

Association of higher diastolic blood pressure levels with cognitive impairment

G. Tsivgoulis, MD
A.V. Alexandrov, MD
V.G. Wadley, PhD
F.W. Unverzagt, PhD
R.C.P. Go, PhD
C.S. Moy, PhD
B. Kissela, MD
G. Howard, DrPH

Address correspondence and reprint requests to Dr. Georgios Tsivgoulis, Comprehensive Stroke Center, University of Alabama at Birmingham, RWUH M226, 1530 3rd Avenue S, Birmingham, AL 35294-3280
tsivgoulisgiorg@yahoo.gr

ABSTRACT

Background: We evaluated the cross-sectional relationship of blood pressure (BP) components with cognitive impairment after adjusting for potential confounders.

Methods: Reasons for Geographic and Racial Differences in Stroke (REGARDS) is a national, longitudinal population cohort evaluating stroke risk in 30,228 black and white men and women ≥ 45 years old. During the in-home visit, BP measurements were taken as the average of 2 measurements using a standard aneroid sphygmomanometer. Excluding participants with prior stroke or TIA, the present analysis included 19,836 participants (enrolled from December 2003 to March 2007) with complete baseline physical and cognitive evaluations. Incremental logistic models examined baseline relationships between BP components (systolic blood pressure [SBP], diastolic blood pressure [DBP], and pulse pressure [PP]) and impaired cognitive status (score of ≤ 4 on 6-Item Screener) after adjusting for demographic and environmental characteristics, cardiovascular risk factors, depressive symptoms, and current use of any antihypertensive medication.

Results: Higher DBP levels were associated with impaired cognitive status after adjusting for demographic and environmental characteristics, risk factors, depressive symptoms, and antihypertensive medications. An increment of 10 mm Hg in DBP was associated with a 7% (95% confidence interval [CI] 1%–14%, $p = 0.0275$) higher odds of cognitive impairment. No independent association was identified between impaired cognitive status and SBP (odds ratio [OR] 1.02, 95% CI 0.99–1.06) or PP (OR 0.99, 95% CI 0.95–1.04). There was no evidence of nonlinear relationships between any of the BP components and impaired cognitive status. There was no interaction between age and the relationship of impaired cognitive status with SBP ($p = 0.827$), DBP ($p = 0.133$), or PP ($p = 0.827$) levels.

Conclusions: Higher diastolic blood pressure was cross-sectionally and independently associated with impaired cognitive status in this large, geographically dispersed, race- and sex-balanced sample of stroke-free individuals. *Neurology*® 2009;73:589–595

GLOSSARY

AD = Alzheimer disease; **ARIC** = Atherosclerosis Risk in Community; **BMI** = body mass index; **BP** = blood pressure; **CES-D-4** = Center for Epidemiologic Studies-Depression-4-item version; **CI** = confidence interval; **DBP** = diastolic blood pressure; **IQR** = interquartile range; **OR** = odds ratio; **PP** = pulse pressure; **REGARDS** = Reasons for Geographic and Racial Differences in Stroke; **SBP** = systolic blood pressure.

Hypertension and dementia are common disorders in elderly individuals. Among people aged 65 years and older, the prevalence of dementia is estimated to be approximately 8%, and the prevalence of hypertension is estimated to be 65%.^{1,2} The relation of blood pressure (BP) with cognitive function and dementia has, in recent years, received much attention from epidemiologic research.^{3–14} However, the findings of cross-sectional studies of BP and cognitive function have varied greatly. Some studies found higher rates of cognitive impairment associated with

From the Comprehensive Stroke Center (G.T., A.V.A.), Department of Medicine (V.G.W.), Department of Epidemiology (R.C.P.G.), and Department of Biostatistics (G.H.), University of Alabama at Birmingham; Department of Neurology (G.T.), Democritus University of Thrace, University Hospital of Alexandroupolis, Greece; Department of Psychiatry (F.W.U.), Indiana University School of Medicine, Indianapolis; National Institute of Neurological Disorders and Stroke (C.S.M.), NIH, Bethesda, MD; and Department of Neurology (B.K.), University of Cincinnati, OH. Supported by a cooperative agreement U01 NS041588 from the National Institute of Neurological Disorders and Stroke, NIH, Department of Health and Human Services. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Neurological Disorders and Stroke or the NIH. Dr. Tsivgoulis is recipient of a neurosonology fellowship grant from the Neurology Department of Eginition Hospital, University of Athens School of Medicine, Athens, Greece.

