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Effect of Blood Pressure and Diabetes Mellitus on Cognitive and Physical Functions in Older Adults: A Longitudinal Analysis of the Advanced Cognitive Training for Independent and Vital Elderly Cohort

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Abstract

OBJECTIVES—To evaluate the effect of blood pressure (BP) and diabetes mellitus (DM) on cognitive and physical performance in older, independent-living adults.

DESIGN—Longitudinal study with secondary data analysis from the Advanced Cognitive Training for Independent and Vital Elderly randomized intervention trial.

SETTING—Six field sites in the United States.

PARTICIPANTS—Two thousand eight hundred two independent-living subjects aged 65 to 94.

MEASUREMENTS—Cognitive functions in different domains and physical functions measured using activities of daily living, instrumental activities of daily living (IADLs), and the physical function subscale from the Medical Outcomes Study Short Form-36 (SF-36) Health Survey.

RESULTS—After the first annual examination, hypertension was associated with a faster decline in performance on logical reasoning tasks (ability to solve problems following a serial pattern), whereas DM was associated with accelerated decline on the Digit Symbol Substitution Test (speed of processing). The reasoning and Digit Symbol Substitution test are executive function tasks thought

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to be related to frontal-lobe function. Hypertension and DM were associated with a significantly faster pace of decline on the SF-36 physical function component score. Individuals with DM had a faster pace of decline in IADL functioning than nondiabetic subjects. There was no evidence for an interaction between BP and DM on cognitive or physical function decline.

CONCLUSION—Hypertension and DM are associated with accelerated decline in executive measures and physical function in independent-living elderly subjects. Further research is needed to determine whether cardiovascular risk modification ameliorates cognitive and functional decline in elderly people.

Keywords

blood pressure; diabetes mellitus; cognitive function; physical function; longitudinal study

The prevalence of high blood pressure (BP) and diabetes mellitus (DM) increases with age, and the numbers of older persons with these cardiovascular risks are expected to grow as the elderly population increases in number.^{1,2} The National Health and Nutrition Examination Survey demonstrated that, in the noninstitutionalized population aged 65 and older, the overall prevalence of hypertension and DM is between 50% and 70% and 18% and 20%, respectively.^{1,2} Hypertension and DM are associated with a variety of cardiovascular conditions, such as peripheral vascular disease, myocardial infarction, and stroke, and impose a heavy public health burden in older people.

DM and high BP, as well as their related cerebral changes,^{3,4} such as stroke, lacunes, and leukoariosis, have been shown to affect cognition, leading to cognitive impairment or dementia.^{5,6} Data from the Syst-Eur trial, a randomized, controlled trial recruiting 2,418 elderly subjects without dementia at baseline, showed that active treatment of hypertension with antihypertensive medications reduced the incidence of dementia by 50% after 2 years of follow-up.⁷ Recent evidence suggests that executive function, the cognitive ability associated with human frontal lobes, appears to be particularly vulnerable to increased loads of cardiovascular risks.^{8,9} Many population-based prospective studies^{10–12} have examined the relation of DM or hypertension to cognitive function, usually assessed using a global cognitive measure or ascertainment of incident dementia cases without further exploration of changes in different cognitive domains. Little is known about which specific cognitive domains elevated BP or DM affect.

Furthermore, the relationship between hypertension and physical function, either cross-sectional or longitudinal, has not been adequately examined. The effect of DM on physical functioning has been examined in several cross-sectional studies. Patients with DM are more likely to report disability,¹³ have more days of restricted activity,¹⁴ and have more physical function limitations.^{15,16} Unfortunately, data from longitudinal studies examining the relationship between DM and functional decline are sparse.

Therefore, we hypothesize that hypertension and DM have adverse effects on cognitive, particularly executive, and physical functions. The overarching goal of this study was to elucidate the predictive role of BP, DM, and their interaction on decline in cognitive and physical performance in later life by examining data from the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial.

