Chapter 2

Blood pressure and cognition

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ABSTRACT

Objectives: To evaluate whether the relationship between blood pressure (BP) measures and cognitive function is different according to age and functional status in older outpatients.

Design: Cross-sectional.

Setting: Outpatient hospital-based Milan Geriatrics 75+ Cohort Study.

Participants: Individuals aged 75 and older (N = 1,540).

Measurements: Blood pressure, Mini-Mental State Examination (MMSE), basic activities of daily living (ADLs), and instrumental activities of daily living (IADLs) were assessed. Associations between BP measures and MMSE score were first analyzed in the total population using linear regression models and were then further examined according to strata of age, ADLs, and IADLs. All analyses were adjusted for sociodemographic factors and presence of comorbidities.

Results: In the total population, higher systolic BP (SBP), diastolic BP (DBP), pulse pressure (PP), and mean arterial pressure (MAP) were all associated with higher MMSE score (all $P < .05$). Each 10-mmHg higher SBP and DBP was associated with a 0.26- and 0.55-point higher MMSE score, respectively. The associations between MMSE score and SBP, DBP, and MAP differed materially according to strata of age and functioning and were most pronounced in those aged 85 and older, with ADL impairments, and with IADL impairments.

Conclusion: Higher BP is associated with better cognitive function in the oldest old and in those with impaired functional status.

INTRODUCTION

Controversy persists on the relationship between blood pressure (BP) and cognitive function in old age[1]. Midlife hypertension has been consistently associated with an increased risk for cognitive impairment and dementia in later life[2-5]. On the contrary, data regarding the association between BP and cognition in older adults are conflicting. Some population-based observational studies have shown an inverse association between higher BP and cognitive function[6], whereas others have shown a direct association[7–9] or no association[10]. Whether this heterogeneity reflects differences in age[11] and level of frailty[12] of the participants is debated. It has been suggested that higher BP may be needed to maintain brain perfusion in biologically older individuals with widespread atherosclerotic vascular damage[13].

Most of the evidence in the literature is for older adults in population-based studies. Less is known about older adults who require outpatient medical assistance. The generalizability of data from population-based studies to clinical practice is questionable. Older outpatients may be frailer than older adults in the general population. In everyday clinical practice, healthcare professionals are confronted with these outpatients' needs. It is of critical importance to investigate this potentially diverse population. Therefore, the current authors investigated the relationship between BP and cognitive function in the Milan Geriatrics 75+ Cohort Study, an outpatient hospital-based cohort study. The objective was to assess whether higher BP is associated with better cognitive function in geriatric outpatients over a wide range of age and functional dependency.

METHODS

Study Design and Participants

The Milan Geriatrics 75+ Cohort Study is an outpatient hospital-based prospective cohort study of outpatients of the Geriatric Unit of the IRCCS Ca' Granda Foundation Maggiore Policlinico Hospital, Milan, Italy. Between January 3, 2000, and March 25, 2004, 3,608 new consecutive outpatients visited the Geriatric Unit. They routinely underwent an extensive standardized structured medical examination and comprehensive geriatric assessment. With the informed consent of these individuals, data were collected in structured paper records that were consecutively numbered and stored in the Geriatric Archive; 3,499 (97.0%) paper records were

retrieved. Of these, 2,267 were for people aged 75 and older at the time of the first visit. Seventy-four individuals had no comprehensive geriatric assessment, and 332 had neither a Mini-Mental State Examination14 (MMSE) nor an activities of daily living[15] (ADLs) score; these individuals were excluded from the final cohort. Therefore, the Milan Geriatrics 75+ Cohort Study includes 1,861 patients aged 75 and older. The current study included 1,540 individuals for whom BP and cognitive evaluation were available. The medical ethical committee of IRCCS Ca' Granda approved the study.

Comprehensive Geriatric Assessment

Outpatients accessed the Geriatric Unit only through the referral for a geriatric visit by a physician (their general practitioner in the majority of cases). The reason for first visit was recorded. Outpatients were required to bring all current medications and all medical documents including letters of discharge from acute-care hospitals, rehabilitation centers or emergency departments, drug prescriptions, reports of visits with other physicians, and reports of the Italian Commissions for the Ascertainment of Civil Disability to their first visit, which was with a trained physician and lasted 2 hours. Physicians collected demographic data, physiological anamnesis, past and present medical history, and current medication use in paper records through structured multiple-choice lists of demographic variables and comorbidities. Physicians also performed a basic neurological examination, took anthropometric measurements, and evaluated functional and cognitive status. Laboratory tests were ordered if recent ones were not available, and the results were recorded. Physicians registered chronic, cyclical, and as-needed drugs, including prescription and over-the-counter medications. Antihypertensive drugs were defined according to Anatomical Therapeutic Chemical (ATC) classification codes C02, C03, C07, C08, and C09[16]. Close relatives frequently accompanied participants to the first visit and acted as informants for the validation of data on functional status and drug assumption.

