximilian Bruchmann, Thomas Duning, Rainer Dziewas, Klaus Berger, E. Bernd Ringelstein

Abstract—While the relation between systolic blood pressure (SBP) and vascular events is linear down to the high-normal range, the relation between SBP and cognition is less clear. We cross-sectionally assessed the relation between SBP and cognition in a cohort extending from mid- to late-life. From a total of 2200 community-dwelling individuals we recruited 377 aged 44 to 82 years (median: 64 years, 171 male) in the SEARCH-Health study (Systematic evaluation and alteration of risk factors for cognitive health). Participants were studied with a comprehensive neuropsychological test battery that provided, based on principal component analysis, 5 composite scores for cognition (learning and memory, attention and executive function, spatial skills, working memory, and verbal skills). Global cognition was calculated from the sum of the composite scores. SBP (corrected \( R^2 = 0.007 \)), education (corrected \( R^2 = 0.203 \)), age (corrected \( R^2 = 0.102 \)), and gender (corrected \( R^2 = 0.011 \)) explained one third of variance in global cognitive performance (\( P < 0.001 \)) on multivariate analyses. Moreover, the relation between SBP (based on 10 mm Hg-categories from \(<120 \text{ mm Hg} \) to \( > 170 \text{ mm Hg} \) ) and global cognitive performance was linear in this range of SBP-values, ie, even in the normotensive range (\( \beta = -0.110, P < 0.05 \)). Subgroup analysis showed that the association of SBP and cognition was driven by results in midlife (\(<60 \text{ years} \)) individuals (\( \beta = -0.291, P < 0.005 \)). Thus, even in the normotensive range increasing systolic blood pressure is inversely related to cognition. *(Hypertension. 2008;51:1-6.)*

Key Words: hypertension ■ cognition ■ age ■ risk factors

Epidemiologic studies have shown that systolic blood pressure (SBP) is linearly associated with the risk of myocardial infarction and stroke.1–3 Cardio- and cerebrovascular diseases are related to cognitive decline in large population and patient-based cohorts.4–11 Recent evidence further indicates that the summation of vascular brain lesions, white matter damage from small vessel disease, and typical Alzheimer pathology interact bidirectionally and jointly contribute to dementia, even when each type of lesion, on its own, would not be severe enough to cause dementia.12,13 However, epidemiological reports suggest that the direct association between blood pressure and cognitive function, eg, without an intermediate clinical outcome such as stroke, is complex and may be life period–dependent. Long-term follow-up studies found that elevated SBP, occurring in midlife, increases the risk of developing clinical manifest dementia in old age.14,15 Along the same line, time survival analyses demonstrate that use of antihypertensive medication is associated with a reduced incidence of dementia.16 Clinical trials showed that antihypertensive treatment in nondemented elderly subjects with a resting systolic blood pressure of more than 160 mm Hg reduced the incidence of subsequent dementia. Thus after 4 years there were only half as many cases of dementia in the treatment as compared with the placebo group.17–19 Conversely, other antihypertensive intervention studies did not reveal significant effects on cognition.20–22 However, problems were patients lost to follow-up, active medication given to placebo patients as their blood pressure exceeded per-set values, and insensitive cognitive testing.23 Observational studies in late-life showed that also low blood pressure was associated with dementia.24,25 In the Kungsholmen project participants with a SBP below 140 mm Hg were more often diagnosed as demented than those with SBP above 140 mm Hg.26,27 The suggestion of a nonlinear J- or even U-shaped relation between cognitive function and SBP raises doubts as to how rigorously blood pressure should be lowered. The aim of our study was to determine the relation between cognitive function and SBP across the full blood pressure range in healthy, nondemented, community-dwelling individuals and to assess possible age-specific effects.

Methods

The Systematic Evaluation and Alteration of Risk factors for Cognitive Health (SEARCH)-Health study examines the contribution of modifiable risk factors for cognitive aging in community-dwelling individuals. The research protocol has been approved by...
the local ethics committee. Participants from 40 to 85 years of age were randomly selected based only on dates of birth from the population register of the city of Muenster, Germany (Figure 1). They were invited to participate in the study by letter and recruited after giving informed consent. From a total of 2200 invited citizens, 525 consented to participate. To reduce possible effects of comorbidity on the relation between blood pressure and cognition we restricted this study to nondemented and nondepressed community-dwelling individuals. We therefore excluded participants with scores below 25 points on the Mini-Mental State Examination (MMSE), and those with scores higher than 17 on the Beck Depression Inventory (BDI). We further excluded participants with a history or imaging evidence of stroke, other severe neurological conditions or psychotropic medication, and patients suffering from atrial fibrillation. These exclusions left a total of 377 community-dwelling individuals for the analyses (Table 1). All participants received a structured clinical face-to-face interview, a physical examination by a trained study physician including anthropometric measurements, blood sampling, and a comprehensive neuropsychological assessment.