METHODS

Study Design and Participants

The ACTIVE trial, which is described in greater detail elsewhere,¹⁷ is a randomized, controlled study designed to evaluate the effectiveness and durability of three cognitive training

interventions (memory training, reasoning training, or speed-of-processing training) on mental abilities and daily functioning in older, independent-living adults. Briefly, persons aged 65 to 94 were enrolled across six field sites in the United States using various sampling frames and recruitment strategies (state driver's license and identification card registries, medical clinic rosters, senior center and community organization rosters, senior housing sites, local churches, and rosters of assistance and service programs for low-income elderly persons) from March 1998 to October 1999. Persons were excluded if they were younger than 65; were cognitively impaired (score of <23 on the Mini-Mental State Examination (MMSE)); had a known diagnosis of Alzheimer's disease; were functionally impaired, requiring assistance in dressing, personal hygiene, or bathing three or more times in the previous 7 days; were medically unstable, predisposing them to imminent functional decline or death; participated currently or recently in other cognitive training; were unavailable during the study; or were impaired in vision, hearing, or communicative ability, making participation in the study impossible. All participants were randomized into three cognitive intervention groups and a no-contact control group. Two-year follow-up data were collected through December 2001.

The institutional review boards at the following institutions approved the study protocol: University of Alabama; Wayne State University; the Hebrew Rehabilitation Center for the Aged; the Johns Hopkins University School of Medicine; Indiana University; Purdue University; Pennsylvania State University; the University of Florida; and the New England Research Institutes. The current study analyzed the effect of hypertension and DM on cognitive and physical functions in the ACTIVE participants. The analytic sample consisted of 2,802 independent-living, otherwise normal older adults.

DM and Blood Pressure Classification

Presence of DM was ascertained using the question: "Has a doctor or a nurse ever told you that you have diabetes?" A trained research assistant assessed BP after 5 minutes of quiet sitting two times, with 2 minutes between each measure. Average systolic BP (SBP) and diastolic BP (DBP) were obtained. Participants were classified in BP groups according to the Seventh Report of the Joint National Committee (JNC 7), defining normal BP as SBP less than 120 mmHg and DBP less than 80 mmHg, prehypertension as SBP between 120 mmHg and 139 mmHg or DBP between 80 mmHg and 89 mmHg, Stage 1 hypertension as SBP between 140 mmHg and 159 mmHg or DBP between 90 mmHg and 99 mmHg, and Stage 2 hypertension as SBP 160 mmHg or greater or DBP 100 mmHg or greater.¹⁸

Cognitive Function Assessment

Cognitive functioning was assessed at baseline, first annual, and second annual examinations. Evaluation of cognitive abilities was performed in several domains: global cognition, memory, reasoning, and speed of processing. Global cognitive function was measured using the MMSE.¹⁹ For memory, a composite score was created from three equally weighted test scores:¹⁷ the Hopkins Verbal Learning Test Related Word Lists,²⁰ Rey Auditory-Verbal Learning Test Unrelated Word Lists,²¹ and the Rivermead Behavioral Memory Test Paragraph Recall task.²² These measures include an immediate and delayed learning condition, critical for the detection of anterograde memory disorders. These properties are associated with loss of newly presented information and are related to compromise of the medial temporal and temporal limbic structures of the brain.²³ A higher memory composite score indicates better memory function.

For the reasoning domain, three outcomes were assessed: Word series,²⁴ letter series,²⁵ and letter sets.²⁶ A reasoning composite was created from three scores, each equally weighted.¹⁷ A higher reasoning composite score indicates better performance. Word series and letter series tasks consisted of a list of months or letters forming increasingly complex repetitive patterns,

requiring the subject to scan the list, generate and reject hypotheses regarding the nature of the pattern, and then select the next stimulus in a list of possible answers. Letter set task required subjects to find a rule common to four of five letter sets, marking the set inconsistent with the rule. These reasoning tests require strategy formation, behavioral spontaneity, and retrieval ability from long-term memory. These properties have been found to be sensitive to compromised frontal lobes and their related subcortical connections.²³

For speed of processing, the ACTIVE battery included the computer-administered Useful Field of View (UFOV),^{27–29} a visual divided attention measure requiring speeded visual processing, and the Digit Symbol Substitution Test (DSST).³⁰ Lower scores on the UFOV and higher scores on the DSST indicate better performance. The DSST measures motor speed of processing and is frequently used as a test sensitive to frontal lobe functions.³¹ The reasoning tasks and the DSST assess frontal lobe-mediated cognitive abilities and are characterized as measures of executive functions.

