

Blood Pressure and Cognitive Impairment in India and the United States

A Cross-National Epidemiological Study

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Objective: To evaluate the relationship between blood pressure (BP) and cognitive impairment in elderly populations in India and the United States in a cross-national epidemiological study.

Design: Cross-sectional comparisons, using standardized cognitive screening and BP measurements.

Participants: We examined 4810 subjects 55 years and older, of whom 595 were 75 years and older, from Ballabgarh, India, and 636 subjects 75 years and older from the Monongahela Valley, Pennsylvania.

Main Outcome Measures: General cognitive impairment, defined as scores at or below the 10th percentile of each cohort on a general mental status test—the Mini-Mental State Examination (United States) and the Hindi Mental State Examination (India)—and memory impairment, defined as scores at or below the 10th percentile of delayed recall of word lists at both sites.

Results: Mean systolic BP (SBP) and diastolic BP (DBP) were 115 and 75 mm Hg (India) and 141 and 76 mm Hg (United States). Logistic regression adjusting for age, sex, and education or literacy was used to calculate odds ratios (ORs) and associated 95% confidence intervals (CIs) for cognitive impairment. In Ballabgarh, for every 10 mm Hg increase in SBP there was a 10% reduction in cognitive impairment (OR, 0.90; 95% CI, 0.83-0.97), and there was a 13% reduction in cognitive impairment (OR, 0.87; 95% CI, 0.76-0.99) with every 10 mm Hg increase in DBP. In the Monongahela Valley, a similar association between DBP and cognitive impairment did not remain significant after adjustment for confounders (OR, 0.83; 95% CI, 0.65-1.06).

Conclusions: In both Indian and American samples, lower DBP was inversely related to cognitive impairment, although not significantly in the latter. Low BP may be an effect of, or a potential risk factor for, degenerative brain disease.

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BY THE year 2020 more than 700 million people aged 60 years and older will be living in developing countries.¹ However, there are very few studies examining the distribution of and risk factors for cognitive impairment in these countries. Cross-national epidemiological studies can shed light on potential risk factors by identifying similarities and differences in disease associations in disparate populations. Such information can help to formulate new etiological hypotheses and to develop preventive strategies.

Previous studies examining the association between blood pressure (BP) and cognitive function in developed countries have provided conflicting results.²⁻¹² Previous longitudinal studies have consistently found an association between elevated midlife BP and late-life cognitive impairment.^{2,10-13} However, cross-sectional relationships between BP and cognitive impairment have varied across studies; some

studies found cognitive impairment to be associated with high BP,^{2,3,9,10} whereas others found associations with low BP.^{4,8} One study reported a relationship with high diastolic BP (DBP),⁷ another reported an association with high systolic BP (SBP),¹⁴ and a third showed no association at all.⁵

The relationship between BP and cognition is probably not simple. Variations in BP may be effects of or potential risk factors for degenerative brain disease. We evaluated the cross-sectional relationship between BP and cognitive impairment in a cross-national epidemiologic study of 2 rural older populations in India and the United States. We believe that this is the first such report in the literature.

METHODS

BACKGROUND

The Indo-US Cross National Dementia Epidemiology Study was a collaborative project be-

tween the Center for Ageing Research in India and the University of Pittsburgh and was funded by the National Institute on Aging from 1991-1999. The Indian sample consisted of 5126 individuals 55 years and older from the Ballabgarh district in the state of Haryana in northern India. The details of the sampling and recruitment of the Ballabgarh sample have been described previously.¹⁵ The US study sample was part of the Monongahela Valley Independent Elders Survey (MoVIES Project) in southwestern Pennsylvania. Further details regarding this sample of elderly persons followed from 1987-2002 have been reported elsewhere.¹⁶⁻¹⁸

COGNITIVE TESTS

Initially, we developed a set of cognitive tests for the largely illiterate, Hindi-speaking, rural, older population of Ballabgarh. These tests included a general mental status test and a brief battery of neuropsychological tests tapping a range of cognitive domains known to be affected in dementia. We have previously reported descriptions of and norms for this Hindi cognitive test battery,^{19,20} which was translated and adapted from the MoVIES cognitive screening battery, which in turn incorporated the Consortium to Establish a Registry for Alzheimer's Disease²¹ neuropsychological test panel. For this report, we defined cognitive impairment based on performance on 2 tests. The general mental status test was the Mini-Mental State Examination (MMSE)²² in the US population and the Hindi Mental State Examination (HMSE), a Hindi adaptation of the MMSE for illiterate Hindi speakers, in India.²⁰ General cognitive impairment was defined as performance at or below the score representing the 10th percentile in each sample, which was 23 on the MMSE in the US sample and 21 on the HMSE in the Indian sample, both out of a possible total of 30 points.