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elevated BP,³⁻⁶ others with low BP,⁷ and other reports documented a U-shaped relationship^{8,9} or lack of any association.¹⁰ Similarly, the results of longitudinal population-based studies investigating the relation between BP and cognitive status are inconsistent with some studies reporting no significant effect of BP on cognition,¹¹ others documenting an association of hypertension with cognitive decline,^{12,13} and recent reports showing a U-shaped relationship between BP and cognitive function.^{7,14} Moreover, interest has recently focused on the potential association of the pulsatile component of BP (pulse pressure [PP]) with impaired cognitive function, with inconsistent results being reported across different studies.¹⁵⁻¹⁷

This study aims to extend previous research by capitalizing on the large, geographically dispersed, race- and sex-balanced sample of the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. The study offers the opportunity to adjust for numerous potential confounders of the relationship between BP and cognitive function and also to evaluate the potential interaction of BP and age on cognitive function.

METHODS Study design. REGARDS is a national, population-based, longitudinal cohort study with oversampling from the Stroke Belt region of the United States, an area that has stroke mortality rates higher than the rest of the country.¹⁸ Beginning in February 2003, a total of 30,000 individuals aged 45 years or older were being enrolled with the goal of equal representation of whites and blacks and men and women.¹⁸ The goal was to select 20% (achieved 21%) of the sample from the “buckle” of the Stroke Belt (coastal plain region of North Carolina, South Carolina, and Georgia), 30% (achieved 35%) from the Stroke Belt states (remainder of North Carolina, South Carolina, and Georgia, plus Alabama, Mississippi, Tennessee, Arkansas, and Louisiana), and the remaining 50% (achieved 44%) from the other 40 contiguous states. Methodologic details are available elsewhere.¹⁸ Cross-sectional analyses reported in this article are drawn from baseline data of subjects, who 1) were enrolled between December 18, 2003, and March 1, 2007; 2) reported no history of stroke, ministroke, or TIA; 3) had completed the baseline home physical; and 4) were administered the Center for Epidemiologic Studies–Depression–4-item version (CES-D-4) and the 6-Item Screener for assessment of cognitive status. The 6-Item Screener was added to the baseline evaluation in December 2003, 11 months after enrollment began (February 2003).

The present analysis was performed on the June 2007 data freeze. At that time, data were available in 27,731 individuals (92% of the eventually recruited 30,228 participants). Of these, 2,833 (10%) were not included in the present analyses because of history of prior stroke or TIA, resulting in 24,898 remaining participants. Of these, cognitive assessments were not available

on 5,062 (20%) individuals. The vast majority of the participants with unavailable cognitive assessments were recruited before December 2003, when the 6-Item Screener was added in the baseline evaluation. The remaining 19,836 individuals were included in the present analyses.

Standard protocol approvals, registration, and consents. The study methods have been reviewed and approved by the institutional review boards of all participating institutions. Written informed consent was obtained from all patients involved in the present study.

Data collection and definitions. Defined according to previously recommended standards, the cooperation rate (participation rate among known eligible participants) was more than 60%, and the response rate (participation rate among known and imputed eligible participants) was between 25% and 40% depending on the assumptions made regarding eligibility among households where no contact was made.¹⁹

Demographic variables included in the present analyses were age, sex, race, and region of residence (categorized as Stroke Belt, Stroke Buckle, or other regions). Definitions of behavioral variables (smoking history, alcohol use, exercise habits, and educational level) and vascular risk factors (diabetes mellitus, hypercholesterolemia, and obesity) have been previously described.¹⁸

BP measurements. BP was taken as an average of 2 measurements taken after the participant was seated for 5 minutes, and was measured by a trained technician using a standard protocol and regularly tested aneroid sphygmomanometer. All BP measurements were taken during the home visits on Monday through Thursday mornings (morning visits conducted because of the requirement for fasting).¹⁸ BP quality control was monitored by central examination of digit preference, and retraining of technicians took place as necessary.