Physical Function Assessment

The study examined self-reported physical functions in activities of daily living (ADLs),^{32, 33} instrumental activities of daily living (IADLs),^{34,35} and the physical function subscale in the Medical Outcomes Study (MOS) Short Form-36 Health Survey (SF-36).^{36,37} These self-reported outcomes were assessed at baseline, first annual, and second annual examinations. ADLs and IADLs were drawn from the Minimum Data Set methodology.³⁸ ADL functioning questions assessed participants' self-reported independent performance in tasks related to bathing, dressing, and personal hygiene. IADL functioning was assessed through a series of self-reported performance and capacity for seven areas: meal preparation, housework, management of finances, management of health care, phone use, shopping, and travel. Lower ADL and IADL scores indicate better functioning, with a minimum score of zero meaning no deficit. The SF-36 has demonstrated reliability and validity^{36,37} and is widely used in health outcomes research. The physical functioning subscale in SF-36, a measure of the physical component of health status,³⁹ assesses limitations in physical activities because of health problems. Scores for physical function subscale in SF-36 range from 0 to 100, with higher scores indicating better physical functioning.

Other Cardiovascular Risk Factors

The ACTIVE protocol included assessments of smoking status, history of stroke, myocardial infarction, and hypercholesterolemia by questionnaire. Body mass index (BMI) was calculated from baseline height and weight, as weight (kg) divided by height (m) squared. BMI was categorized according to the National Institutes of Health obesity standards (< 18.5 = underweight, 18.5–24.9 = normal weight, 25.0–29.9 = overweight, and >30 = obese).⁴⁰

Characteristics of Study Sample

Baseline BP status, history of DM, performance of cognitive and physical function, and other cardiovascular risk factors and covariates were summarized using descriptive statistics. Mean scores and standard deviations were determined for each component of cognitive and physical performance. There are many zero values in the ADL and IADL scores (meaning no deficit), and the distributions of both scores are right skewed. Thus, ADL and IADL scores were transformed to $\log(\text{ADL}+1)$ and $\log(\text{IADL}+1)$, respectively. This procedure reduced skewness.

Cross-Sectional Analysis

Cross-sectional association between exposures (BP and history of DM) and outcomes (cognitive and physical functioning) were assessed based on data from the baseline examination. Multiple linear regression was used while controlling for the influence of other

cardiovascular risk factors and covariates, including age, sex, race or ethnicity, study site, intervention group, and years of education. Both JNC 7 BP categories (indicator variable) and values of averaged SBP (continuous variable) were used to assess the effect of BP on cognitive and physical function. Interaction terms between averaged SBP value and history of DM, or BP category and history of DM were separately created and assessed in the multivariate model to look for possible statistical interaction.

Longitudinal Analysis

The longitudinal associations between BP, history of DM, and changes in cognitive and physical performance were conducted using a generalized estimating equation approach.⁴¹ Repeated measures of cognitive and physical functions were regressed, separately, on time, baseline BP, DM, and control variables. Time was modeled as a linear function for functional outcomes and as a two-part piecewise function for cognitive outcomes. The latter strategy was an attempt to model separately a possible retest effect. All models used an exchangeable correlation structure to account for the within-subject correlation of the repeated observations and allow possible imbalance in the number of assessments over time (i.e., loss to follow-up).⁴² JNC 7 BP categories were used to evaluate the effect of BP on cognitive and physical functions in the longitudinal analysis by interacting these factors with time (or piecewise time). To capture a possible effect of cognitive interventions on outcomes over time, an interaction between intervention groups and time (or piecewise time) was included in the model in addition to all covariates adjusted in the cross-sectional analysis. Interactions between BP categories and DM and time were also examined. Data management and analysis were performed using Stata 8.0 (Stata Corporation, College Station, TX).