Blood Pressure

Arterial BP was measured during the first visit using a mercury sphygmomanometer at heart level, with an adjustable cuff, in the seated position, after at least 5 minutes of rest and no

vigorous exercise in the preceding 30 minutes. A special cuff was available for obese subjects. Systolic BP (SBP) and diastolic BP (DBP) were manually auscultated. Pulse pressure (PP) was calculated as SBP minus DBP and mean arterial pressure (MAP) as 1/3SBP + 2/3DBP.

Cognitive and Functional Status

Cognitive function was assessed using the 30-item Mini-Mental State Examination (MMSE)[14]. Functional status was assessed using the Katz ADLs15 and Lawton IADLs[17] questionnaires. ADLs included six items (rising or lying down, feeding, dressing, bathing, toileting, urinary and fecal continence), and IADLs included eight items (using a telephone, shopping, doing housework, doing laundry, preparing meals, using transportation, taking medications, managing money). ADL scores range from 0 to 6 and IADL scores from 0 to 8, with 0 indicating total dependence and the maximum score total independence. Information on functional status was checked with close informants.

Comorbidities and Lifestyle Factors

Hypertension was defined as diagnosis of hypertension or treatment with antihypertensive drugs. Coronary heart disease was defined according to a history of acute myocardial infarction or angina pectoris or therapy with nitrates. History of transient ischemic attack or stroke, diabetes mellitus, atrial fibrillation, claudication, and Parkinson's disease was confirmed using medical documents. Diagnosis of probable Alzheimer's disease was based on international criteria[18,19]. Dementia with Lewy bodies, frontotemporal dementia, and primary progressive aphasia were classified as other neurodegenerative conditions. Alcohol abuse was defined as intake of 70 g of alcohol per day or more. Cancer was defined according to a diagnosis within the previous 5 years. Glomerular filtration rate (GFR), which is an index of renal function, was calculated using the Modification of Diet in Renal Disease Study Group formula[20]. Symptoms of anxiety and depression were self-reported or stated in medical documents. Smoking was dichotomized as never or ever (current or previous). Education was defined as years of school attended.

Medications

Number of medications was defined as the number of drugs taken chronically or cyclically. Antihypertensive drugs were defined as ATC classification codes C02 (antiadrenergics), C03 (diuretics), C07 (beta-blockers), C08 (calcium-channel blockers), and C09 (agents acting on the renin-angiotensin system)[16]. Psychotropic drugs were defined as ATC classification codes N05A (antipsychotics), N05B (anxiolytics), N05C (sleep-inducers or sedatives), and N06A (antidepressants).

Statistical Analysis

In summary statistics, categorical variables were reported as percentages and continuous variables as medians and interquartile ranges (IQRs) when skewed. Linear regression models were used to analyze associations between variables of interest. Analyses were performed in four steps. Model 1 presents unadjusted MMSE mean scores. In Model 2, a minimally adjusted model, analyses were adjusted for age, sex, and education. In Model 3, analyses were adjusted for relevant comorbidities and medication use; each variable was entered in the model separately. In Model 4, a fully adjusted model, analyses were further adjusted for renal function. The relationship between BP measures (predictors) and MMSE score (dependent variable) was examined in total population and within age, ADL, IADL, and BP control strata. Three age strata were defined (75–79, 80–84, ≥85). The total population was divided into two ADL strata (preserved ADL function (ADL score = 6); impaired ADL function (ADL score < 6)) and two IADL strata (IADL score < 5 (median); IADL score ≥5). Subjects were classified into three groups of BP control: normotension (no history of hypertension, SBP < 140 mmHg, DBP < 90 mmHg), controlled hypertension (history of hypertension, SBP < 140 mmHg, DBP < 90 mmHg), and uncontrolled hypertension (history of hypertension, SBP ≥ 140 mmHg, DBP ≥ 90 mmHg). Interaction between BP measures and age, ADLs, and IADLs in relation to cognition was assessed. Interaction terms were calculated by multiplying BP measures by age and ADL and IADL scores, using age and ADL and IADL scores as continuous variables. Sensitivity analyses were performed after exclusion of SBP and DBP outliers; outliers were subjects with SBP or DBP measurements 2 standard deviations or more below or above the

mean of the total population. All analyses were performed using SPSS version 20.0.0 (SPSS, Inc., Chicago, IL).

