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Research Article

Does Antihypertensive Use Moderate the Effect of Blood Pressure on Cognitive Decline in Older People?

Matthew J. Lennon, MD,[1,2,*] Ben Chun Pan Lam, PhD,[1,2] John Crawford, PhD,[1,2] Henry Brodaty, DSc,[1,2,3] Nicole A. Kochan, PhD,[1,2] Julian N. Trollor, MD,[2,4] Katya Numbers, PhD,[1,2] Brian Draper, MD,[2,5] Anbupalam Thalamuthu, PhD,[1,2] and Perminder S. Sachdev, PhD[1,2,6]

[1]Faculty of Medicine, University of New South Wales, Sydney, Australia. [2]Centre for Healthy Brain Aging (CHeBA), School of Psychiatry, University of New South Wales, Sydney, Australia. [3]Dementia Centre for Research Collaboration, School of Psychiatry, University of New South Wales, Sydney, Australia. [4]Neuropsychiatric Institute, Eastern Suburbs Mental Health Service, Randwick, Australia. [5]Eastern Suburbs Older Persons' Mental Health Service, Randwick, Australia. [6]Department of Developmental Disability Neuropsychiatry, School of Psychiatry, University of New South Wales, Sydney, Australia.

*Address correspondence to: Matthew Lennon, MD, Faculty of Medicine, University of New South Wales, High Street, Sydney, NSW 2052, Australia. E-mail: matthew.lennon@unsw.edu.au

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Abstract

Background: While midlife hypertension is deleterious, late-life hypertension has been associated with better cognitive outcomes in several studies. Many questions remain, including the relative benefit or harm of a blood pressure (BP) target and antihypertensive therapy of <120 in very old individuals.

Methods: The Sydney Memory and Aging Study (n = 1015) comprises a cohort of 70- to 90-year-olds, who were followed biennially for 8 years. Global cognition was assessed with a battery of 10 neuropsychological tests. Blood pressure was measured at Waves 1 and 2 and classified into 3 systolic groupings: group 1 (≤120 mmHg), group 2 (121–140 mmHg), and group 3 (>140 mmHg). Multiple regression, linear mixed modeling, and Cox regression examined the effect of BP and antihypertensives.

Results: There were no overall significant differences in global cognition or dementia between the disparate BP groups. However, in those not taking antihypertensives, the systolic BP (SBP) > 140 mmHg group had a significantly worse global cognitive trajectory compared to SBP ≤ 120 mmHg (b = –0.067, 95% CI [–0.129, –0.006], p = .030). Within the SBP ≤ 120 mmHg group those taking antihypertensives had significantly worse global cognition trajectories compared to those not taking antihypertensives even when controlling for past history of hypertension (b = –0.077, 95% CI [–0.147, –0.007], p = .030).

Conclusions: Untreated hypertension in old age is related to worse global cognitive decline. However, ongoing treatment at new recommendations of lower SBP targets may be related to poorer cognitive decline and should be considered carefully in older populations.

Keywords: Aging, Cognition, Hypertension, Longitudinal studies, Medications

Between 31% and 48% of dementia has been attributed to modifiable risk factors (1,2). One of the most prevalent risk factors for cognitive decline is hypertension, estimated to affect approximately 1 billion individuals worldwide (3). There is strong evidence that hypertension in midlife contributes to cognitive decline in late life (4) but, in contrast, 2 meta-analyses found no significant relationship between late-life hypertension (>65 years of age) and dementia (5,6).

Longitudinal studies of cognition in older people have variously found weak negative (7,8), null (9–11), or positive associations between hypertension (12–14) and cognition. In the Rotterdam and Gothenburg H-70 studies, it was found that there was an 11% reduction in dementia risk for every 10-mmHg increase in systolic blood pressure (SBP) (13). It is hypothesized that older adults, particularly those with long-standing hypertension, will have worsened

atherosclerosis and arteriolosclerosis, requiring higher cerebral perfusion pressures to sustain cerebral metabolic demands (13). Therefore, lower blood pressures (BPs) in people with a history of hypertension may put them at risk of poorer cognitive function. Animal studies have found that cerebral hypoperfusion is linked with cognitive decline and upregulated amyloid precursor protein (15). Thus, there is evidence that optimal BP for cognition varies with age and that higher BPs may be protective against cognitive decline in late life.

Given the complexity of the relationship between BP and cognitive decline, the question of whether treating high BP in older people improves cognitive outcomes remains unclear. The American Heart Association found that observational studies demonstrated a progressive effect of hypertension on cerebrovascular damage, and although several trials indicated that antihypertensive use may improve cognition in late life (16), the overall evidence was not conclusive (17). Iatrogenic hypotension, falls, poor cerebral perfusion, and renal impairment, which can result from antihypertensive use, may worsen cognitive outcomes (18). However, the increased risk of hemorrhagic or ischemic strokes and cerebrovascular disease from untreated hypertension may be of greater clinical significance for cognition (16). Those on antihypertensives, but who are still hypertensive, may have better cognitive outcomes than those with normal or low BP (13). Particular classes of antihypertensives (eg, angiotensin receptor blockers/angiotensin converting enzyme inhibitors) may also have a significantly better impact on cognitive performance suggesting that there may be direct positive cognitive effects from these particular drugs in addition to lowering BP (19,20).