RESULTS

The baseline characteristics of the ACTIVE participants are provided in Table 1. The majority of the ACTIVE participants were female, white, and functionally independent.

Cross-Sectional Analysis

Elevated BP was associated with selective impairment in executive function (reasoning task) but not with memory performance (Table 2). After multivariate adjustment, each 10-mmHg increase in baseline SBP was associated with a 0.049 decrease ($P = .008$) in reasoning composite score. JNC 7 BP categories (indicator variable) were then used to reassess the effect of BP on cognitive function, which found that subjects with Stage 2 hypertension had a significantly lower reasoning score than normotensive subjects ($\beta = -0.37$, $P = .01$). Although an association was found between elevated BP and better SF-36 physical function score ($\beta = 0.46$, $P = .01$), this relationship was no longer significant, and a nonlinear relationship was noted after using BP category as indicator variable (β s for prehypertension, Stage 1 hypertension, and Stage 2 hypertension were 1.55, 0.95, and 2.14, respectively).

The presence of DM was independently associated with impairment in multiple cognitive domains, including global cognition, memory, and speed of processing, after multivariate adjustment. In addition, DM was independently associated with functional problems, as reflected in ADL scores and SF-36 physical function component measures. The interaction between BP and DM on cognitive and physical functioning was investigated, but no evidence was found of a clinically meaningful or statistically significant interaction.

Longitudinal Analysis of Cognitive Performance

Changes in cognitive scores were examined using a piece-wise model for time; two parameters for time captured separately the change from baseline to first annual examination and from first to second annual examination. The adjusted mean scores of cognitive function from

baseline to second annual examinations are summarized in Table 3. The piecewise approach was indicated based on evidence from exploratory data analysis of repeated measures of cognitive performance. From baseline to first annual examination, there was considerable retest improvement in the scores of the reasoning task and speed of processing (Table 3). Subjects with Stage 2 hypertension had a much lower average reasoning composite score at baseline examination than normotensive subjects and a significantly faster pace of increase in scores on the reasoning composite (Table 4). However, as subjects were followed from first annual to second annual examinations, it was found that people with Stage 1 and Stage 2 hypertension had a selectively faster pace of decline in reasoning performance than normotensive subjects (β for Stage 1 hypertension = -0.18 , $P = .03$; β for Stage 2 hypertension = -0.28 , $P = .005$) (Table 4). In addition, from first to second annual examinations, there was a dose-response effect showing that reasoning performance declined significantly faster as BP increased in the JNC 7 categories ($P = .002$ for linear trend). Presence of hypertension was not associated with changes in other cognitive domains over 2 years of follow-up.

History of DM was selectively associated with accelerated decline in performance of speed of processing. From first annual to second annual examinations, subjects with DM demonstrated a faster decline on the DSS than nondiabetic subjects ($\beta = -0.97$, $P = .02$) (Table 4). A history of DM was not associated with changes in other cognitive domains. No evidence was found of an interaction between DM and hypertension on changes of cognitive performance over 2 years.

Cognitive intervention has been shown to improve targeted cognitive abilities in a previous ACTIVE report,¹⁷ but no statistically significant or meaningful interactions were found between the cognitive intervention and the BP or DM effect on cognitive decline in the analysis.

Longitudinal Analysis of Physical Function

In the generalized estimating equation model examining the relationship between BP or DM and physical function, the cognitive intervention was not associated with changes in physical function. An adverse effect of elevated BP and DM was found on changes of physical function after 2 years of follow-up. Subjects with Stage 1 and Stage 2 hypertension had a significantly greater decline in the SF-36 physical function subscale score than normotensive subjects (P for Stage 1 hypertension = -1.14 , $P = .03$; β for Stage 2 hypertension = -1.67 , $P = .007$) (Table 5).

