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Midlife hypertension and 20-year cognitive change: The Atherosclerosis Risk in Communities Neurocognitive Study

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Abstract

Importance—Hypertension is a treatable potential cause of cognitive decline and dementia, but its greatest influence on cognition may occur in middle age.

Objective—To evaluate the association between midlife (48–67 years of age) hypertension and the 20-year change in cognitive performance.

Design, Setting, and Participants—The Atherosclerosis Risk in Communities cohort(1990–1992 through 2011–2013) underwent evaluation at field centers in Washington County, Maryland, Forsyth County, North Carolina, Jackson, Mississippi, and the Minneapolis, Minnesota suburbs. Of 13,476 African American and white participants with baseline cognitive data; 58.0% of living participants completed the 20-year cognitive follow-up.

Exposures—Hypertension, prehypertension, or normal blood pressure (BP) at visit 2 (1990–1992) constituted the primary exposure. Systolic BP at visit 2 or 5 (2011–2013) and indication for treatment at visit 2 based on the Eighth Joint National Committee (JNC-8) hypertension guidelines constituted the secondary exposures.

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Disclosures: Dr. Knopman serves as Deputy Editor for Neurology®; serves on a Data Safety Monitoring Board for Lundbeck Pharmaceuticals and for the Dominantly Inherited Alzheimer's Disease Treatment Unit. He has served on a Data Safety Monitoring Board for Lilly Pharmaceuticals (completed 2012); served as a consultant to Tau RX (Completed 2012), was an investigator in clinical trials sponsored by Baxter and Elan Pharmaceuticals in the past 2 years (both completed in 2012); and receives research support from the NIH. Other authors have no disclosures beyond NIH funding.

Main Outcome—Prespecified outcomes included the 20-year change in scores on the Delayed Word Recall Test, Digit Symbol Substitution Test, and Word Fluency Test and in global cognition.

Results—During 20 years, baseline hypertension was associated with an additional decline of 0.056 global *z* score points (95% CI −0.100 to −0.012)and prehypertension was associated nonsignificantly with 0.040 more global *z* score points of decline (95% CI −0.085 to 0.005)compared with normal BP. Individuals with hypertension who used antihypertensives had less decline during the 20 years than untreated individuals with hypertension (0.050 [95% CI 0.003–0.097] - vs 0.079 [95% CI 0.002–0.156] global z score points). Having a JNC-8-specified indication for initiating antihypertensive treatment at baseline was associated with a greater 20-year decline (0.044 [95% CI −0.085 to −0.003] global *z* score points) than not having an indication. We observed effect modification by race for the continuous systolic BP analyses (p=0.01), with each 20 mm Hg increment at baseline associated with an additional 0.048 (95% CI −0.074 to −0.022)points in global cognitive *z* score in whites, but not in African Americans(decline, −0.020 [95% CI −0.026 to 0.066] points). Systolic BP at the end of follow-up was not associated with the preceding 20 years of cognitive change in either group. Methods to account for bias owing to attrition strengthened the magnitude of some associations.

Conclusion and Relevance—Midlife hypertension and elevated midlife but not late-life systolic BP was associated with more cognitive decline during the 20 years of the study. Greater decline is found with higher midlife BP in whites than in African Americans.

Keywords

hypertension; cognition; epidemiology; blood pressure

Introduction

Accumulating evidence suggests that hypertension is an important risk factor for cognitive change and dementia. Midlife (45–55 years of age) hypertension may be a stronger risk factor than late-life hypertension, as demonstrated in the Honolulu-Asia Aging Study (midlife blood pressure (BP) was associated with dementia[1,2] and late-life cognitive function[3]) and in a Finnish cohort (for dementia[4] and cognitive performance[5]). In the Atherosclerosis Risk in Communities (ARIC) study, hypertension was more strongly associated with hospitalizations with dementia when defined in midlife versus late-life.[6] Other studies showed hypertension, especially in midlife, predicted cognitive decline in certain cognitive domains,[7–14] but these studies had a short follow-up, examined a primarily white population, did not address the role of antihypertensives, or did not address attrition.

The ARIC study is uniquely situated to explore the effects of hypertension (independent of confounders such as educational level and other vascular risk factors) by evaluating change on the results of 3 cognitive tests completed at several points. These tests represent domains usually affected by vascular processes (psychomotor speed and executive function) and by Alzheimer neurodegeneration (memory). Identifying midlife hypertension as an important risk factor for cognitive decline yields a potential treatable target, with the recognition that treatment might need to be implemented for decades. Herein, we evaluate the relationship of

midlife hypertension with 20-year cognitive change in the ARIC study, with particular attention to low systolic BP (SBP).

Methods

Study population

We recruited ARIC participants aged 45–64 years(n=15,792) from November 24, 1986 through March 29, 1990 by probability sampling,[15] from the following 4 U.S. communities: Washington County, Maryland; Forsyth County, North Carolina; the Minneapolis, Minnesota suburbs; and Jackson, Mississippi. Participants were seen five times(figure 1), and called annually. The study was approved by each field center's institutional review board, and all participants provided written informed consent.

Of the 14,348 participants who attended ARIC visit 2 (the "baseline" cognitive assessment [1990–1992]), we excluded those not identified as African American nor white (n=42), the few African Americans living in Washington County or Minneapolis (n=49), and participants missing baseline cognitive data (n=217), BP data (n=1), or covariates included in regression models (n=563). After exclusions, 13,476 participants remained.