In 2016, several meta-analyses found that stricter (ie, "intensive") BP targets of <120 mmHg resulted in significantly better cardiovascular, renal, and mortality outcomes when compared to traditional targets of <140 mmHg. This remained true in clinical trials (16,21) of older individuals, which demonstrated reduced risk of mortality was associated with a target BP of ≤120 for persons aged 65, 75, and 80 years. Accordingly, definitions of hypertension and BP recommendations have changed for all populations over the years to become stricter (22). Importantly, studies have not yet examined the question of whether there is a trade-off between cognitive decline and reduced risk of mortality when employing intensive BP targets. Our study explores whether new BP targets are associated with cognitive outcomes or dementia in late life (>70 years old) and if these relationships are moderated by antihypertensive drug use in a large, well-characterized cohort study of older Australians.

Method

Participants

Between 2005 and 2007, 1015 individuals without dementia aged 70–90 years old were recruited from the eastern suburbs of Sydney following a random approach to 8914 individuals on the electoral roll to participate in the Sydney Memory and Aging Study (see Figure 1) (23). Inclusion criteria were the ability to speak and write English sufficiently well to complete a psychometric assessment and self-report questionnaires. Exclusion criteria included any major psychiatric diagnoses, acute psychotic symptoms, or a current diagnosis of multiple sclerosis, motor neuron disease, developmental disability, progressive malignancy, or dementia. Additional exclusion criteria included a Mini-Mental State Examination (MMSE; score of <24, adjusted for age, education, and a non-English-speaking background at baseline). More detailed methods of recruitment and baseline

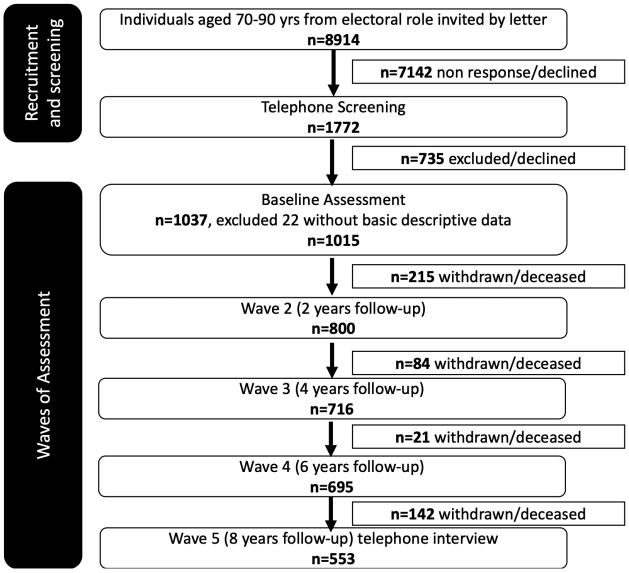

Figure 1. Flow chart of the Sydney Memory and Aging Study recruitment and waves of assessment adapted from Sachdev et al (33).

demographics have been previously published (23). Comprehensive neuropsychological, medical, biochemical, and genetic assessments were performed biennially, in addition to a collateral interview from a knowledgeable support (ie, an informant). Individuals were assessed in person every 2 years (Wave 2 at 2 years, Wave 3 at 4 years, and Wave 4 at 6 years). For Wave 5 (8-year follow-up), the assessment protocol for participants was administered over the phone and included basic demographics, medical history, subjective complaints, a brief telephone screen for dementia, and self-reported ability to perform daily activities.

Neuropsychological Test Scores

Trained psychology graduates administered a comprehensive neuropsychological test battery covering 5 major cognitive domains: attention/processing speed (Trail Making Test A (24), Digit-Symbol Coding (25)); language (Boston Naming Test (30-item) (26), Category Fluency (Animals) (27)); memory (Benton Visual Retention Test (Recognition) (28), Logical Memory Story A delayed recall (29), Rey Auditory Verbal Learning Test (Total learning, Immediate recall and delayed recall) (30)); executive function (Letter fluency (FAS) (31), Trail Making Test B (24)); visuospatial (Block Design) (32). The individual test scores for each participant were transformed into *Z*-scores using the means and standard deviations (*SD*s) of scores within a healthy reference group at baseline, comprising a baseline subsample of participants who were free from having a history of major illnesses that could affect cognition. If necessary, the signs of the *Z*-scores were reversed, so that higher scores reflect better performance for all tests. Domain scores were calculated by first obtaining the average of the *Z*-scores of tests comprising each domain. These averages were then transformed to *Z*-scorers to form standardized domain scores using the means and *SD*s within the healthy baseline subsample. Global cognition scores for each wave were calculated in a similar manner, by first obtaining the average of the cognitive domain scores at each wave and then standardizing these by transformed to *Z*-scores using the mean and *SD* or this average within the healthy baseline reference group. If the skewness of the domain or global cognition scores were outside the range of

positive one to negative one, they were transformed using the logarithmic, or other appropriate, function to more closely approximate the normal distribution (24,25,32).

Clinical Diagnoses

Diagnoses of dementia were made at each wave in a consensus conference involving at least 3 clinicians from an expert panel of neuropsychologists, neuropsychiatrists, and old age psychiatrists after review of all clinical data and collateral information from an informant (33). Dementia was diagnosed according to the criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and required deficits in at least 2 cognitive domains, including memory, and impairment in activities of daily living (34). If a participant was diagnosed with dementia at baseline, they were excluded from the study.

Definition of Hypertension and Other Covariates

Standardized measurement of BP was taken 3 times (and averaged) at each wave using an automated electronic sphygmomanometer (OMRON HEM-7121) on the right arm in a seated position after a period of rest. The BP was taken either at a study center or in the participants home if they were incapable of visiting the center. In the current study, if the mean BP in both Waves 1 and 2 was elevated, then the individual was grouped into the higher BP group. If BP was not elevated in both waves, then the participant was grouped into the lower of the 2 BP groups (eg, if SBPs were 135 and 115 mmHg, then they would be grouped into the <120 mmHg group). Cases were grouped into 3 categories based only on measured BP: group 1 (≤120 mmHg), group 2 (121–140 mmHg), and group 3 (>140 mmHg), according to the 2017 consensus guidelines (22). Following the SPRINT-MIND trial, which examined only the SBP targets, we examined systolic rather than diastolic BPs (16). In addition, lifetime history of hypertension as diagnosed by a physician, and current antihypertensive treatment information were also obtained.