Likewise, subjects with DM showed faster decline in the SF-36 physical function component than nondiabetic subjects ($\beta = -1.53$, $P = .005$). In addition, a significantly faster decline in IADL function was demonstrated in subjects with DM than in nondiabetic subjects ($\beta = 0.06$, $P = .03$). The interaction between BP and DM on changes in physical function over 2 years was assessed, and no significant result was found.

DISCUSSION

The results of this study indicate that elevated BP and DM in elderly people are associated with poor cognitive performance and a selective decline in executive function over 2 years. These findings support and extend previous cross-sectional studies showing that cardiovascular risk factors had a specific deleterious effect on executive measures in elderly people.^{8,9} Interestingly, when these subjects were followed longitudinally from baseline to first annual examination, performance on frontal-lobe mediated measures (reasoning tests, the DSST, and the UFOV) showed considerable improvement. Moreover, the rate of improvement in reasoning tasks was even higher for hypertensive subjects than normotensive subjects (Tables 3 and 4). Because baseline differences in measures of frontal cognitive abilities are large between groups, the magnitude of differences across exposure groups between baseline and

first annual examination probably reflect, to some extent, a regression to the mean.⁴³ Additionally, performance on many neuropsychological tests may be improved simply by prior exposure to testing stimuli and procedures.^{44,45} The duration of the beneficial practice effects after exposure to neuropsychological tests can vary from weeks to years.⁴⁴

After the first annual examination, the results indicated that elevated BP and DM were associated with accelerated cognitive decline in frontal lobe-mediated cognitive functions but not in memory function in initially cognitively normal older adults. In addition, the adjusted means are more similar across exposure groups at the first annual examination, so regression effects are not likely candidates to explain the different magnitude of changes between the first and second examinations. The adverse effect of hypertension and DM on frontal cognitive abilities may have overcome any lingering practice effect. The present study has the strength of examining the cross-sectional and longitudinal relationships between cardiovascular risk factors and a variety of cognitive domains and suggests that hypertension and DM play a role in the decline of frontal lobe-mediated cognitive functions once residual practice effects are accounted for.

The study also demonstrated that hypertension and DM are related to deterioration in functional status and play an important role in the progression of functional disability in older adults. These findings are consistent with two recent longitudinal studies^{46,47} in which DM has been shown to predict functional decline in older people. However, these studies had problems with generalizability regarding their study populations: one analyzed 729 physically impaired older women,⁴⁶ and the other focused its analysis on 1,789 older Mexican Americans.⁴⁷ The present study has the advantage of examining the independent role of hypertension and DM in physical function using a group of relatively independent, geographically dispersed, and ethnically diverse older people. To the authors' knowledge, this is the first study showing the predictive roles of both elevated BP and DM in the decline of functional status in elderly people.

The following mechanisms may explain why hypertension and DM are associated with decline of executive and physical function. Frontal lobes mediate executive abilities orchestrating complex planning, organizing, and multitasking activities. Integrity of the frontal-subcortical circuits, a series of pathways interconnecting various regions of the frontal lobes to subcortical structures, are essential to maintain gait and balance, as well as executive function,⁴⁸ but these circuits are sensitive to increased loads of cardiovascular risks and are often interrupted by development of ischemic small-vessel injuries in cerebral watershed areas. Disruption of the frontal-subcortical systems may selectively impair executive function. In addition, the ischemic microangiopathic lesions may interfere with long loop reflexes mediated by deep white matter sensory and motor tracts and interrupt the descending motor fibers arising from medial cortical areas, which are important for lower extremity motor control,⁴⁹ further affecting gait, balance, and physical function. In addition, executive dysfunction may interfere with some goal-directed abilities such as cooking, dressing, financing, and housework that are measured using ADL and IADL measures.⁵⁰

This study has several limitations that deserve comment. The follow-up period of 2 years was short. There is often a crucial interaction effect between DM and hypertension on a variety of clinically important vascular outcomes such as stroke and myocardial infarction. Although this study assessed the interaction effect between BP and DM on changes of cognitive and physical functions, no evidence was found of a clinically meaningful or statistically significant interaction, possibly a consequence of the short follow-up period. An additional limitation of this study was that the questionnaire used for DM ascertainment did not include measurement of fasting glucose. Some subjects with fasting glucose levels 126 mg/dL or greater might be mis-classified as nondiabetic. Therefore, the effect of DM on cognitive and physical functions might have been underestimated.