The memory test was Delayed Recall of a 10-Item Word List (DRWL)²³ at both sites. Auditory rather than visual presentation of words was used because of the illiteracy of the Indian sample.¹⁹ Memory impairment was defined as performance at or below the 10th percentile score, which was 3 of 10 on the DRWL at both sites.

BP MEASUREMENT

Blood pressure was measured with a mercury sphygmomanometer in the right arm in the sitting position after the subject had rested for 5 minutes both in Ballabgarh and the Monongahela Valley.

STUDY SAMPLES

Ballabgarh, India

Of the 5126 participants from Ballabgarh, 4810 completed cognitive screening and are the basis of this article. The 316 participants who were not cognitively screened included 269 participants who died before screening, 36 who refused to be tested, and 11 with inadequate hearing. All 4810 screened participants had complete data on the HMSE and BP, and 4796 had data on both BP and the DRWL.

Monongahela Valley, Pennsylvania

The original US sample consisted of 1681 individuals 65 years and older who underwent cognitive screening at study entry (wave 1). At approximately 2-year intervals, surviving participants underwent cognitive retesting, completing 6 biennial data collection waves over the course of the study. At waves 2, 3, 4, 5, and 6, the numbers of participants were 1342, 1165, 1016, 845, and 651. As the cohort aged, attrition between waves was

primarily due to mortality (9%-14%) and less for other reasons, such as drop out and relocation (mean, 2.8%). For this report, we present cross-sectional data collected at wave 6, the first wave at which BP data were collected on all participants completing cognitive testing. At wave 6, a total of 651 participants were evaluated; 636 had complete data on both the MMSE and BP, and 568 had complete data on both the DRWL and BP.

DATA COLLECTION

Informed consent was obtained from all individuals according to the protocols approved by the University of Pittsburgh Institutional Review Board, and, for the Ballabgarh site, also by the Human Volunteers Protection Committee of the Centre for Ageing Research in India. Trained field workers or research associates performed cognitive screening of consenting participants, with training and supervision from the project neuro-psychologist at each site.

STATISTICAL METHODS

Data analysis was performed using SAS statistical software (version 8.0; SAS Institute Inc, Cary, NC). The Pearson χ^2 test was used to test for significant differences between groups on categorical data, and the Wilcoxon rank sum test or Kruskal-Wallis test, as appropriate, was used to test differences between groups on continuous variables. Multiple logistic regression models were fit to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for associations between BP and cognitive impairment adjusting for age, sex, literacy or education, and history of stroke. Two separate models, with the cognitive impairment variables as outcomes, were constructed to assess the association of BP with cognitive functioning. The dependent variable in the first model was general cognitive impairment, defined as a score at or below the 10th percentile on the HMSE or MMSE; in the second model, the dependent variable was memory impairment, defined as a score at or below the 10th percentile on the DRWL. Age was treated as a continuous variable, and the other variables were categorical: sex (male vs female), literacy (literate vs illiterate, in Ballabgarh) or education (less than high school vs more than or equal to high school, in the Monongahela Valley), and history of stroke (absent vs present). Systolic and diastolic BPs were recoded into categories with each unit increase representing an increase in 10 mm Hg. Adequacy of the models was assessed using the Hosmer and Lemeshow goodness-of-fit statistic,²⁴ and there was no lack of fit.

RESULTS

DEMOGRAPHIC CHARACTERISTICS

The Indian study sample (n=4810) had a mean (SD) age of 66.5 (7.2) years; 52.7% were men, and 72.1% (61.8% of women and 38.2% of men) were illiterate (**Table 1**). In the US sample (n=636), the mean (SD) age was 81.7 (4.2) years; 67.0% were women, and 33.8% (36.7% of men and 32.4% women) had less than a high school education.

BP AND COGNITIVE IMPAIRMENT

BP by Cognitive Impairment

Mean (SD) SBP and DBP were examined among those with and without cognitive impairment in the Indian and US samples (**Table 2** and **Table 3**). In Ballabgarh, SBP was 114.8 (12.3) mm Hg, and DBP was 74.3 (7.3) mm Hg. Both

SBP and DBP were significantly lower in participants with impaired scores on the HMSE and the DRWL. In the Monongahela Valley, SBP was 141.3 (18.4) mm Hg, and DBP was 76.2 (9.9) mm Hg. Only DBP was significantly lower in participants with lower MMSE scores.