RESULTS

Table 1 summarizes the characteristics of participants at first visit according to tertile of SBP. The median age of the study population was 82 (range 75–101), and 70% were female. Median SBP was 145 mmHg, and median DBP was 80 mmHg. Participants with higher SBP were more likely to be female and had a higher prevalence of hypertension and antihypertensive use. Participants with higher SBP were more likely to use alpha-antiadrenergics and angiotensin-converting enzyme inhibitors or angiotensin II antagonists; participants with lower SBP used antipsychotics more frequently. Participants in the lowest tertile of SBP had the highest prevalence of Parkinson's disease (all $P < .05$).

Table 2 shows the association between BP measures and cognitive function in the total population. Higher SBP, DBP, PP, and MAP were associated with higher MMSE score in all models of adjustment (all $P < .05$). In the fully adjusted model, a 10-mmHg increase in SBP was associated with a 0.26-point higher MMSE score (95% confidence interval (CI) = 0.13–0.40), a 10-mmHg increase in PP with a 0.20-point higher MMSE score (95% CI = 0.03–0.37), a 10-mmHg increase in DBP with a 0.55-point higher MMSE score (95% CI = 0.27–0.83), and a 10-mmHg increase in MAP with a 0.50-point higher MMSE score (95% CI = 0.27–0.74). In the fully adjusted model, subjects in the lowest SBP tertile (SBP <140 mmHg) had the lowest MMSE score; subjects in the lowest and middle DBP tertiles (DBP <90 mmHg) had lower MMSE scores than those in the highest DBP tertile.

Table 3 presents the age-stratified analyses of the association between BP measures and cognitive function. Age significantly modified the association between MMSE score and SBP, DBP, and MAP (all P-values for interaction < .05 except in Model 4 for SBP ($P = .15$) and MAP ($P = .05$)). The interaction between age and PP was not significant. In all adjusted models, the association between higher SBP, DBP, and MAP and MMSE score was most pronounced in participants aged 85 and older.

The modifying effect of functional status (ADL and IADL scores) on the relationship between BP measures and MMSE score is shown in Figure 1. In the unadjusted model, all P-values for

interaction between all BP measures and ADL/IADL score were less than .05 (Figure 1). In the fully adjusted model, P-values for interaction between SBP, DBP, and MAP and ADL score were less than .10; all P-values for interaction between all BP measures and IADL score were less than .05. In all models, higher BP measures were associated with higher MMSE score in subjects with at least partial dependence in ADLs (ADL score < 6) but not in subjects with full independence (ADL score = 6). Similarly, higher BP was related to better cognitive function in subjects with worse IADL performance (IADL score < 5). Conversely, no association was observed in those with better IADL score (IADL score ≥ 5). Estimates of mean MMSE scores in Figure 1 are derived from the unadjusted model; results were similar in the fully adjusted model (data not shown).

No difference in MMSE scores was observed in the fully adjusted model between participants with normotension and those with controlled hypertension, between participants with normotension and those with uncontrolled hypertension, or between participants with controlled hypertension and those with uncontrolled hypertension (data not shown).

In sensitivity analyses after exclusion of BP outliers (n = 105), higher SBP, DBP, PP, and MAP remained associated with higher MMSE score in the total population and in subjects with impaired ADL or IADL status, even after full adjustment (all P < .05, data not shown).

DISCUSSION

Higher BP measures were associated with better cognitive function in outpatients aged 75 and older and particularly in those aged 85 and older. The association was significantly stronger in those with impaired functional status, as measured by internationally validated ADL and IADL scale scores.

Both age and functional status modified the relationship between BP and cognitive function. The correlation between SBP, DBP, and MAP and MMSE score becomes more pronounced with increasing age. In those aged 85 and older, higher BP measures were consistently associated with higher MMSE scores. Likewise, the positive association between BP measures and cognitive function was detected in participants with worse functional impairment, although this association was absent in those with better preserved functional status.

The results of this study are consistent with those of earlier reports showing that lower BP was associated with worse cognitive performance in the oldest adults[7] and in centenarians[8]. The age-dependent relationship between BP and cognitive function has been previously hypothesized[1]. The modifying effect of functional status is a novel finding. In the population-based Leiden 85-plus Study, higher SBP and PP were associated with lower annual decline in MMSE score in the oldest adults with greater physical disability, although interactions were not significant[7]. All of these studies have used population samples. The current study showed that the positive association between high BP and good cognitive performance in frail older adults can be extrapolated to the outpatient clinic.