Assessment of cognitive status. Designed for either in-person or telephone administration, the 6-Item Screener is a test of global cognitive function derived from the widely used Mini-Mental State Examination.²⁰ The 6-Item Screener has been validated against the Mini-Mental State Examination, other cognitive measures, and diagnoses of dementia and cognitive impairment in the absence of dementia in 2 populations: a community-based survey of 344 black adults with a second-stage formal diagnostic evaluation and a clinical sample of 651 adults (16.1% black) with the same diagnostic evaluation.²⁰ Items assess recall and temporal orientation. Scores range from 0 to 6; a score of 4 or fewer correct indicates cognitive impairment.²¹

Assessment of depressive symptoms. The CES-D-4 was used to evaluate depressive symptoms. Scores range from 0 to 12; a score ≥ 4 indicates an elevated level of psychological distress.²²

Statistical analyses. The relationship between BP variables (systolic blood pressure [SBP], diastolic blood pressure [DBP], and PP) and cognitive impairment was evaluated in a set of incremental logistic regression models. All BP variables were entered in the logistic regression models as continuous variables. First, crude associations were estimated (model I) followed by subsequent adjustment for 1) demographic factors (age, sex, race, and region) (model II); 2) further adjustment for environmental factors (smoking, alcohol use, exercise habits, and educational level) (model III); (3) additional adjustment for vascular risk factors (diabetes mellitus, hypercholesterolemia, and obesity) (model IV); (4) additional adjustment for depressive symptoms (model V); and (5) final adjustment for current use of any antihypertensive medication (model VI). Unadjusted and ad-

justed odds ratios (ORs) with 95% confidence intervals (95% CIs) were estimated. Because an interaction between age and BP components on risk for cognitive impairment and dementia has been suggested,²³ we also investigated the presence of interactions between SBP, DBP, or PP with age on the likelihood of cognitive impairment.

RESULTS The sample of 19,836 individuals included in the present analyses had a mean age of 64.6 years (SD 9.5 years) and was 42.3% black, 39.2% male, and 57.2% from the Stroke Belt (table 1). Demographic characteristics, environmental and stroke risk factors, and prevalence of depressive symptoms and cognitive impairment are also presented in detail in table 1. Impaired cognitive status was identified in 1,505 individuals (7.6%). A total of 9,844 (49.6%) individuals were under antihypertensive medications. After comparing baseline characteristics and BP variables between individuals enrolled in the present analyses and individuals excluded because of missing cognitive assessments or prior history of stroke or TIA, we documented higher SBP (130 ± 17 vs 127 ± 17 mm Hg, $p < 0.001$), DBP (77.1 ± 10 vs 76.7 ± 10 mm Hg, $p = 0.002$), and PP (53 ± 14 vs 51 ± 13 mm Hg, $p < 0.001$) levels in the group of patients who were excluded from the analyses. Also, patients who were excluded from the analyses were older (68 ± 9 vs 64 ± 10 years, $p < 0.001$) and had a higher prevalence of diabetes mellitus (26% vs 21%, $p < 0.001$) compared with patients who were included in the analyses. In addition, they were more frequently using antihypertensive medications (57.3% vs 49.6%, $p < 0.001$).

Results of incremental logistic regression models estimating ORs for impaired cognitive status appear in table 2. Higher SBP (OR 1.13, 95% CI 1.10–1.17), DBP (OR 1.08, 95% CI 1.02–1.14), and PP (OR 1.17, 95% CI 1.12–1.21) levels were associated with cognitive impairment in unadjusted logistic regression models. In multivariable analysis, higher DBP levels were associated with impaired cognitive status after adjusting for demographic (model II) and environmental (model III) characteristics, vascular risk factors (model IV), depressive symptoms (model V), and current use of any antihypertensive medication (model VI). An increment of 10 mm Hg in DBP was associated with a 7% (95% CI 1%–14%, $p = 0.0275$) higher odds of cognitive impairment in the final multivariable logistic regression model. No independent association was identified between impaired cognitive status and SBP (OR 1.02, 95% CI 0.99–1.06) or PP (OR 0.99, 95% CI 0.95–1.04) after adjusting for demographics, vascular risk factors, environmental behaviors, depressive symptoms, and antihypertensive medications.