Logistic Regression Analysis

General Cognitive Impairment. In Ballabgarh, there were significant inverse associations between general cognitive impairment (HMSE score ≤ 21) and both SBP and DBP (**Table 4**). For every 10 mm Hg increase in SBP there was a 10% reduction in general cognitive impairment (OR, 0.90; 95% CI, 0.83-0.97), and with every 10 mm Hg increase in DBP there was a 13% reduction in general cognitive impairment (OR, 0.87; 95% CI, 0.76-0.99). In the Monongahela Valley, a similar association between DBP and general cognitive impairment (MMSE score) was found but did not remain significant after adjustment for age, sex, education, and history of stroke (OR, 0.83; 95% CI, 0.65-1.06). When the analysis in Ballabgarh was restricted to participants aged 75 years and older, the associations between SBP and general cognitive impairment became weaker (OR, 0.85; 95% CI, 0.71-1.01; $P = .06$), and the association between DBP and general cognitive impairment was not significant (OR, 0.92; 95% CI, 0.69-1.20) after adjusting for confounders.

Specific Memory Impairment. In the Ballabgarh cohort, there was a significant inverse association between memory impairment (DRWL scores ≤ 3) and SBP (OR, 0.87; 95% CI, 0.81-0.94) (Table 4). A similar inverse association between DRWL scores and DBP approached significance ($P = .06$) after adjusting for confounders (OR, 0.89; 95% CI, 0.79-1.00). However, in the Monongahela Valley cohort, there was no significant association between performance on the DRWL and either SBP or DBP. Restricting the analysis in Ballabgarh to participants aged 75 years and older, the associations between SBP and memory impairment still remained significant (OR, 0.77; 95% CI, 0.65-0.91), whereas the association between DBP and memory impairment was not significant (OR, 0.88; 95% CI, 0.68-1.20) after adjusting for confounders.

BP AND ANTIHYPERTENSIVE MEDICATION

None of the Indian sample reported taking antihypertensive medication, whereas 229 (36.0%) of the US sample did so. In the US sample, mean (SD) SBP was 142.3 (19.9) mm Hg and DBP was 76.5 (9.7) mm Hg among those taking medication. These were not significantly different from the mean (SD) SBP of 140.7 (17.5) mm Hg and DBP of 76.0 (9.9) mm Hg among those not taking medication. There was no association between taking antihypertensive medication and general cognitive impairment ($\chi^2_1 = 0.21, P = .64$) or memory impairment ($\chi^2_1 = 2.96, P = .08$).

COMMENT

In our sample in Ballabgarh, India, analyses adjusted for age, sex, literacy, and stroke history revealed that older

Table 1. Sample Demographic Characteristics*

Characteristic	Ballabgarh, India (n = 4810)	Monongahela Valley, Pennsylvania (n = 636)
Age group, y		
55-64	2333 (48.5)	NA
65-74	1882 (39.1)	NA
75-84	505 (10.5)	493 (77.5)
≥ 85	90 (1.9)	143 (22.5)
Women	2277 (47.3)	426 (67.0)
Literacy or education		
More educated (\geq high school)	NA	421 (66.2)
Literate (able to write a sentence and read a newspaper)	1301 (27.0)	NA

Abbreviation: NA, not applicable.

*Data are given as the number (percentage) of participants.

adults with general cognitive impairment were significantly more likely than those without impairment to have lower SBP and DBP. On the specific memory test, there was a significant inverse association between memory impairment and SBP; a similar association with DBP was only of borderline significance after adjusting for confounders. In our Monongahela Valley sample, we failed to find similar associations between cognitive impairment and BP, suggesting a potential cross-national difference in risk factors.