These findings may have different biological explanations. First, cognitive impairment itself lowers BP. The central nervous system is involved in BP regulation; brain atrophy and Alzheimer-type lesions in the prefrontal areas involved in central BP regulation may cause a decline in BP[21]. Alternatively, low BP and cognitive impairment share common risk factors such as decreasing cardiac function. However, in the current study, the associations between BP measures and cognitive performance remained significant after adjustment for risk factors and comorbidities that affect cardiac function. Finally, low BP may increase the risk of worse cognitive function. Episodic or sustained hypotension, and possibly excessive treatment of hypertension, may induce brain hypoperfusion, leading to ischemia and hypoxia, which may enhance the development of neurodegenerative processes[22]. Longitudinal studies have showed that declining BP over time correlates with incident dementia and with imaging and biological markers of neurodegenerative processes. The Kungsholmen Project reported that BP markedly decreased 3 years before a dementia diagnosis and continued to decline thereafter[23]. In the Rotterdam Scan Study, elderly adults without dementia with a decline of more than 10 mmHg in DBP had more cortical atrophy than subjects with stable BP over a 20-year period.24 Longitudinal decrease in MAP was found to be associated with an increase in p-tau181, a cerebrospinal fluid biomarker of Alzheimer's disease, in subjects with hypertension[25].

Why should functional status affect the relationship between BP and cognition? Functional status may be seen as a reflection of the biological age of older adults. Of note, functional status has been shown to affect the association between BP and subsequent mortality risk. In the National Health and Nutrition Examination Survey, functional status was assessed as walking speed for a 20-foot distance in individuals aged 65 and older. High SBP (>140 mmHg) was associated with greater mortality in fast walkers, whereas the association was inversed in those

who did not manage to complete the walking test[26]. Likewise, in the population-based Longitudinal Ageing Study Amsterdam, low DBP was associated with higher all-cause mortality risk in the oldest adults and in participants with a combination of physical and cognitive dysfunction, whereas BP was not related to mortality in more-vital older individuals[27]. Moreover, in the Leiden 85-plus Study, functional status modified the association between higher BP and risk of stroke in the oldest adults[28].

Functional impairment may be a consequence of hypertension, because most of the subjects with low BP late in life had higher BP earlier in life[24]. Functional impairment thus reflects the lifelong atherosclerotic burden of elderly adults. Atherosclerotic damage stiffens brain arteries and impairs brain perfusion regulation. Therefore, subjects with more atherosclerosis are more susceptible to episodic or sustained hypotension because they have a lower critical threshold for cerebral hypoperfusion[22]. In the Kungsholmen Project, the association between SBP decline and increased risk of dementia was observed only in people with baseline SBP less than 160 mmHg or vascular disease. In subjects with vascular disease, there was a dose-response relationship between SBP decline and risk of dementia[23].

Disentangling the relationship between BP and cognition in frail older people has significant clinical implications. Given the increasing life expectancy of populations worldwide[29], dementia is a leading cause of disability[30]. Therefore, a major public health challenge is prevention of dementia through management of its modifiable risk factors. BP is a major target, but optimal BP goals are unclear in individuals aged 80 and older[31] and in frail elderly adults[32]. The Systolic Blood Pressure Intervention Trial (SPRINT), which aims to assess whether individuals aged 75 and older differ from younger individuals in their response to hypertension treatment, specifically addresses this. Moreover, the nested substudy, SPRINT Memory and cognition IN Decreased hypertension (SPRINT-MIND), is designed to evaluate the effect of treatment on age-related decline in cognition and incidence of all-cause dementia[33].

The few previous clinical trials on the prevention of dementia with antihypertensive treatment have provided conflicting results, partly because of short follow-up and the heterogeneity of antihypertensive drugs. The Systolic Hypertension in the Elderly Program[34] and the Medical Research Council[35] trials failed to show any difference in effect on cognition between placebo and active treatment with diuretics or beta-blockers as first-line antihypertensive agents. In contrast, the Systolic Hypertension in Europe[36] showed that antihypertensive therapy starting

with the dihydropyridine calcium channel blocker nitrendipine reduced the incidence of dementia by 55% over a median follow-up of 3.9 years. In the Perindopril Protection Against Recurrent Stroke Study trial[37], combined treatment with perindopril and indapamide reduced stroke-related dementia by 50%. The Hypertension in the Very Elderly Trial (HYVET)[38] failed to show a significant reduction in the incidence of dementia with treatment with indapamide and perindopril. The HYVET data, when combined in a meta-analysis with other placebo-controlled trials of antihypertensive treatment, provided evidence that antihypertensive treatment is beneficial for reducing incidence of dementia in fit elderly adults. Nevertheless, a major weakness of these trials is the inclusion of relatively healthy subjects, which limits the generalizability of results to other populations. A recent community-based study found that only 9% of the oldest adults with hypertension were eligible for inclusion in HYVET.39 As further proof of the selective recruitment of fit elderly adults, the incidence of dementia in the placebo group of the trials was lower than in population-based studies[36,40]. Evidence of the generalizability of the results of clinical trials to the population of elderly outpatients is even more limited.