There was no significant evidence of nonlinear relationships between any of the BP components and

Table 1 Characteristics of the REGARDS population (n = 19,836)

Characteristic	No. (%) of participants*
Race/sex	
Black male	2,848 (14.4)
White male	4,917 (24.8)
Black female	5,522 (27.9)
White female	6,541 (33.0)
Age, mean (SD), years	64.6 (9.5)
Region of country	
Stroke belt	7,427 (37.5)
Stroke buckle	3,900 (19.7)
Other region	8,493 (42.9)
Smoking, median (IQR), pack-years	0.1 (17.5)
Alcohol consumption	
Moderate/heavy: >1 drink/day on average	1,242 (6.4)
Light: ≤1 drink/day on average	8,826 (45.4)
None	9,392 (48.3)
Exercise	
≥4 times/week on average	5,570 (28.5)
1–3 times/week on average	7,209 (36.9)
None	6,786 (34.7)
Educational level	
Less than high school	2,209 (11.5)
High school graduate	5,247 (26.5)
Some college	5,431 (27.4)
College graduate	6,875 (34.7)
Diabetes mellitus	3,871 (20.9)
Hypercholesterolemia	2,198 (11.5)
Weight assessment	
Underweight/normal: BMI ≤25 kg/m ²	4,877 (25.0)
Overweight: BMI >25 kg/m ² and ≤30 kg/m ²	7,003 (35.9)
Obese: BMI >30 kg/m ²	7,611 (39.1)
Depressive symptoms†	2,170 (11.0)
Cognitive impairment‡	1,505 (7.6)
Blood pressure variables, mean (SD), mm Hg	
Systolic blood pressure	127.9 (16.8)
Diastolic blood pressure	76.7 (9.7)
Pulse pressure	51.3 (13.4)
Antihypertensive medication	9,844 (49.6)

*Data are presented as number (percentage of participants) unless otherwise indicated; continuous variables are expressed as mean (SD) or as median (interquartile range [IQR]).

†Score ≥4 on Center for Epidemiologic Studies Depression-4-item.

‡Score ≤4 on the 6-Item Screener.

REGARDS = Reasons for Geographic and Racial Differences in Stroke; BMI = body mass index.

Model	n [†]	OR (95% CI)	p Value
I: unadjusted			
SBP (per 10-mm Hg increment)	19,672	1.13 (1.10-1.17)	<0.0001
DBP (per 10-mm Hg increment)	19,628	1.08 (1.02-1.14)	0.0057
PP (per 10-mm Hg increment)	19,608	1.17 (1.12-1.21)	<0.0001
II: adjusted for demographics			
SBP (per 10-mm Hg increment)	19,646	1.03 (1.00-1.07)	0.0619
DBP (per 10-mm Hg increment)	19,602	1.07 (1.01-1.13)	0.0246
PP (per 10-mm Hg increment)	19,582	1.01 (0.97-1.05)	0.5909
III: adjusted for demographics and environmental factors			
SBP (per 10-mm Hg increment)	18,453	1.02 (0.98-1.05)	0.3989
DBP (per 10-mm Hg increment)	18,412	1.05 (0.99-1.12)	0.0873
PP (per 10-mm Hg increment)	18,393	0.99 (0.95-1.04)	0.6921
IV: adjusted for demographics, environmental factors, and stroke risk factors			
SBP (per 10-mm Hg increment)	16,857	1.02 (0.98-1.06)	0.3115
DBP (per 10-mm Hg increment)	16,820	1.07 (1.00-1.14)	0.0389
PP (per 10-mm Hg increment)	16,803	0.99 (0.95-1.04)	0.6579
V: adjusted for demographics, environmental factors, stroke risk factors, and depressive symptoms			
SBP (per 10-mm Hg increment)	16,719	1.02 (0.98-1.06)	0.3198
DBP (per 10-mm Hg increment)	16,682	1.07 (1.00-1.14)	0.0379
PP (per 10-mm Hg increment)	16,665	0.99 (0.94-1.04)	0.6302
VI: adjusted for demographics, environmental factors, stroke risk factors, depressive symptoms, and current use of any antihypertensive medication			
SBP (per 10-mm Hg increment)	16,719	1.02 (0.99-1.06)	0.2312
DBP (per 10-mm Hg increment)	16,682	1.07 (1.01-1.14)	0.0275
PP (per 10-mm Hg increment)	16,665	0.99 (0.95-1.04)	0.7342

*From incremental logistic regression models; order of entry: blood pressure variables, demographics (age, sex, race, region), environmental factors (smoking, exercise, alcohol consumption, education), risk factors (diabetes mellitus, hypercholesterolemia, weight assessment), depressive symptoms, and current use of any antihypertensive medication.

[†]Number of participants included in the analyses.

OR = odds ratio; CI = confidence interval; SBP = systolic blood pressure; DBP = diastolic blood pressure; PP = pulse pressure.

impaired cognitive status ($p > 0.05$). There was no evidence of interaction between age and the relationship of impaired cognitive status with SBP ($p = 0.827$), DBP ($p = 0.133$), or PP ($p = 0.827$) levels. Also no interaction was identified between race and the relationship of impaired cognitive status with SBP ($p = 0.899$), DBP ($p = 0.966$), or PP ($p = 0.858$) levels.