Covariates were participants' self-reported medical history of regular smoking, atrial fibrillation, stroke, transient ischemic attack, diabetes, and acute myocardial infarction. Alcohol use was included as an ordinal variable based on daily use (0 standard drinks/day, 1 drink/day, >1 drink/day). Genetic analysis was performed to assess apolipoprotein E (APOEe4) genotype (33).

Statistical Analysis

Baseline characteristics of the groups were compared using analysis of variance (ANOVA) for continuous variables and chi-squared for discrete variables. Linear mixed models were used to assess the effect of hypertension on cognition over 6 years (there was only 6 years of follow-up for neuropsychological testing). To avoid multicollinearity, time in study was centered at the average follow-up time of 4.6 years (only including up to Wave 4). Multiple regression models were used to assess the associations at baseline. The 121–140 mmHg and >140 mmHg groups were both individually compared with the ≤120 mmHg group. For the linear mixed models and regressions, 2 sets of models were performed: Model 1 was partially adjusted for demographics, including age, sex, and education (Model Construction: *Time in study, Age, Sex, Education, BP group, BP group*Time in study*). Model 2 was fully adjusted to include the additional covariates (Model Construction: *Time-in-study, Age, Sex, Education, BP group, Antihypertensive use, Years of antihypertensive use, acute myocardial infarction, atrial fibrillation, diabetes, stroke, transient ischemic attack, history of regular smoking, alcohol use, BP group*Time in Study*). To assess the effect of antihypertensives use at Wave 1 on cognitive change, a third model was run that included a 3-way interaction between antihypertensives, BP group, and time in study, as well as 2-way interactions among these predictors. Intercept and time (slopes) were treated as random effects to account for between-participant heterogeneity and within-participant correlations across waves. The same models were applied both using (as a replacement for Hypertension group) "physician diagnosis of hypertension" and SBP as continuous variables, and examining continuous SBP variables as time-varying predictor. This method used to partition the between- and within-person effects of SBP was taken from Hedeker and Gibbons (35). Model fit was assessed using Akaike and Bayesian information criteria. Results were treated as significant if $p < .05$.

Cox proportional hazards models were used to estimate the association of hypertension and incident dementia over 8 years. Two models were run, similar to what was performed with the linear mixed model, the first included age, sex, and education and the second including all of the relevant covariates.

Results

Baseline Characteristics and Attrition

Overall attrition of the sample at Wave 4 (6 years follow-up) was 31.5% (13.5% deceased) and at Wave 5 (8 years of follow-up) was 45.5% (20.9% deceased), with similar rates of attrition between BP groups over previous waves. Compared to those retained in Wave 5, those who dropped out were significantly older, less educated, used more antihypertensives, and had higher rates of previous hypertension, acute myocardial infarction, atrial fibrillation, stroke, and transient ischemic attack (see Supplementary Table 1). For SBP groupings, the 121–140 mmHg and >140 mmHg groups were more likely to be male, older, and APOE*4 carriers at baseline than those with SBP ≤ 120 (see Table 1). In the ≤120 mmHg group those on antihypertensives had significantly higher rates of previous hypertension diagnoses compared to those not on antihypertensives (75.0% vs 4.9%).

Hypertension and Cognition

There was no significant difference between the ≤120 mmHg, 121–140 mmHg, and >140 mmHg and for global cognition either at baseline or over 6 years (see Table 2).

Supplementary analyses revealed no significant effect of physician-diagnosed hypertension, or SBP, as a continuous variable, on global cognition either at baseline or over 6 years (see Supplementary Tables 2 and 3).

Antihypertensives and Cognition

There was a significant 3-way interaction between the systolic >140 mmHg group (vs the systolic ≤120 mmHg group), antihypertensive use, and time in study ($b = 0.102$, 95% CI [0.023, 0.181], $p = .008$; see Table 3), such that being on antihypertensives or not affected the relationship between the SBP group (>140 mmHg compared to ≤120 mmHg) and the rate of cognitive decline.

Over the 6 years for those individuals not on antihypertensives, those with SBP >140 mmHg had stronger decline in global cognition compared with those with SBP ≤120 mmHg ($b = -0.067$, 95% CI [−0.129, −0.006], $p = .030$). Conversely, for those on antihypertensives there was no significant difference between the