In conclusion, this study found that elevated BP and DM are associated with increased risks for cognitive decline in executive measures and decline in physical function in otherwise nondemented, independent elderly subjects. There is no significant interaction between BP and DM on cognitive function, physical function, and their decline over 2 years. These findings have important clinical and public health implications because identification and management of those high-risk patients may help prevent or delay the development of cognitive and functional complications. Future research is needed to determine whether cardiovascular risks modification ameliorates cognitive and functional decline in elderly people.

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Table 1
Baseline Characteristics of Participants (N = 2,802)

Characteristic	Value
Age, mean $\pm$ SD	73.6 $\pm$ 5.9
Female, n (%)	2,126(75.9)
Race/ethnicity, n (%)	
White	2,017(72.0)
Black/African American	724 (25.8)
Hispanics	15(0.5)
Other *	46(1.7)
Education, years, mean $\pm$ SD	13.5 $\pm$ 2.7
Blood pressure status, n (%) [†]	
Normal	592(21.1)
Prehypertension	991 (35.3)
Stage 1 Hypertension	772 (27.6)
Stage 2 Hypertension	370(13.2)
Unknown	77 (2.8)
Diabetes mellitus, n (%)	358 (12.8)
Body mass index category, n (%) [‡]	
Normal	609(21.7)
Underweight	30(1.1)
Overweight	1067(38.1)
Obese	1008(36.0)
Unknown	88(3.1)
Current smoker, n (%)	208 (7.4)
History of high cholesterol, n (%)	1226(43.8)
History of myocardial infarction, n (%)	309(11.0)
History of stroke, n (%)	195(7.0)
Cognitive performance score, mean $\pm$ SD	
Global cognition (Mini-Mental State Examination score)	27.3 $\pm$ 2.0
Memory composite	0.0 $\pm$ 2.5
Executive function	
Reasoning composite	0.0 $\pm$ 2.7
Digit Symbol Substitution Test	40.4 $\pm$ 11.2
Visuospatial (Useful Field of View composite score) [§]	942.6 $\pm$ 288.0
Functional performance score, mean $\pm$ SD	
Activities of daily living [§]	0.3 $\pm$ 0.9
Instrumental activities of daily living [§]	4.3 $\pm$ 4.9
SF-36 physical function	68.8 $\pm$ 24.1

* Includes Asian, native Hawaiian, Pacific Islander, American Indian, and Alaska native.

[†] Blood pressure classification is according to the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.¹⁸

[‡]Categories were defined according to the following criteria: Normal 18.5–24.9 kg/m², underweight < 18.5 kg/m², overweight 25.0–29.9 kg/m², and obese >30kg/m².⁴⁰

[§]Smaller values reflect better performance.

SD = standard deviation.

Table 2
Regression Coefficients Expressing Effects of Baseline Systolic Blood Pressure (SBP) and Diabetes Mellitus (DM) on Cognition and Physical Functions: Cross-Sectional Analysis

Variable	10-mmHg Increase in SBP*			DM†		
	$\beta^{\ddagger}$	SE	P-value	$\beta^{\S}$	SE	P-value
Cognitive performance						
Global cognition (Mini-Mental State Examination)	−0.021	0.016	.19	−0.305	0.108	.005
Memory composite	−0.020	0.019	.30	−0.303	0.130	.02
Reasoning composite	−0.049	0.019	.008	−0.108	0.126	.39
Speed of processing						
Digit Symbol Substitution test	−0.020	0.082	.80	−2.371	0.559	<.001
Useful Field of View score//	3.049	2.170	.16	60.936	14.647	<.001
Functional performance						
ADL//¶	−0.005	0.003	.15	0.074	0.023	.001
IADL//¶	0.012	0.007	.11	0.021	0.048	.67
SF-36 physical function	0.459	0.187	.01#	−5.097	1.272	<.001

* Regression coefficients were adjusted for age, sex, years of education, race, intervention group, study site, smoking status, body mass index, history of DM, history of hypercholesterolemia, myocardial infarction, and stroke.