The following factors were independently associated with a higher likelihood of cognitive impairment in multivariate analysis (table 3): higher age, lower educational level, depressive symptoms, and higher DBP values. Individuals with light alcohol consumption and moderate exercise habits had lower

Factor	OR (95% CI)	p Value
Age (per 1-year increment)	1.05 (1.05-1.06)	<0.0001
DBP (per 10-mm Hg increment)	1.07 (1.01-1.14)	0.0275
Exercise		0.0050
≥4 times/week on average	0.98 (0.84-1.16)	
1-3 times/week on average	0.80 (0.68-0.93)	
None	1.00 (reference)	
Alcohol consumption		0.0270
None	1.00 (reference)	
Light	0.83 (0.73-0.95)	
Moderate/heavy	0.91 (0.69-1.19)	
Education		<0.0001
College graduate	1.00 (reference)	
Some college	1.19 (1.00-1.42)	
High school graduate	1.53 (1.29-1.80)	
Less than high school	1.93 (1.60-2.34)	
Depressive symptoms	1.62 (1.37-1.92)	<0.0001

*Variables included in the logistic regression model: diastolic blood pressure, demographics (age, sex, race, region), environmental factors (smoking, exercise, alcohol consumption, education), risk factors (diabetes mellitus, hypercholesterolemia, weight assessment), depressive symptoms, and current use of any antihypertensive medication.

OR = odds ratio; CI = confidence interval; DBP = diastolic blood pressure.

odds of cognitive impairment compared with patients with no alcohol consumption and no exercise habits. In the final multivariable analyses, we also evaluated the relationship of hypertension with impaired cognitive status (BP components were substituted by hypertension in the incremental logistic regression models). Hypertension (defined as SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg or currently taking antihypertensive medication) was not related to impaired cognitive status after adjustment for potential confounders (OR 0.91, 95% CI 0.79-1.05, $p = 0.1981$). Moreover, no interaction was identified between antihypertensive medication and the relationship of impaired cognitive status with SBP ($p = 0.138$), DBP ($p = 0.133$), or PP ($p = 0.225$) levels. Finally, we evaluated the relationship of BP variables with impaired cognitive status after including patients with prior stroke or TIA in our analyses. An increment of 10 mm Hg in DBP was associated with an 8% (95% CI 2%-15%, $p = 0.008$) higher odds of cognitive impairment in the final multivariable logistic regression model. No independent association was identified between impaired cognitive

status and SBP (OR 1.02, 95% CI 0.99–1.06) or PP (OR 0.99, 95% CI 0.95–1.03).

DISCUSSION Our cross-sectional study showed a linear relationship between higher DBP levels and impaired cognitive status in individuals without prior history of stroke or TIAs. This relationship persisted after adjustment for demographic characteristics, vascular risk factors, health behaviors, depressive symptoms, and antihypertensive medications. Although both higher PP and SBP values were related to cognitive impairment in unadjusted analyses, these associations were no longer significant after accounting for demographics, health behaviors, and vascular risk factors. We also found no evidence of interaction between age or race and the relationship between BP and cognitive function.

In our data set, a 10-mm Hg increment of DBP was associated with 7% higher odds of impaired cognitive status. This finding is concordant, though at an attenuated level, with an Italian cross-sectional survey²⁴ where each 10-mm Hg increment in DBP was cross-sectionally associated with a 29% higher odds for cognitive impairment. Likewise, a similar cross-sectional relationship was previously documented in a male Swedish cohort, with each SD difference in DBP values being associated with a 45% higher likelihood of low cognitive function.²⁵ Interestingly, another study after evaluating longitudinally the association of BP with cognitive status in the Framingham Study documented that elevated BP levels were linearly correlated to a higher likelihood of impaired cognitive functioning in individuals receiving no antihypertensive medications.²⁶ In contrast, the East Boston²⁷ and the Maastricht²⁸ Aging Studies reported no cross-sectional association between BP and cognitive function, whereas in the Indo-US Cross National Epidemiologic Study each 10-mm Hg difference in DBP or SBP was related to more than a 10% decrement in cognitive impairment.²⁹ Moreover, higher SBP (and not DBP) levels were related to cognitive impairment in other reports.^{4,30} Finally, a recent report from the Women's Health Initiative Memory Study failed to detect any longitudinal independent associations between hypertension or high BP levels with mild cognitive impairment or probable dementia in older (mean age 71 ± 4 years), cognitively intact, postmenopausal women.³¹ Important methodologic disparities related to the different study samples with regard to age and race, different definitions of impaired cognitive status, different BP cutoffs, and different confounders taken into account in the multivariate analyses may account for these discrepant results.