Table 1. Summary of Baseline Characteristics for Population

	Group 1 (<120)	Group 2 (121–140)	Group 3 (>140)	*p* Value	Total
Number at baseline	121 (100)	453 (100)	458 (100)		1015
Wave 2 follow-up (% baseline)	101 (83.5)	406 (89.6)	379 (82.8)		800 (78.8)
Wave 3 follow-up (% baseline)	90 (74.4)	364 (80.4)	336 (73.4)		716 (70.5)
Wave 4 follow-up (% baseline)	82 (67.8)	329 (72.6)	294 (64.2)		695 (68.5)
Wave 5 (phone) follow-up (% baseline)	69 (57.0)	272 (60.0)	232 (50.7)		553 (54.5)
Mean time in study for Wave 4 (mean ± *SD*)	4.4 ± 2.3	4.8 ± 2.0	4.4 ± 2.2	.459	4.6 ± 2.1
Age at baseline (mean ± *SD*)	78.1 ± 4.9	78.5 ± 4.7	79.4 ± 4.8	.004	78.8 ± 4.8
Sex (% female) (F/M)	62.8 (76/45)	60.5 (274/179)	47.8 (219/239)	.000	55.2%
Education (mean ± *SD*)	11.7 ± 3.6	11.4 ± 3.4	11.7 ± 3.5	.441	11.5 ± 3.5
Antihypertensive use (yes %)	66.1	63.7	65.1	.557	62.1%
Previous diagnoses of hypertension for those using vs not using antihypertensives (% vs %)[a]	75.0 vs 4.9	82.9 vs 13.4	90.3 vs 22.0	.000	85.3 vs 16.2
Years of antihypertensive use (mean ± *SD*) (excluding those not on antihypertensives)	12.4 ± 10.2	12.1 ± 10.5	12.9 ± 10.7	.925	12.6 ± 10.7
Previous diagnosis of hypertension (%)	51.2	57.6	66.5	.000	60.9%
Acute myocardial infarction (%)	15.7	11.5	10.7	.010	11.6%
Atrial fibrillation (%)	9.3	6.0	6.8	.041	6.7%
Diabetes (%)	8.3	13.3	12.1	.011	12.2%
Stroke/transient ischemic attack (%)	3.3/4.2	5.1/7.5	2.9/6.6	.002/.040	4.0%/6.7%
Ever smoked regularly (%)	60.3	50.8	55.3	.000	54%
Alcohol use (% none, 1 std/day, >1 std/day)	17.4, 37.2, 45.5	14.3, 37.7, 47.9	9.6, 38.0, 52.4	.000	12.6, 37.7, 49.7
APOE4 carrier (%)	18.8	23.2	22.6	.126	22.6%

Notes: Summary of characteristics at baseline for 3 BP groupings by systolic measures. Between-group comparisons made by ANOVA and Pearson's chi-squared analyses. ANOVA = analysis of variance; APOE4 = apolipoprotein E4; BP = blood pressure; *SD* = standard deviation.

[a]The percentages reflect the proportion of those previously diagnosed with hypertension first in the group taking antihypertensives and second in those not taking antihypertensives (eg, 85.3 vs 16.2 indicates 85.3% of those taking antihypertensives had previously been diagnosed with hypertension and whereas only 16.2% of those not taking antihypertensives had a previous diagnosis).

SBP >140 mmHg group and the SBP ≤120 mmHg group on the change in global cognition over time (b = 0.034, 95% CI [−0.014, 0.083], p = .168) (see Supplementary Tables 5 and 6 for raw scores).

Alternatively, this significant 3-way interaction could be thought of as the effect of taking antihypertensives on cognitive decline being different depending on the SBP group. Among systolic ≤120 mmHg individuals, those on antihypertensives had a significantly worse decline in global cognition compared to those not on antihypertensives (b = −0.077, 95% CI [−0.147, −0.007], p = .030). By comparison, within those with systolic >140 mmHg, taking antihypertensives did not significantly affect the rate of cognitive decline (b = 0.025, 95% CI [−0.010, 0.061], p = .170); see Supplementary Tables 8 and 9.

Dementia Outcomes

There was no significant association between SBP and risk of dementia over 8 years (see Table 4). In the subgroup analyses for those on or not on antihypertensives there was also no significant difference in risk (see Supplementary Tables 4 and 7).

Discussion

In the Untreated Population Higher SBPs Are Associated With Worse Cognitive Function

Our study found that participants who were not on antihypertensives had significantly worse global cognitive decline in the systolic >140 mmHg group compared to the systolic ≤120 mmHg group. On average those with systolic >140 mmHg had a worse decline of 0.067 *SD*s of global cognition per year compared to those with systolic ≤120 mmHg, which over 6 years would translate to a 0.40-*SD* worsened decline. It is difficult to given an objective clinical interpretation of this given that global cognition is a composite of multiple cognitive tests; however, to give a relative interpretation, the average overall decline over 6 years in the whole cohort was 0.40 *SD* meaning that a systolic of >140 mmHg would approximately double that decline over the same time period. Compared to the normative sample a deviation of 0.40 SD would translate to a drop of 15% in the percentile rank. This is in contrast to several studies which found that, specifically for older individuals (>75 years old), higher BPs are protective for cognitive decline and dementia diagnosis, although they did not examine the interaction between BP and antihypertensive use (36,37).

Antihypertensive Use in Patients With Lower SBP Is Associated With Worsened Cognitive Trajectories

Our study showed that patients with systolic ≤120 mmHg on antihypertensives had a significantly worse trajectory of global cognition compared to those not on antihypertensives. This may indicate that iatrogenic lowering of BP may have adverse cognitive effects particularly at the lower end of BP. As a potential confounder to this finding, those on antihypertensives in this ≤120 mmHg group had significantly higher rates of previous diagnosis of hypertension compared to those not on antihypertensives (75.0% vs 4.9%). The difference in these cognitive trajectories may relate to this previous diagnosis of hypertension rather than the current BP and antihypertensive use. However, if this were the case we would anticipate that there would be a significant difference between the 2 groups at baseline, which there was not, and also when including

Table 2. Summary of Effects of BP on Global Cognition

Variable	Model 1[a]				Model 2[b]			
	Coefficient (95% CI)	*p* Value	Coefficient (95% CI)	*p* Value	Coefficient (95% CI)	*p* Value	Coefficient (95% CI)	*p* Value
	Systolic 121–140 vs <121		**Systolic >140 vs <121**		**Systolic 121–140**		**Systolic >140**	
Time	**−0.113 (−0.147 to −0.080)**	**.000***			**−0.111 (−0.145 to −0.076)**	**.000***		
BP Group	−0.094 (−0.359 to 0.171)	.489	−0.039 (−0.307 to 0.227)	.769	−0.063 (−0.337 to 0.210)	.650	−0.055 (−0.330 to 0.220)	.695
BP Group × Time	−0.000 (−0.038 to 0.037)	.988	−0.002 (−0.040 to 0.036)	.916	−0.000 (−0.038 to 0.038)	.983	−0.005 (−0.044 to 0.033)	.783

Notes: Summary of linear mixed model results examining effect of various measures of BP on global cognition, a composite standardized measure of performance on the battery of neuropsychological tests. Time has been grand mean centered and thus the effect of the "BP group" is at study midpoint. The effect of time is for the <120 group. BP = blood pressure. Significant results in bold.