† Regression coefficients were adjusted for age, sex, years of education, race, intervention group, study site, smoking status, body mass index, blood pressure, hypercholesterolemia, myocardial infarction, and stroke.

‡ Parameter estimates (β) can be interpreted as differences in mean cognitive performance or physical performance score at baseline for each 10-mmHg increase in SBP.

§ Parameter estimates (β) can be interpreted as differences in mean cognitive performance or physical performance score at baseline for subjects with versus without DM.

// Smaller values reflect better performance.

¶ Transformed values based on the formula: $\log(x+1)$, where x = activity of daily living (ADL) or instrumental activity of daily living (IADL).

The relationship between SF-36 physical function and blood pressure was nonsignificant and nonlinear after controlling for hypertension category.

SE = standard error.

Table 3
Adjusted Mean Scores of Cognitive Function According to Blood Pressure Classification and History of Diabetes Mellitus (DM) from Baseline to Second Annual Examination*

Variable	Baseline	First Annual	Second Annual
Memory composite			
Normotensive	− 0.005	−0.197	0.516
Prehypertension	− 0.034	−0.313	0.405
Stage 1 hypertension	0.080	−0.187	0.567
Stage 2 hypertension	−0.001	− 0.334	0.314
Reasoning composite			
Normotensive	0.299	0.765	0.945
Prehypertension	0.116	0.616	0.704
Stage 1 hypertension	0.209	0.793	0.793
Stage 2 hypertension	−0.081	0.658	0.557
Digit Symbol Substitution			
Normotensive	40.445	41 .920	41 .694
Prehypertension	40.357	41.841	41.949
Stage 1 hypertension	41.076	42.687	42.101
Stage 2 hypertension	40.199	41.895	41.298
UFOV			
Normotensive	895.92	820.35	827.25
Prehypertension	902.86	827.74	819.33
Stage 1 hypertension	903.38	810.47	812.75
Stage 2 hypertension	913.79	823.22	835.04
Memory composite			
Non-DM	0.062	−0.205	0.516
DM	− 0.231	− 0.583	0.173
Reasoning composite			
Non-DM	0.184	0.732	0.794
DM	0.052	0.559	0.609
Digit Symbol Substitution			
Non-DM	40.930	42.407	42.246
DM	38.560	40.313	39.185
UFOV			
Non-DM	895.00	814.35	814.01
DM	957.10	858.85	869.02

* Adjusted mean scores in four different blood pressure groups were adjusted for age, sex, race, years of education, intervention group, intervention group/time interaction, study site, smoking status, body mass index, history of DM, high cholesterol, stroke, and myocardial infarction, where adjusted mean scores in the groups with and without DM were adjusted for age, sex, race, years of education, intervention group, intervention group/time interaction, study site, smoking status, body mass index, blood pressure category, history of high cholesterol, stroke, and myocardial infarction.

‡ Transformed values based on the formula: $\log(x + 1)$, where x = activity of daily living (ADL) or instrumental activity of daily living (IADL). UFOV = Useful Field of View.