A strength of this study is that it investigated the connection between BP and cognition in an unselected population of elderly outpatients. To the knowledge of the authors, this is the largest study to be performed in a general geriatric unit. Another strength is that it proves the utility of categorizing elderly adults on the basis not only of chronological age, but also of markers of biological age as ADL and IADL scores. Any trained physician can collect this information. The main limitation of this study is the cross-sectional observational design, which prevents causality relationships from being inferred. Second, the MMSE, a widely used global measure of cognitive function, might have missed variation in executive function, the domain of cognition that hypertension particularly affects. Third, a single BP measurement was used in the analyses. Because BP is highly variable in older adults, participants may have been misclassified, although is it likely that misclassification would have occurred randomly, possibly leading to underestimation of true associations. Nevertheless, the data add further evidence of low BP as a risk factor for frail older adults in an outpatient setting.

In conclusion, higher BP is associated with better cognitive function in older individuals aged over 85 and in those with impaired functional status. The optimal threshold of BP may depend on both chronological and biological age (reflected by functional status). Therefore, BP management in older adults should be personalized, taking into account functional status.

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Table 1. Characteristics of study population according to tertile of systolic blood pressure (starts)

Characteristic	Total population	Systolic blood pressure tertile			p-value
	n = 1,540	Low n=431	Middle n=601	High n=508	
Demographic					
Age, years median [IQR]	82 [78, 86]	81 [78, 87]	81 [78, 85.5]	82 [79, 86]	0.222
Females, n (%)	1,075 (69.8)	288 (66.8)	404 (67.2)	383 (75.4)	0.004
Education, years, median [IQR]	6 [5, 12]	7 [5, 12]	6 [5, 11]	6 [5, 11]	0.615
Blood pressure (mmHg)					
Systolic, median [IQR]	145 [130, 160]	130 [120, 130]	140 [140, 150]	170 [160, 175]	<0.001
Diastolic, median [IQR]	80 [80, 90]	80 [70, 80]	80 [80, 90]	90 [80, 95]	<0.001
Pulse, median [IQR]	60 [50, 70]	50 [40, 55]	60 [60, 70]	80 [70, 90]	<0.001
Mean arterial, median [IQR]	103 [97, 110]	93 [87, 97]	103 [100, 107]	113 [110, 120]	<0.001
Cognitive and functional status					
MMSE, median [IQR]	26 [20, 28]	25 [17, 28]	25 [21, 29]	26 [21, 29]	0.003
ADL, median [IQR]	5.5 [4, 6]	5 [3.5, 6]	5.5 [4.5, 6]	5.5 [4.5, 6]	<0.001
IADL, median [IQR]	5 [2, 8]	4 [1, 7]	5 [3, 8]	5 [3, 8]	<0.001
Cardiovascular risk factors					
Ever smoker, n (%)	551 (35.8)	165 (38.3)	210 (34.9)	176 (34.6)	0.440
Hypertension, n (%)	1095 (71.1)	266 (61.7)	429 (71.4)	400 (78.7)	<0.001
Co-morbidities					
Diabetes mellitus, n (%)	180 (11.7)	37 (8.6)	76 (12.6)	67 (13.2)	0.059
Atrial fibrillation, n (%)	218 (14.2)	67 (15.5)	82 (13.6)	69 (13.6)	0.621
Coronary heart disease, n (%)	361 (23.4)	103 (23.9)	144 (24.0)	114 (22.4)	0.809
Claudication, n (%)	94 (6.1)	27 (6.3)	35 (5.8)	32 (6.3)	0.934
Depression/anxiety, n (%)	762 (49.5)	218 (50.6)	293 (48.8)	251 (49.4)	0.845
Stroke/TIA, n (%)	258 (16.8)	79 (18.3)	96 (16.0)	83 (16.3)	0.579
Cancer, n (%)	136 (8.8)	48 (11.1)	51 (8.5)	37 (7.3)	0.108
Alcohol abuse, n (%)	62 (4.0)	14 (3.2)	28 (4.7)	20 (3.9)	0.520
Alzheimer's dementia, n (%)	389 (25.3)	118 (27.4)	158 (26.3)	113 (22.2)	0.149
Parkinson's disease, n (%)	22 (1.4)	12 (2.8)	2 (0.3)	8 (1.6)	0.004
Other neurod., n (%)	15 (1.0)	6 (1.4)	6 (1.0)	3 (0.6)	0.459
GFR, mL/min, median [IQR]	64.9 [55.6, 84.5]	66.0 [55.5, 85.4]	64.8 [55.4, 84.0]	65.2 [55.9, 84.1]	0.765