[a]Model 1 adjusted for sex, age, and education.

[b]Model 2 adjusted for sex, age, education, antihypertensive use, years of antihypertensive use, acute myocardial infarction, atrial fibrillation, diabetes, stroke, transient ischemic attack, history of regular smoking, and alcohol use.

*$p < .05$.

Table 3. Summary of Effects of SBP and Antihypertensive Use on Global Cognition

Variable	Model 1[a]				Model 2[b]			
	Coefficient (95% CI)	*p* Value	Coefficient (95% CI)	*p* Value	Coefficient (95% CI)	*p* Value	Coefficient (95% CI)	*p* Value
Systolic	**Systolic 121–140**		**Systolic >140**		**Systolic 121–140**		**Systolic >140**	
Time	**−0.066 (−0.120 to −0.011)**	**.018***			**−0.064 (−0.118 to −0.009)**	**.021***		
BP Group	−0.210 (−0.654 to 0.233)	.352	−0.376 (−0.824 to 0.071)	.100	−0.116 (−0.559 to 0.327)	.607	−0.336 (−0.783 to 0.111)	.140
BP Group × Time	−0.039 (−0.100 to 0.021)	.205	**−0.064 (−0.126 to −0.003)**	**.040***	−0.033 (−0.094 to 0.027)	.275	**−0.067 (−0.129 to −0.006)**	**.030***
Antihypertensives (y/n)	−0.443 (−0.938 to 0.052)	.080			−0.372 (−0.886 to 0.141)	.155		
Antihypertensives × BP Group	0.187 (−0.366 to 0.741)	.507	0.530 (−0.026 to 1.09)	.062	0.095 (−0.467 to 0.658)	.739	0.460 (−0.103 to 1.02)	.109
Antihypertensives × Time	**−0.077 (−0.146 to −0.008)**	**.028***			**−0.077 (−0.147 to −0.007)**	**.030***		
Antihypertensives × BP Group × Time	0.063 (−0.014 to 0.140)	.109	**0.100 (0.022 to 0.178)**	**.012***	0.055 (−0.022 to 0.134)	.163	**0.102 (0.023 to 0.181)**	**.011***

Notes: Summary of linear mixed model results examining effect of BP and antihypertensive use on global cognition, a composite standardized measure of performance on the battery of neuropsychological tests. Time has been grand mean centered and thus the effect of the "BP group" is at study midpoint. BP = blood pressure; SBP = systolic blood pressure. Significant results in bold.

[a]Model 1 adjusted for sex, age, and education.

[b]Model 2 adjusted for sex, age, education, antihypertensive use, years of antihypertensive use, acute myocardial infarction, atrial fibrillation, diabetes, stroke, transient ischemic attack, history of regular smoking, and alcohol use.

*$p < .05$.

Table 4. Cox Proportional Hazards Ratios for Dementia Risk

Risk of Dementia	Model 1[a] HR (95% CI)	*p* Value	Model 2[b] HR (95% CI)	*p* Value
≤120 mmHg	1.00		1.00	
121–140 mmHg	1.069 (0.657 to 1.738)	.789	1.096 (0.648 to 1.852)	.733
>140 mmHg	1.089 (0.791 to 1.500)	.599	1.049 (0.735 to 1.497)	.792

Notes: Summary of Cox proportional hazards ratios examining the effect of systolic BP (grouped into 3 groups) on risk of all-cause dementia. BP = blood pressure; HR = hazard ratio.

[a]Model 1 adjusted for sex, age, and education.

[b]Model 2 adjusted for sex, age, education, antihypertensive use, years of antihypertensive use, acute myocardial infarction, atrial fibrillation, diabetes, stroke, transient ischemic attack, history of regular smoking, and alcohol use.

previous diagnosis of hypertension as a covariate in the model the significant results would disappear, but the results were unchanged. Thus, the results seem to reflect the impact of antihypertensive use rather than previous diagnosis of hypertension.

The above 2 results taken together are consistent with the inverted U-shaped cognition–BP relationship, such that there was steeper cognitive decline in both the high and low BP (38–40). This suggests that those at the higher end of BP suffer from ongoing hypertensive insults and also those in the systolic ≤120 mmHg group who have their BP lowered further suffer from ongoing hypotensive insults. A number of studies have demonstrated this inverted U-shaped relationship. The lower cut point for SBP at which cognition is affected varies between studies (eg, East Boston Cohort Study <130, Duke Population Study <110), but generally new BP target recommendations (SBP < 120) are related to worse cognition. The putative basis for poorer cognitive outcomes with lower BP is that because of a loss of cerebral vascular autoregulation and arteriolosclerosis, higher cerebral perfusion pressures are needed to prevent cerebral ischemia and subsequent deficits (41).