Neuropsychological Assessment
Trained technicians supervised by a clinical neuropsychologist conducted the neuropsychological assessment. The test battery was designed to assess a full range of cognitive functions. Tests and their particular neurocognitive scope are listed in Table 2. To determine meaningful composite scores of cognitive domains we performed a principal component analysis of single test performances, followed by an oblique (Oblimin with Kaiser-normalization) rotation. The same test was not included in more than 1 composite score. The resulting 5 factors of the principal component analysis were z-transformed with a mean score of 0 and a standard deviation of 1.

To obtain a measure for global cognitive performance, we used the sum of the single composite scores allowing for equal loading of different cognitive domains.

Independent Variables
Blood Pressure was measured after a 20 to 40 minute rest period while subjects sat in an upright position. Three measurements were taken from the left arm, 1 from the right arm. Blood pressure values were then calculated from the average over the last 2 measures of the left arm plus the measure from the right arm. Categorical classification of systolic blood pressure was defined by 7 SBP ranges: <120 mm Hg, 120 to 130 mm Hg, 130 to 140 mm Hg, 144 to 150 mm Hg, 150 to 160 mm Hg, 160 to 170 mm Hg, and >170 mm Hg. Education was assessed as categorical variable (5 versus 7 versus 9 years of secondary school versus tertiary education).

Statistical Analyses
Multiple linear regression analysis models were used to test independently the effect of age, gender, education, and systolic blood pressure on global cognitive performance. Interactions between factors were considered using a stepwise regression analysis. The categorical classification of systolic blood pressure was used in a multiple regression model to reveal the average change (expressed as standardized regression coefficient) in global cognitive performance between different systolic blood pressure levels. The analyses were carried out using SPSS version 13.

Results
Principle component analysis derived 5 factors, which explained 66% of the total variance of all tests and proved theoretically meaningful measures for learning and memory, attention and executive function, spatial skills, working memory, and verbal skills. Their explained variance varied between 36.4% (factor “learning and memory”) and 5.6% (factor “verbal skills”).

On multiple regression analysis age, education, gender, and systolic blood pressure explained one third of variance in global cognitive performance (corrected $R^2=0.323$, $P<0.001$) (Table 3). On reiterating the regression model with categorical SBP-variables the relation between SBP and cognition proved linear in the range from $<120$ mm Hg to $>170$ mm Hg ($\beta=-0.110$, $P<0.05$) (Figure 2).

All regression models were also calculated with “use of antihypertensive medication” as additional covariate to exclude the effect of specific treatment on cognitive performance. There was no effect of antihypertensive medication on the outcome of any regression analysis. Note that many

<table>
<thead>
<tr>
<th>Table 1. Characteristics of Participants (n=377)</th>
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<td>SBP</td>
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<td>DBP*</td>
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<td>Hypertension in history</td>
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<td>Hypertensive on examination†</td>
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<td>Comorbid disease‡</td>
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*DBP indicates diastolic blood pressure. †SBP: $\leq 140$ mm Hg. ‡Myocardial infarction, coronary artery disease, cancer, or diabetes.
participants had elevated SBP despite medication and that we used actual measures of SBP as dependent variable. Additionally, we tested for effects of other potential confounders including body mass index, smoking pack years, alcohol use, serum cholesterol, and glycosylated hemoglobin A. By univariate analysis only body mass index and HbA1c rendered significant relations. However, including these factors as covariates did not change the relation between SBP and cognition.

Subgroup analysis for mid- and late-life (midlife individuals 40 to 60 years of age and late-life individuals 60 years of age) revealed that in midlife education (corrected $R^2=0.145$) and SBP (corrected $R^2=0.092$) were significant predictors for global cognitive performance ($P<0.001$). In late-life the effect of SBP on global cognitive performance did not reach significance.