Table 1. Characteristics of study population according to tertile of systolic blood pressure (continues)

Characteristic	Total population	Systolic blood pressure tertile			p-value
	n = 1,540	Low n=431	Middle n=601	High n=508	
Medications					
On antihypertensives, n (%)	993 (64.5)	248 (57.5)	391 (65.1)	354 (69.7)	0.001
Anti-adrenergics, n (%)	58 (3.8)	9 (2.1)	18 (3.0)	31 (6.1)	0.002
Diuretics, n (%)	344 (22.3)	104 (24.1)	141 (23.5)	99 (19.5)	0.164
Beta-block., n (%)	139 (9.0)	37 (8.6)	49 (8.2)	53 (10.4)	0.390
Calcium-channel block., n (%)	370 (24.0)	88 (20.4)	155 (25.8)	127 (25.0)	0.113
ACE-inhibitors/AA, n (%)	566 (36.8)	129 (29.9)	217 (36.1)	220 (43.3)	<0.001
Antipsychotics, n (%)	136 (8.8)	56 (13.0)	52 (8.7)	28 (5.5)	<0.001
Anxiolytics, n (%)	404 (26.2)	103 (23.9)	164 (27.3)	137 (27.0)	0.427
Hypnotics/sedatives, n (%)	116 (7.5)	39 (9.0)	40 (6.7)	37 (7.3)	0.344
Antidepressants, n (%)	197 (12.8)	60 (13.9)	72 (12.0)	65 (12.8)	0.655
N of medications, median [IQR]	3 [2, 5]	3 [2, 5]	3 [2, 5]	3.5 [2, 5]	0.219

Abbreviations: n = number; IQR = inter quartile range; mmHg: millimeter of mercury; MMSE = Mini Mental State Examination; ADL = Activities of Daily Living; IADL = Instrumental Activities of Daily Living; TIA = transient ischemic attack; neurod = neurodegenerative; GFR= glomerular filtration rate; mL/min = millilitre/minute; block = blockers; ACE = angiotensin converting enzyme inhibitors; AA = angiotensin II antagonists.

Table 2. MMSE score according to tertile of blood pressure

	Tertiles			
	Low	**Middle**	**High**	**p-value**
SBP				
n	431	601	508	
Range of SBP (mmHg)	85 - 135	140 - 150	155 - 260	
Mean SBP (SD) (mmHg)	124.3 (8.4)	144.3 (4.8)	169.5 (12.9)	
MMSE score, mean (SE)	22.2 (0.3)	23.6 (0.3)*	24.2 (0.3)*	**<0.001**
DBP				
n	307	737	496	
Range of DBP (mmHg)	45 - 75	80 - 85	90 - 130	
Mean DBP (SD) (mmHg)	69.1 (4.6)	80.7 (1.7)	93.7 (5.8)	
MMSE score, mean (SE)	21.6 (0.4)	23.6 (0.2)*	24.1 (0.3)*	**<0.001**
PP				
n	451	465	624	
Range of PP (mmHg)	20 - 55	60 - 65	70 - 130	
Mean PP (SD) (mmHg)	46.9 (6.2)	60.8 (1.8)	79.9 (11.0)	
MMSE score, mean (SE)	22.9 (0.3)	23.1 (0.3)	23.9 (0.3)*	**0.013**
MAP				
n	476	544	520	
Range of MAP (mmHg)	66.7 -98.3	100 – 108.3	110 – 173.3	
Mean MAP (SD) (mmHg)	91.3 (5.7)	102.9 (2.9)	116.9 (7.6)	
MMSE score, mean (SE)	22.3 (0.3)	23.6 (0.3)*	24.2 (0.3)*	**<0.001**

Abbreviations: mmHg: millimeter of mercury; MMSE: Mini Mental State Examination; SD: standard deviation; SE: standard error; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; MAP: mean arterial pressure. MMSE scores are presented as unadjusted means (Standard Error). P-values are computed using blood pressure measures as continuous variables and are derived from the unadjusted model. *p-value<0.05 for difference between the low tertile and the middle/high tertile.