In a recent systematic review of 7 clinical trials including adults >60 years old, Weiss et al (42) found there was no evidence that antihypertensive treatment was linked to worse cognition. However, 6 out of 7 of these trials had a standard BP target of <150 mmHg. The Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (43) (ACCORD-MIND trial), a randomized control antihypertensive trial of diabetics aged 55 and older, examined differences in intensive BP treatment (<120 mmHg) and standard treatment (<150 mmHg). While there were no differences at 3.3 years follow-up in cognitive performance, they did find significantly diminished whole brain volume in the intensive treatment group, suggesting that there may have been subclinical effects of intensive therapy.

There have been very few studies that have examined the effect of BP treatment on cognition while stratifying for initial BP. However, in the cardiovascular disease literature a recent meta-analysis (44) of 10 antihypertensive trials stratifying for baseline BP found that for those patients with SBP of <140 mmHg antihypertensive treatment increased cardiovascular mortality by 15% (relative risk 1.15, 95% CI 1.00–1.32). The authors suggest that intensive treatment causes insufficient blood flow to vital organs (44) and that particularly in patients with arterial stiffening, frequently found in diabetic and older patients, perfusion is especially reliant on SBP.

The recent HYVET (21) and SPRINT (16) trials have made strong cases for intensive BP therapy for individuals >75 years given significant mortality benefits. However, our study suggests that ongoing antihypertensive treatment of patients with SBP <120 may have deleterious cognitive effects. Further trials of antihypertensive use in older people are needed to clarify the nature and size of these effects.

The Relationship Between Late-Life Hypertension and Dementia May Be Obscured by a Latency of BP Effect and Participant Dropout

Consistent with recent meta-analyses (5,6), we found no significant association between late-life SBP and incident dementia, in contrast with the established link between midlife hypertension and dementia (45). There are several reasons that a putative relationship between hypertension and dementia in late life may be obscured. First, there is a considerable latency effect (about 8–22 years) between metabolic disease onset to eventual diagnosable dementia (46). Second, hypertension has different impacts on cognitive function at different ages and, as discussed previously, may have protective or negligible effects for dementia in late life (11). Third, given the small numbers of diagnosed dementia patients in our study the analysis may be underpowered to detect significant differences in rates of diagnosis between the groups. Finally, particularly for studies in late life, cognitively impaired and hypertensive participants are more likely to drop out from longitudinal studies due to death or discontinuation, which may partially obscure true associations (in our study in those retained 41% had BP > 140 compared with 50% of those who dropped out).

Strengths and Limitations

Our study had several strengths including a community-dwelling, reasonably representative sample, detailed neuropsychological evaluation of participants, longitudinal long-term follow-up, multiple assessments of BP, and assessment of dementia diagnoses by an expert panel.

Several limitations of this study should be considered. As an inevitable part of longitudinal studies of aging, there was the considerable loss to follow-up (45.5% of the population over 6 years of the study) due to death, disability, and discontinuation. Those with hypertension and those poorer cognition both were more likely than average to drop out likely contributing to attrition bias. Linear mixed models were used to minimize the nonrandom attrition bias introduced. Dementia screening at Wave 5 (8 years) was performed over the telephone using the Modified Telephone Interview for Cognitive Status (TICS-M) and informant-rated basic and instrumental activities of daily living function, without assistance of comprehensive neuropsychological testing. While this is not the gold standard the TICS-M has been validated demonstrating good predictive ability for incident dementia (sensitivity = 77%; specificity = 88%) (47). Measurement of BP did not use 24-hour monitoring, measure of arterial stiffness, examination of systolic diastolic gap, nor reports of reliability of measures of BP. Interpretation of our results is challenged by potential reverse causation. That is, neurodegenerative processes may lead to the development of autonomic dysregulation and hypotension (48) rather than the other way around.

Key to our study was the examination of antihypertensive medications. However, we did not examine distinction between the different types of medication, the number of antihypertensives, or the degree of compliance to the medication regime, each of which may have confounding effects for cognitive outcomes. Antihypertensives may have direct deleterious or protective effects aside from their BP

modification effects and thus positive effects may not be generalizable to all BP-lowering agents. Aside from this, the confounding effects such as the degree of health consciousness of diagnosed hypertensive participants and unmeasured comorbidities cannot be controlled for in cohort studies and our findings should be corroborated in a randomized control trial.

A challenge with all BP research is that of accurate BP monitoring and measurement. Automatic BP measurements have a tendency to underestimate true BP and office BP reading tends to overestimate due to the well-documented white coat hypertension effect (49). Twenty-four-hour ambulatory BP measurement is the gold standard in diagnosing hypertension, but it was overly burdensome for older participants in a community cohort. To minimize the effect of the variability, we used 3 measurements of BP within each follow-up and incorporated 2 waves of BP measurement into the diagnosis of hypertension.

Conclusion

Our study found that untreated hypertension in old age is related to worse global cognitive decline. However, ongoing treatment at new recommendations of lower SBP targets may be also be related to worse cognitive decline. Further trials examining the difference between traditional and intensive BP targets should be performed.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflicts of Interest

None declared.

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Author Contributions

All authors have contributed to the work, agree with the presented findings, and that the work has not been published before nor is being considered for publication in another journal.

Ethics Approval

Ethics approval was granted for the Memory and Aging Study (Sydney MAS) by the Ethics Committees of the University of New South Wales, and the South Eastern Sydney and Illawarra Area Health Service. Written informed consent was taken from the participating individuals and their informants. Each participant was free to refuse a specific part of the assessment (such as blood sampling or MRI) or to withdraw from the study. Data are securely stored at the University of New South Wales.