**Discussion**

The main finding of the present study was that there is an inverse relation between systolic blood pressure and cognition that is linear and extends into the normotensive range i.e., below 140 mm Hg. Thus, the relation between SBP and cognitive function parallels the established linear relation between SBP and vascular risk.1–3,39 Importantly this relation is driven by effects in midlife rather than late-life. The strengths of this study are the community-based design, the wide age range, the exclusion of depressed or demented individuals. Note that because we used a MMSE of 25 to exclude dementia, individuals with mild cognitive impairment participated. Additionally we adjusted for potential confounders and performed in-depth neuropsychological testing. However, several methodological issues deserve mention. First, data were obtained from cross-sectional observation. This introduces variability attributable to unrelated differences between subjects. We tried to minimize variability by setting inclusion criteria to obtain a homogenous sample and testing for confounders. Second, blood pressure in our cohort was measured only on the day of examination. Although we took care to have subjects rest and follow a standardized protocol, white coat hypertension is always a concern. However, if there had been a white coat effect in our cohort resulting in higher SBP measures, this would indicate that people can already be cognitively impaired when they show high-normal SBP only under stress—and presumably...
not outside the clinic. Further, no reliable information could be obtained on the history and duration of blood pressure increase. Use of antihypertensive medication did not affect any of the correlations investigated. Missing information on duration of hypertension may have decreased the sensitivity in this study. Data on the duration of increased SBP would have been particularly helpful for late-life individuals who are likely to have longer and more variable duration of SBP increase.

Although there was a significant major effect for SBP on cognition in the overall cohort (Figure 1), on subgroup analysis only the effect in midlife remained significant—but not the one in individuals older than 60 years of age. It has been suggested that in late-life because of greater atherosclerotic blood flow resistance, individuals may require increased SBP to maintain cerebral perfusion pressure whereas normal SBP would lead to insufficient cerebral blood supply.24,40 This concept was derived from observations in cohorts in which participants up to 101 years of age were included, and in which dementia was not an exclusion criterion.29 Here low blood pressure may additionally be the consequence rather than the cause of neurodegeneration because neurodegeneration may decrease cognition and SBP in parallel.9,41,42 Thus in late-life cohorts—like in our late-life subgroup—different and partially counterpoising factors may complicate the relation between SBP and cognition.

In midlife there was a strong inverse relation between SBP and cognition. This cross-sectional finding extends previous work. Systolic hypertension in midlife was shown to increase the risk of cognitive decline after more than 6 years.7,11,15,43,44 Additionally, Elias and colleagues in a series of studies described the correlation between hypertension and cognitive impairment.6,45,46 Here we show that the linear negative relation between SBP and cognition not only holds for hypertension but also for high normal SBP, ie, below 140 mmHg. Although high-normal SBP or prehypertension

<table>
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<th>Table 3. Regression Coefficients and Coefficients of Determination, Dependent Variable: Global Cognitive Performance, SBP as Continuous Variable</th>
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<tr>
<td>Variables*</td>
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<td>Midlife subgroup, n=88†</td>
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<td>Late-life subgroup, n=289</td>
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*B indicates raw regression coefficient; SE, standard error; β, standardized regression coefficient.
†Excluded variables: age, gender.

Figure 2. Adjusted means of the global cognitive score for each 10 mm Hg—category of systolic blood pressure (n=377). Assuming constant scores for all other neuropsychological tests and a continuous linear trend (regression coefficient β=−0.110), each 10 mm Hg increase in SBP would approximate 2 words recalled less on long term retrieval (AVLT–recall trial 7), where the average number of words recalled in our cohort was 11 of 15.
has become a major research focus in relation to stroke and heart attack, its relation to cognition had so far not been appreciated. High-normal SBP seems to be a starting point in the cardiovascular disease continuum.\(^7\) High-normal SBP is associated with higher cardiovascular risk.\(^8\) Lowering high-normal SBP decreases the progression of atherosclerosis suggesting that high-normal SBP contributes to subclinical target organ damage.\(^9\) Our data indicate that not only above normal but also high normal SBP leads to cerebral endorgan damage that functionally manifests as poorer cognition. This observation parallels recent evidence in individuals younger than 40 years of age with high-normal blood pressure who show preclinical cardiac disease.\(^10\)

Cognitive impairment at high-normal SBP is likely associated with structural brain damage. Future studies will have to determine how such changes can best be determined with high-resolution MRI.\(^11\) For practical purposes the most urgent question at this point is whether cognition and preservation of cognitive function in individuals with high-normal SBP can be improved by timely lowering of blood pressure to low normal levels.

**Perspectives**

The present cross-sectional analysis revealed a linear negative correlation between systolic blood pressure and cognition. Notably, this relation also held for high-normal systolic blood pressure suggesting a continuum of brain damage beginning at per-hypertension levels. Because the relation was driven by results in midlife, these findings link tight control of medical parameters early in life to the growing epidemic of cognitive impairment and dementia in late life. The present findings raise the question how much cognitive benefit could be gained from antihypertensive medication started in mid- rather than late life and at rigorous preset blood pressure values.

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**Disclosures**

None.

**References**


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