Table 4

Multivariate Regression Longitudinal Analysis for Effect of Blood Pressure (BP) and Diabetes Mellitus (DM) on Cognitive Functions from a Generalized Estimation Equations Model

Effect of BP or DM	Memory Composite	Reasoning Composite	Digit Symbol Substitution Test	Useful Field of View Score [§]
	β ± Standard Error			
Effect of BP [*]				
From baseline to first annual exam				
Prehypertension	-0.087 ± 0.093	0.034 ± 0.075	0.008 ± 0.342	0.447 ± 11.99
Stage 1 hypertension	-0.076 ± 0.099	0.118 ± 0.079	0.136 ± 0.361	-17.349 ± 12.650
Stage 2 hypertension	-0.141 ± 0.120	0.272 ± 0.094 ^{//}	0.221 ± 0.430	-14.999 ± 15.104
Trend	-0.038 ± 0.036	0.086 ± 0.028 ^{//}	0.079 ± 0.128	-7.115 ± 4.564
From first to second annual exam				
Prehypertension	0.005 ± 0.096	-0.092 ± 0.078	0.334 ± 0.360	-15.309 ± 12.783
Stage 1 hypertension	0.042 ± 0.101	-0.180 ± 0.083 [¶]	-0.360 ± 0.381	-4.613 ± 13.519
Stage 2 hypertension	-0.065 ± 0.121	-0.281 ± 0.099 ^{//}	-0.371 ± 0.454	4.912 ± 16.139
Trend	-0.008 ± 0.036	-0.093 ± 0.030 ^{//}	-0.203 ± 0.135	2.242 ± 4.877
Effect of DM [†]				
From baseline to first annual exam	-0.085 ± 0.103	-0.041 ± 0.082	0.276 ± 0.374	-17.598 ± 13.170
From first to second annual exam	0.035 ± 0.107	-0.013 ± 0.088	-0.967 ± 0.406 [#]	10.507 ± 14.341

Note: Parameter estimates (β) can be interpreted as rate of change in cognitive performance for each high BP category versus normotensive subjects and for subjects with versus without DM.

* Adjusted covariates were age, sex, race, years of education, intervention group, intervention group/piecewise time interaction, study site, smoking status, body mass index, history of DM, hypercholesterolemia, myocardial infarction, and stroke.

[†] Adjusted covariates were age, sex, race, years of education, intervention group, intervention group/piecewise time interaction, study site, smoking status, body mass index, history of DM, hypercholesterolemia, myocardial infarction, and stroke.

[§] Smaller values reflect better performance.

^{//} $P \leq .005$;

[¶] $P \leq .03$;

[#] $P \leq .02$.

Table 5
Multivariate Regression Longitudinal Analysis for Effect of Blood Pressure (BP) and Diabetes Mellitus (DM) on Functional Implications Over 2 Years from a Generalized Estimation Equations Model

BP Category or DM	ADL ^{*,†,§}	ADL ^{*,†,§}	36-Item Physical Function
	$\beta \pm \text{Standard Error}$		
Effect of BP [†]			
Prehypertension	0 ± 0.013	−0.025 ± 0.025	−0.278 ± 0.487
Stage 1 hypertension	−0.003 ± 0.014	−0.035 ± 0.026	−1.136 ± 0.513 ^{**}
Stage 2 hypertension	0.008 ± 0.017	−0.044 ± 0.031	−1.667 ± 0.616 ^{//}
Trend	0.001 ± 0.005	−0.015 ± 0.009	−0.594 ± 0.185 ^{//}
Effect of DM [§]	0.010 ± 0.015	0.059 ± 0.027 [¶]	−1.531 ± 0.540 ^{//}

Note: Parameter estimates (B) can be interpreted as rate of change in physical performance score for each high blood pressure category compared to normotensive subjects for subjects with and without DM.

* Smaller values reflect better performance.

[†] Transformed values based on the formula: $\log(x+1)$, where x = activity of daily living (ADL) or instrumental activity of daily living (IADL).

[‡] Adjusted covariates include age, sex, race, years of education, intervention group, interaction group/time interaction, study site, smoking status, body mass index, history of DM, hypercholesterolemia, myocardial infarction, and stroke.

[§] Adjusted covariates include age, sex, race, years of education, intervention group, interaction group/time interaction, study site, smoking status, body mass index, BP classification, history of hypercholesterolemia, myocardial infarction, and stroke.

^{//} $P \leq .007$;

[¶] $P \leq .03$