References

1. Prince MJ, Wu F, Guo Y, et al. The burden of disease in older people and implications for health policy and practice. *Lancet*. 2015;385(9967):549–562. doi:10.1016/S0140-6736(14)61347-7
2. Ashby-Mitchell K, Burns R, Shaw J, Anstey KJ. Proportion of dementia in Australia explained by common modifiable risk factors. *Alzheimers Res Ther*. 2017;9(1):11. doi:10.1186/s13195-017-0238-x
3. Bloch MJ. Worldwide prevalence of hypertension exceeds 1.3 billion. *J Am Soc Hypertens*. 2016;10(10):753–754. doi:10.1016/j.jash.2016.08.006
4. Gąsecki D, Kwarciany M, Nyka W, Narkiewicz K. Hypertension, brain damage and cognitive decline. *Curr Hypertens Rep*. 2013;15(6):547–558. doi:10.1007/s11906-013-0398-4
5. Guan JW, Huang CQ, Li YH, et al. No association between hypertension and risk for Alzheimer's disease: a meta-analysis of longitudinal studies. *J Alzheimers Dis*. 2011;27(4):799–807. doi:10.3233/JAD-2011-111160
6. Power MC, Weuve J, Gagne JJ, McQueen MB, Viswanathan A, Blacker D. The association between blood pressure and incident Alzheimer disease: a systematic review and meta-analysis. *Epidemiology*. 2011;22(5):646–659. doi:10.1097/EDE.0b013e31822708b5
7. Insel KC, Palmer RF, Stroup-Benham CA, Markides KS, Espino DV. Association between change in systolic blood pressure and cognitive decline among elderly Mexican Americans: data from the Hispanic established population for epidemiology study of the elderly. *Exp Aging Res*. 2005;31(1):35–54. doi:10.1080/03610730590882837
8. Kuo H, Jones RN, Milberg ÃWP, et al. Effect of blood pressure and diabetes mellitus on cognitive and physical functions in older adults: a longitudinal analysis vital elderly cohort. *Am J Geriatr*. 2005;53:1154–1161. doi:10.1111/j.1532-5415.2005.53368.x
9. Hassing LB, Hofer SM, Nilsson SE, et al. Comorbid type 2 diabetes mellitus and hypertension exacerbates cognitive decline: evidence from a longitudinal study. *Age Ageing*. 2004;33(4):355–361. doi:10.1093/ageing/afh100
10. Hebert LE, Scherr PA, Bennett DA, et al. Blood pressure and late-life cognitive function change: a biracial longitudinal population study. *Neurology*. 2004;62(11):2021–2024. doi:10.1212/01.wnl.0000129258.93137.4b
11. Li G, Rhew ÃIC, Shofer JB, et al. Age-varying association between blood pressure and risk of prospective cohort study. *J Am Geriatr Soc*. 2007;55:1161–1167. doi:10.1111/j.1532-5415.2007.01233.x
12. Skoog I, Lernfelt B, Landahl S, et al. 15-year longitudinal study of blood pressure and dementia. *Lancet*. 1996;347(April):1141–1145. doi:10.1016/s0140-6736(96)90608-x
13. Ruitenberg A, Skoog I, Ott A, et al. Blood pressure and risk of dementia: results from the Rotterdam study and the Gothenburg H-70 Study. *Dement Geriatr Cogn Disord*. 2001;12(1):33–39. doi:10.1159/000051233
14. Joas E, Bäckman K, Gustafson D, et al. Blood pressure trajectories from midlife to late life in relation to dementia in women followed for 37 years. *Hypertension*. 2012;59(4):796–801. doi:10.1161/HYPERTENSIONAHA.111.182204
15. de la Torre JC, Pappas BA, Prevot V, et al. Hippocampal nitric oxide upregulation precedes memory loss and A beta 1-40 accumulation after chronic brain hypoperfusion in rats. *Neurol Res*. 2003;25(6):635–641. doi:10.1179/016164103101201931
16. The SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med [Internet]*. 2015;373(22):2103–2116. doi:10.1056/NEJMoa1511939
17. Iadecola C, Yaffe K, Biller J, et al. Impact of hypertension on cognitive function: a scientific statement from the American heart association. *Hypertens (Dallas, Tex 1979)*. 2016;68(6):e67–e94. doi:10.1161/HYP.0000000000000053
18. Walker KA, Power MC, Gottesman RF. Defining the relationship between hypertension, cognitive decline, and dementia: a review. *Curr Hypertens Rep*. 2017;19(3):24. doi:10.1007/s11906-017-0724-3