Previous studies have reported mixed results regarding the relationship of cognitive impairment and BP. Cross-sectionally, Scherr et al⁵ found no association between either SBP or DBP and cognitive performance; Wallace et al⁷ found that only elevated DBP was associated with poor memory performance; and Budge et al¹⁴ reported that higher MMSE scores were significantly associated with lower SBP. A prospective study by Launer et al¹¹ found that elevated midlife SBP was a significant predictor of poor cognitive functioning in later life. In a large community-based elderly Swedish cohort, Guo et al⁸ found that those with lower baseline SBP had an almost 2-fold elevated risk of low MMSE scores at 3-year follow-up. In another cohort study, Glynn et al¹² showed that those with lower SBP were more likely to have incident cognitive impairment. In the Framingham study, Farmer et al⁴ found that participants 75 years and older with isolated systolic hypertension had better cognitive performance than those without systolic hypertension, but not after adjusting for confounding variables. Our findings from the Monongahela Valley are similar to those reported from the Framingham cohort⁴ and the Honolulu-Asia Aging Study,¹⁰ in which there was no cross-sectional association between BP and cognitive performance. There are no previous studies from developing countries or from South Asia to which we can compare our findings from Ballabgarh.

The difference in findings between the Ballabgarh and Monongahela Valley samples could be at least partly explained by differences in the distribution of BP between them, which itself was at least partly a function of age differences. Mean SBPs in Ballabgarh and the Monongahela Valley were 115 mm Hg and 146 mm Hg, respectively, whereas the mean DBP in both populations were

Table 2. Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) by Cognitive Impairment in the Ballabgarh, India, Sample

	No. of Subjects	SBP		DBP	
		Mean (SD), mm Hg	P Value	Mean (SD), mm Hg	P Value
Total sample	4810	114.8 (12.3)	NA	74.3 (7.3)	NA
Age group, y					
55-64	2333	115.0 (12.0)] <.001*	74.6 (7.4)] <.001*
65-74	1882	115.1 (12.6)		74.4 (6.9)	
75-84	505	113.4 (12.7)		73.3 (6.9)	
≥85	90	111.8 (11.6)		73.0 (6.8)	
General cognitive impairment					
Unimpaired, HMSE score >21	4174	115.2 (12.4)] <.001†	74.5 (7.4)] <.001†
Impaired, HMSE score ≤21	636	112.7 (11.7)		73.3 (6.7)	
Memory impairment					
Unimpaired, DRWL score >3	4070	115.2 (12.4)] <.001†	74.5 (7.4)] <.001†
Impaired, DRWL score ≤3	726	112.9 (11.8)		73.6 (7.0)	

Abbreviations: DRWL, Delayed Recall of a 10-Item Word List; HMSE, Hindi Mental State Examination; NA, not applicable.

*Kruskal-Wallis test.

†Wilcoxon rank sum test.

Table 3. Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) by Cognitive Impairment in the Monongahela Valley, Pennsylvania, Sample

	No. of Subjects	SBP		DBP	
		Mean (SD), mm Hg	P Value*	Mean (SD), mm Hg	P Value*
Total sample	636	141.3 (18.4)	NA	76.2 (9.9)	NA
Age group, y					
75-84	493	141.5 (17.8)] .86	76.8 (9.7)] .01
≥85	143	140.5 (20.4)		74.3 (10.1)	
General cognitive impairment					
Unimpaired, MMSE score >23	553	141.7 (17.7)] .30	76.6 (9.8)] .02
Impaired, MMSE score ≤23	83	138.6 (22.1)		73.6 (9.8)	
Memory impairment					
Unimpaired, DRWL score >3	484	141.9 (17.3)] .98	76.7 (9.8)] .17
Impaired, DRWL score ≤3	84	141.6 (20.5)		74.9 (9.8)	

Abbreviations: DRWL, Delayed Recall of a 10-Item Word List; MMSE, Mini-Mental State Examination; NA, not applicable.

*All comparisons are based on the Wilcoxon rank sum test.

Table 4. Association of Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) With Cognitive Impairment

Impairment	Ballabgarh, India				Monongahela Valley, Pennsylvania			
	SBP		DBP		SBP		DBP	
	Unadjusted*	Adjusted†	Unadjusted*	Adjusted†	Unadjusted*	Adjusted†	Unadjusted*	Adjusted†
General cognitive impairment‡	0.83 (0.77-0.90)	0.90 (0.83-0.97)	0.77 (0.68-0.88)	0.87 (0.76-0.99)	0.90 (0.79-1.02)	0.91 (0.80-1.03)	0.74 (0.59-0.94)	0.83 (0.65-1.05)
Memory impairment§	0.84 (0.78-0.90)	0.87 (0.81-0.94)	0.84 (0.75-0.94)	0.89 (0.79-1.00)	0.99 (0.87-1.13)	0.96 (0.82-1.12)	0.83 (0.66-1.01)	0.95 (0.73-1.25)

*Odds ratio (95% confidence interval) using logistic regression analysis.