Interestingly, the Atherosclerosis Risk in Community (ARIC) investigators, who evaluated the second largest population sample of 13,840 individuals, 25% of whom were of African-American origin, documented an independent cross-sectional association between hypertension (defined as $\geq 160/95$ mm Hg) and lower scores on cognitive tests. However, the potential linear relationships of BP variables with low cognitive function were not reported in the ARIC cohort.³ A pooled analysis of studies where BP variables were not dichotomized and were evaluated as continuous variables may provide some more definitive data to support the notion that higher BP levels are linearly associated with cognitive functioning independent of age, health behaviors, and stroke risk factors. In addition, the causal link between hypertension and cognitive impairment can be established only in well-designed and adequately powered longitudinal studies. Indeed, after completion of the 4-year follow-up data in the REGARDS data set, we aim to perform similar analyses to evaluate the reported cross-sectional associations between higher DBP and impaired cognitive status in a longitudinal fashion.

It is intriguing that DBP but not SBP (nor PP) was independently related to impaired cognitive status in our data set. Experimental studies have shown that small cerebral arterioles, which are influenced profoundly by DBP, undergo vascular atrophy progressively with age.³² Neuropathologic data indicate that elevated DBP levels accelerate this process and lead to formation of ischemic white matter lesions in subcortical areas of the brain.³³ Moreover, higher DBP levels have been associated with the severity of white matter disease both cross-sectionally and longitudinally in large randomly selected samples from 2 population-based studies.³⁴ Furthermore, higher DBP (and not SBP or PP) was an independent predictor of white matter hyperintensity progression in elderly individuals both without neuropsychiatric disease³⁵ and with Alzheimer disease (AD).³⁶ Interestingly, a recent longitudinal study showed that higher DBP in persons untreated for hypertension 5 years before MRI was the only BP component that predicted more atrophy of structures affected by AD, such as the hippocampus and amygdala, on brain MRI 5 years later, whereas higher severity of white matter lesions coexisted with more prominent hippocampal atrophy.³⁷ In view of the former considerations, it may be hypothesized that diastolic hypertension accelerates arteriosclerotic changes in the brain, predisposing to arteriosclerosis and arteriolar tortuosity of small cerebral vessels. These vascular changes, incorporating medial thickening and intimal proliferation, result in a reduction of luminal diameter, which in turn causes increased resistance to

flow and decline in cerebral perfusion. Such hypoperfusion may produce discrete regions of small cerebral infarctions and diffuse ischemic changes in the periventricular and deep white matter (leukoaraiosis), causing vascular cognitive impairment and also contributing to the pathogenesis of AD by destabilizing neurons and synapses.

Certain limitations of the present study need to be acknowledged. For one, the cross-sectional design of the study does not provide evidence of a causative relation between BP levels and cognitive impairment. Moreover, the interpretation of cross-sectional relationships between BP and cognitive function is problematic because cognitive impairment itself may affect BP levels through its effects on diet and weight loss. Another study limitation is the lack of imaging data, confining the ability to link BP and its control to neuropathology and cognitive deficits. Furthermore, because BP measurements were performed only in the sitting position, we were unable to assess the potential association of orthostatic hypotension with impaired cognitive status in our data set. It may also be argued that the imbalances between patients who were included and excluded from the present analyses may have influenced the documented association between DBP and impaired cognitive status. However, the older age, the higher prevalence of diabetes mellitus, and the more elevated BP variables in the group of patients who were excluded from the analysis may be attributed to the fact that all patients with prior history of stroke or TIA were not included in our final sample of 19,836. Interestingly, we documented the same independent association between higher DBP and impaired cognitive status when we repeated our multivariable logistic regression analyses after including patients with a prior history of stroke or TIA. Finally, the possibility of confounding due to central obesity (which shows a stronger relationship with cognitive function than body mass index),^{38,39} undetected sleep apnea, and concomitant nonstroke cardiovascular disease (such as myocardial infarction or congestive heart failure) should be acknowledged as another possible limitation of the present analyses.

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