19. Levi Marpillat N, Macquin-Mavier I, Tropeano AI, Bachoud-Levi AC, Maison P. Antihypertensive classes, cognitive decline and incidence of dementia: a network meta-analysis. *J Hypertens*. 2013;31(6):1073–1082. doi:10.1097/HJH.0b013e3283603f53
20. Shah K, Qureshi SU, Johnson M, Parikh N, Schulz PE, Kunik ME. Does use of antihypertensive drugs affect the incidence or progression of dementia? A systematic review. *Am J Geriatr Pharmacother [Internet]*. 2009;7(5):250–261. Accessed March 24, 2020. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med6&NEWS=N&AN=19948301.
21. Peters R, Beckett N, Forette F, et al. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. *Lancet Neurol*. 2008;7:683–689. doi:10.1016/S1474-4422(08)70143-1
22. Whelton PK, Carey RM, Aronow WS, et al. Clinical practice guideline 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology. *Hypertension*. 2018;71:13–115. doi:10.1161HYP.0000000000000065
23. Connors MH, Sachdev PS, Kochan NA, Xu J, Draper B, Brodaty H. Cognition and mortality in older people: the Sydney Memory and Ageing Study. *Age Ageing*. 2015;44(6):1049–1054. doi:10.1093/ageing/afv139
24. Reitan RM, Wolfson D. *The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation*. 2nd ed. Tucson, AZ: Neuropsychology Press; 1993.
25. Wechsler D. *Wechsler Adult Intelligence Scale-III*. San Antonio, TX: The Psychological Corporation; 1997.
26. Kaplan E, Goodglass H, Weintraub S, Goodglass H. *Boston Naming Test*. Philadelphia, PA: Lea & Febiger; 1983.
27. Spreen O, Benton AL. *Neurosensory Centre Comprehensive Examination for Aphasia Manual (NCCEA)*. Victoria, BC, Canada: University of Victoria; 1969.
28. Benton A. A visual retention test for clinical use. *Arch Neurol Psychiatry [Internet]*. 1945;54(3):212–216. doi:10.1001/archneurpsyc.1945.02300090051008
29. Wechsler D. *Wechsler Adult Intelligence Scale-3rd Edition (WAIS-3)*. San Antonio, TX: Harcourt Assessment; 1997.
30. Rey A. *L'Examen Clinique en Psychologie*. Paris: Presses Universitaires de France; 1964.
31. Benton AL. Problems of test construction in the field of aphasia. *Cortex*. 1967;3:32–58. doi:10.1016/S0010-9452(67)80005-4
32. Wechsler D. *WAIS-R Manual*. New York: The Psychological Corporation; 1981.
33. Sachdev PS, Brodaty H, Reppermund S, et al. The Sydney Memory and Ageing Study (MAS): methodology and baseline medical and neuropsychiatric characteristics of an elderly epidemiological non-demented cohort of Australians aged 70-90 years. *Int Psychogeriatr*. 2010;22(8):1248–1264. doi:10.1017/S1041610210001067
34. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM IV)*. 4th ed. Washington, DC: American Psychiatric Press, Inc.; 1994.
35. Hedeker D, Gibbons RD. *Longitudinal Data Analysis*. Hoboken, NJ: Wiley-Interscience; 2006. xx, 337–xx, 337 (Wiley Series in Probability and Statistics).
36. Nilsson SE, Read S, Berg S, Johansson B, Melander A, Lindblad U. Low systolic blood pressure is associated with impaired cognitive function in the oldest old: longitudinal observations in a population-based sample 80 years and older. *Aging Clin Exp Res*. 2007;19(1):41–47. doi:10.1007/BF03325209
37. Launer LJ, Masaki K, Petrovitch H, Foley D, Havlik RJ. The association between midlife blood pressure levels and late-life cognitive function. The Honolulu-Asia Aging Study. *JAMA*. 1995;274(23):1846–1851. doi:10.1001/jama.1995.03530230032026
38. Guo Z, Fratiglioni L, Winblad B, Viitanen M. Blood pressure and performance on the mini-mental state examination in the very old. Cross-sectional and longitudinal data from the Kungsholmen Project. *Am J Epidemiol*. 1997;145(12):1106–1113. doi:10.1093/oxfordjournals.aje.a009073
39. Glynn RJ, Beckett LA, Hebert LE, Morris MC, Scherr PA, Evans DA. Current and remote blood pressure and cognitive decline. *JAMA*. 1999;281(5):438–445. doi:10.1001/jama.281.5.438
40. Bohannon AD, Fillenbaum GG, Pieper CF, Hanlon JT, Blazer DG. Relationship of race/ethnicity and blood pressure to change in cognitive function. *J Am Geriatr Soc*. 2002;50(3):424–429. doi:10.1046/j.1532-5415.2002.50104.x
41. Xing CY, Tarumi T, Meijers RL, et al. Arterial pressure, heart rate, and cerebral hemodynamics across the adult life span. *Hypertension*. 2017;69(4):712–720. doi:10.1161/HYPERTENSIONAHA.116.08986
42. Weiss J, Freeman M, Low A, et al. Benefits and harms of intensive blood pressure treatment in adults aged 60 years or older: a systematic review and meta-analysis. *Ann Intern Med*. 2017;166(6):419–429. doi:10.7326/M16-1754
43. Williamson JD, Supiano MA, Applegate WB, et al. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged ≥75 years: a randomized clinical trial. *JAMA*. 2016;315(24):2673–2682. doi:10.1001/jama.2016.7050
44. Brunström M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. *BMJ*. 2016;352:i717. doi:10.1136/bmj.i717
45. Lennon MJ, Makkar SR, Crawford JD, Sachdev PS. Midlife hypertension and Alzheimer's disease: a systematic review and meta-analysis. *J Alzheimers Dis*. 2019;71(1):307–316. doi:10.3233/JAD-190474
46. Vermunt L, Sikkes SAM, van den Hout A, et al. Duration of Alzheimer disease in the preclinical, prodromal and dementia stage: a multi-state model analysis. *Alzheimer's Dement J Alzheimer's Assoc* [Internet]. 2017;13(7):P585–P586. doi:10.1016/j.jalz.2017.07.212
47. Bentvelzen AC, Crawford JD, Theobald A, et al. Validation and normative data for the modified telephone interview for cognitive status: the Sydney Memory and Ageing Study. *J Am Geriatr Soc*. 2019;67(10):2108–2115. doi:10.1111/jgs.16033
48. Passant U, Warkentin S, Gustafson L. Orthostatic hypotension and low blood pressure in organic dementia: a study of prevalence and related clinical characteristics. *Int J Geriatr Psychiatry*. 1997;12(3):395–403.
49. Muntner P, Shimbo D, Carey RM, et al. Measurement of blood pressure in humans: a scientific statement from the American Heart Association. *Hypertension [Internet]*. 2019;73(5):e35–e66. doi:10.1161/HYP.0000000000000087