Table 3. Associations between blood pressure measures and Mini Mental State Examination score, stratified by age (starts)

	75 – 79 years (n=534)		80 – 84 years (n=497)		85+ years (n=509)		p-value for interaction
	β-coefficient (95% CI)	p-value	β-coefficient (95% CI)	p-value	β-coefficient (95% CI)	p-value	
SBP							
Model 1[a]	0.17 [-0.11; 0.44]	0.235	0.27 [-0.02; 0.56]	0.065	0.73 [0.45; 1.01]	**<0.001**	**0.001**
Model 2[b]	0.29 [0.04; 0.54]	**0.025**	0.23 [-0.06; 0.51]	0.114	0.64 [0.38; 0.90]	**<0.001**	**0.005**
Model 3[c]	0.19 [-0.04; 0.42]	0.104	0.25 [0.01; 0.49]	**0.045**	0.44 [0.22; 0.66]	**<0.001**	**0.006**
Model 4[d]	0.18 [-0.06; 0.43]	0.146	0.24 [-0.03; 0.51]	0.080	0.33 [0.10; 0.56]	**0.005**	0.146
DBP							
Model 1[a]	0.53 [-0.02; 1.09]	0.060	0.37 [-0.19; 0.94]	0.195	1.57 [0.96; 2.18]	**<0.001**	**<0.001**
Model 2[b]	0.57 [0.05; 1.08]	**0.030**	0.23 [-0.32; 0.78]	0.407	1.27 [0.71; 1.83]	**<0.001**	**0.001**
Model 3[c]	0.40 [-0.06; 0.85]	0.087	0.36 [-0.12; 0.83]	0.138	1.00 [0.53; 1.48]	**<0.001**	**0.002**
Model 4[d]	0.30 [-0.20; 0.80]	0.244	0.32 [-0.20; 0.83]	0.230	0.91 [0.42; 1.40]	**<0.001**	**0.041**

Table 3. Associations between blood pressure measures and Mini Mental State Examination score, stratified by age (continues)

PP							
Model 1[a]	0.06 [-0.29; 0.41]	0.740	0.27 [-0.09; 0.64]	0.140	0.63 [0.28; 0.98]	**<0.001**	**0.036**
Model 2[b]	0.25 [-0.08; 0.57]	0.137	0.26 [-0.09; 0.61]	0.150	0.57 [0.25; 0.89]	**0.001**	0.069
Model 3[c]	0.14 [-0.15; 0.43]	0.333	0.24 [-0.07; 0.54]	0.126	0.34 [0.07; 0.61]	**0.013**	0.061
Model 4[d]	0.18 [-0.14; 0.48]	0.268	0.23 [-0.10; 0.57]	0.170	0.20 [-0.09; 0.49]	0.172	0.438
MAP							
Model 1[a]	0.40 [-0.06; 0.85]	0.091	0.43 [-0.05; 0.90]	0.081	1.41 [0.92; 1.89]	**<0.001**	**<0.001**
Model 2[b]	0.53 [0.10; 0.95]	**0.015**	0.32 [-0.15; 0.78]	0.181	1.19 [0.74; 1.64]	**<0.001**	**0.001**
Model 3[c]	0.36 [-0.02; 0.74]	0.064	0.40 [-0.00; 0.80]	0.052	0.88 [0.50; 1.26]	**<0.001**	**0.001**
Model 4[d]	0.31 [-0.11; 0.72]	0.146	0.37 [-0.07; 0.82]	0.099	0.73 [0.33; 1.13]	**<0.001**	0.053

Abbreviations: CI: confidence interval; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; MAP: mean arterial pressure. Beta-coefficients represent change in Mini Mental State Examination score for each 10 mmHg increase in blood pressure measures. [a] Model 1: unadjusted. [b] Model 2: adjusted for age, sex and education. [c] Model 3: adjusted for age, sex, education, smoke, hypertension, diabetes mellitus, atrial fibrillation, coronary heart disease, claudication, depression/anxiety, history of transient ischemic attack or stroke, Alzheimer's disease, present cancer, alcohol abuse, Parkinson's disease, other neurodegenerative conditions, number of medication, anti-adrenergics, diuretics, beta-blockers, calcium-channel blockers, angiotensin converting enzyme inhibitors/angiotensin II antagonists, antipsychotics, anxiolytics, sleep-inducers and sedatives, antidepressants. [d] Model 4: Model 3 plus glomerular filtration rate.