†Odds ratio (95% confidence interval) adjusted for age, sex, history of stroke, and literacy (India) or education (United States) using logistic regression analysis.

‡General cognitive impairment defined as a Hindi Mental State Examination score of 21 or lower for the Indian group and a Mini-Mental State Examination score of 23 or lower for the US group.

§Memory impairment defined as a score of 3 or lower on the Delayed Recall of a 10-Item Word List test.

similar, 75 mm Hg and 76 mm Hg, respectively. Notably, 36% of participants in our US cohort, but none of our Indian cohort, were taking antihypertensive medication. However, there were no significant differences in the mean SBP and DBP between those taking and not tak-

ing antihypertensive medication and no association between cognitive impairment and antihypertensive medication use in the US cohort. This finding is similar to the reports from the Honolulu-Asia Aging Study,¹⁰ the Framingham Study,³ and the Goteborg study²⁵ in which

no association was found between antihypertensive medication use and development of cognitive decline or dementia. These findings are, however, at odds with those of the prospective community-based studies in Kungsholmen, Sweden, and Indianapolis, Ind, in which antihypertensive medication use reduced the risk of developing cognitive impairment.^{8,26} The findings of Launer et al¹⁰ that elevated midlife SBP predicted later-life cognitive impairment were interpreted as suggesting that adequate treatment of midlife SBP would help in preventing cognitive impairment in later life. Possible mechanisms for this reduced risk include reduced risk of severe complications of hypertension (eg, cerebral lesions) in those who have been treated for hypertension.²⁷

Cross-sectional and prospective population-based studies have found that both SBP and DBP were inversely related to the prevalence or subsequent incidence of dementia in elderly people.²⁸⁻³⁰ Although Skoog³¹ also found a similar relationship, he suggested that age-related changes in the brain may contribute to low BP in very elderly persons, with the low BP being an effect rather than a cause of dementia. Burke et al,³² examining BP records of autopsy-proven AD patients, found sustained BP declines in subjects with AD starting 3 to 4 years after AD was diagnosed. They postulated that BP is altered as neurons that regulate BP, including the C-1 tonic vasomotor neurons, degenerate in AD.³²

One possible mechanism by which the reverse might occur, ie, why low BP might cause cognitive impairment, is reduced cerebral blood flow in white matter (WMCBF). In a study examining WMCBF and its relationship to SBP, all participants with AD had low WMCBF as compared with control subjects. The SBP was significantly lower in the AD group and was positively correlated with WMCBF.³³ Zuccala et al³⁴ reported that low SBP (<130 mm Hg) in participants with heart failure predicted cognitive impairment. They suggested that low SBP in heart failure patients may reflect left ventricular dysfunction or increase the impact of reduced ventricular function on cerebral blood flow.³⁴ Both lower SBP and DBP values have been associated with white matter lesions.³⁵ Increased frequency of white matter lesions has been reported in association with cognitive impairment³⁶⁻³⁸ and AD.³⁸⁻⁴¹ Neuropathological studies have also demonstrated that chronic hypoperfusion can lead to subcortical alterations.^{42,43} Mesial temporal ischemia might account for memory difficulties given that hippocampal cells are exquisitely sensitive to hypoxia. Diminished BP during surgery following exsanguinating trauma frequently results in loss of short-term memory. However, we do not have neuroimaging data with which to determine the prevalence of white matter lesions in either of our populations. Further, although severe hypotension can cause white matter injury in vascular watershed areas, mean BP values in the range described in our study have been associated with less, rather than more, white matter abnormalities in the Atherosclerosis Risk in Communities Study.⁴⁴

To our knowledge this is the first report comparing the association between cognitive impairment and BP in samples drawn from developed and developing countries. A limitation is its cross-sectional nature, which does

not allow us to establish a temporal relationship between exposure (ie, low BP) and outcome (ie, cognitive impairment). Thus, the association we found in Ballabgarh can only suggest that low BP is a potential risk factor for cognitive impairment or dementia. The reverse could also be true, ie, low BP could be an effect rather than a cause of dementia, as suggested by Skoog.³¹ Further, because cross-sectional studies examine all prevalent cases without regard to their duration, they are subject to length bias; cases of longer duration will be overrepresented and may skew the results. Thus, true causal relationships can only be identified through cohort studies. Future prospective studies from both developed and developing countries starting at younger ages with longer follow-up periods and with serial measurements of both BP and cognitive functioning will help determine whether BP is a modifiable risk factor for cognitive impairment and dementia.

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