Figure 1. MMSE score in tertiles of blood pressure stratified for ADL and IADL

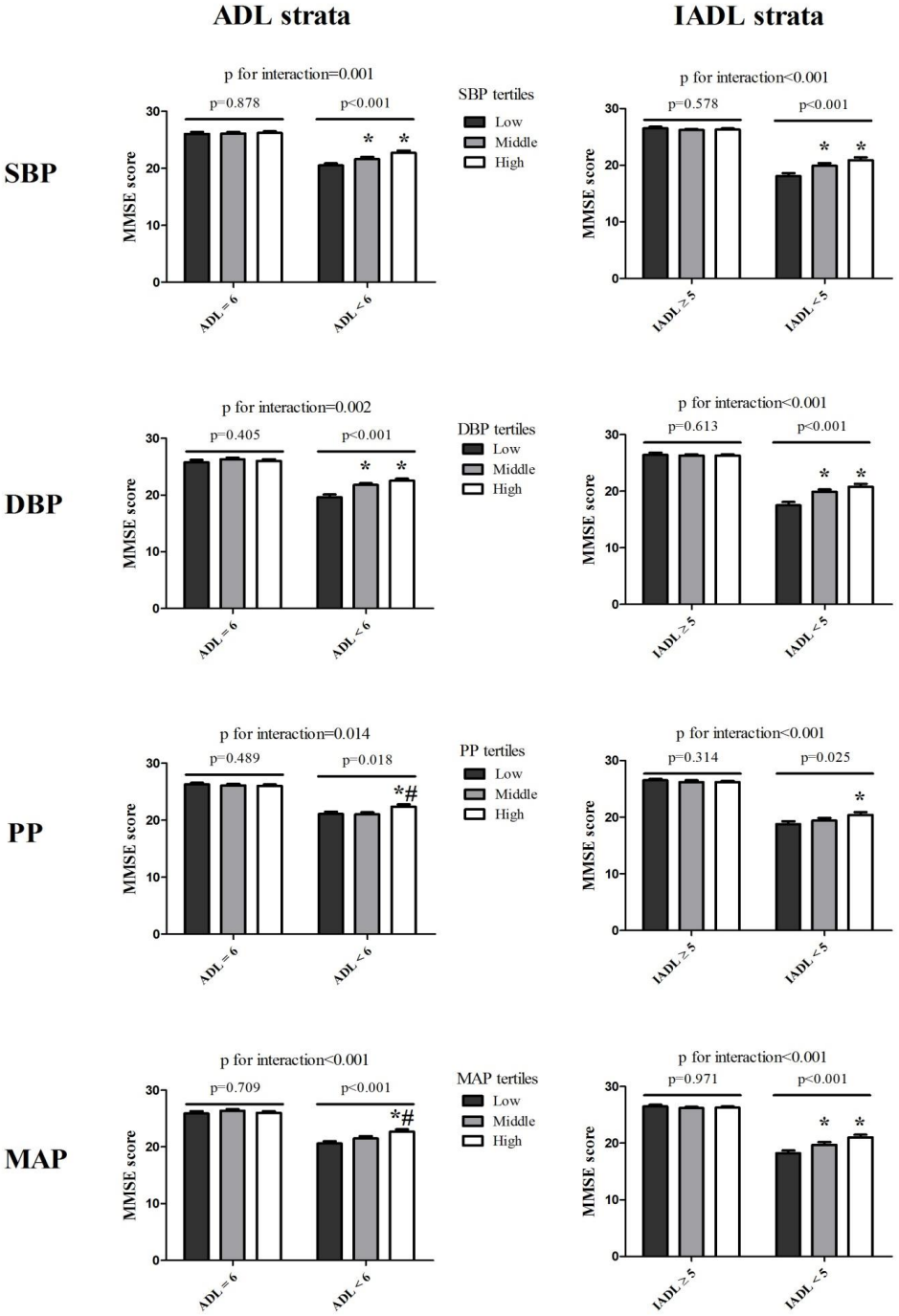

Figure 1. Bars represent unadjusted MMSE score means (with standard error). Abbreviations: MMSE = Mini Mental State Examination; ADL = Activities of Daily Living; IADL = Instrumental Activities of Daily Living; SBP = systolic blood pressure, DBP = diastolic blood pressure, PP = pulse pressure, MAP = mean arterial pressure. P-values for interaction indicate the interaction between blood pressure measures and ADL/IADL (interaction terms were calculated by multiplying continuous blood pressure measures by continuous ADL/IADL scores). The other p-values indicate the trend (linear regression). The symbol * indicates a significant difference between the low tertile and the middle/high tertile. The symbol # indicates a significant difference between the middle and high tertile. P-values for interaction, p-values for trend and differences between tertiles are computed in the unadjusted model.