Cognitive evaluation

The Delayed Word Recall Test (DWRT),[16] Digit Symbol Substitution Test (DSST),[17] and Word Fluency Test (WFT),[18] were administered at visit 2 (1990–1992), visit 4 (1996–1998), and the ARIC Neurocognitive Study at visit 5 (2011–2013) in a quiet room by trained examiners using standardized protocols. Recordings were reviewed for quality control.

The DWRT evaluates verbal learning and short-term memory. Participants learn ten nouns, use them in sentences and, after 5 minutes, are asked to recall them. The score is the number of nouns recalled(maximum of 10).[16] In a normative healthy sample of similarly aged ARIC participants, mean DWRT scores range from 5.2–6.7 depending on educational level and race group.[19] The DSST evaluates executive function and processing speed. Participants use a key to write symbols corresponding to numbers in 90 seconds. The score, ranging from 0 to 93, is the number of correctly written symbols.[17] The ARIC normative means range from 20.3–48.2. The WFT evaluates executive function and expressive language. Participants generate as many words as possible within 60 seconds starting with F, A, and S, with one trial per letter. The total score is the sum of all correct words generated,[20] with ARIC normative means ranging from 19.4 to 39.5.

We generated *z* scores for each cognitive test score per visit, standardized using the visit 2 mean(SD). We calculated mean test *z* scores to create global cognition *z* scores, which we standardized using the visit 2 global *z* mean (SD).

Covariates

Covariates and their interactions with time were included in multivariable models as potential confounders. From visit 1, age, sex, race, and educational level (less than high school; high school, General Educational Development Test, or vocational school; or at least some college)were self-reported; race was further classified by combining race and study

center. At visit 2, body mass index (calculated as weight in kilograms divided by height in meters squared) was measured (<25, 25-<30, or ≥30), with diabetes mellitus defined as self-reported history of a physician's diagnosis, use of diabetes medications, fasting blood glucose level of at least 126 mg/dL, or nonfasting glucose level of at least 200 mg/dL (to convert gluose levels to millimoles per liter, multiply by 0.0555). At visit 2, history of alcohol use and smoking were self-reported (current, former, or never); apolipoprotein E ε4 was genotyped (0, 1, or 2 alleles); and prevalent stroke was based on self-reported history before visit 1 or adjudicated stroke follow-up.

BP measurement

We measured SBP and diastolic BP (DBP) using a random zero sphygmomanometer, with 5 minutes of rest before each measurement. The mean of 2 measurements was used as the BP for each visit. Antihypertensive status was recorded (yes or no).

Blood pressure was categorized as: normal (SBP of <120 mm Hg, DBP of <80 mm Hg, and no antihypertensive use), prehypertension (SBP of 120–139 mm Hg or DBP of 80–89 mm Hg), and hypertension (SBP of ≥140 mm Hg, DBP of ≥90 mm Hg, or antihypertensive use).[21,22] In a secondary analysis, we divided hypertension based on medication use status. We also undertook continuous and categorical SBP and DBP analyses.

An additional analysis categorized all individuals by whether or not treatment would be recommended, defined at visit 2 (when the mean age was 57 years)based on the Eighth Joint National Committee (JNC-8) hypertension guidelines.[23] *Treatment not indicated* defined participants without diabetes mellitus and without chronic kidney disease (estimated gloumerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration equation,[24] of <60mL/min/1.73 m^2) who were 60 years or older, with SBP of less than 150 mm Hg and DBP of less than 90 mm Hg or younger than 60 years with SBP of less than 140 mm Hg and DBP of less than 90 mm Hg, and who were not using antihypertensives. *Indication for treatment* defined all participants 60 years or older with SBP of at least 150 mm Hg or DBP of at least 90 mm Hg, or younger than 60 years with SBP of at least 140 mm Hg or DBP of at least 90 mm Hg, not using any antihypertensives; or all participants with diabetes mellitus or chronic kidney disease (any age) and SBP of at least 140 mm Hg or DBP of at least 90 mm Hg.

Statistical analysis

Statistical analysis was performed using commercially available software (SAS, version 9.3 [SAS Institute Inc] and Stata, version 13.0 [StataCorp]). A p-value of <0.05 was significant, and tests were 2-sided. Linear regression models fit with generalized estimating equations were used to evaluate associations with cognitive performance trajectories, using robust variance and an unstructured correlation matrix. Models included adjustment for visit 2 age, square of age, sex, center or race-center, education, body mass index, diabetes mellitus, alcohol consumption, smoking status, apolipoprotein Eε4 genotype, and stroke history. Linear spline terms represented time since baseline (knot at 6 years, corresponding to the visits 2–4 interval). We included interaction terms for each covariate with each time spline term, except alcohol by time and stroke by time spline (nonsignificant). Based on the

interactions of hypertension (or SBP) by time, we calculated the additional 20-year decline associated with each hypertension definition. We found a significant effect modification(p=0.01 for interaction) by race for the continuous SBP models, so for SBP, we report only race-stratified models. Categorical models did not show race interactions, so for these we present race-combined and race-stratified results. Model diagnostics confirmed adequate model fit. All participants with baseline cognitive testing contributed data to the generalized estimating equation analysis. In a sensitivity analysis, we omitted all cognitive test scores after an adjudicated stroke.

Sensitivity analyses

To account for death and drop-out, we used the inverse probability of attrition weighting (IPAW)model (eMethods 1 and eTable 1 in the Supplement).[25] The IPAW model weighted study participants by the inverse of the probability that they will die or drop out, estimated using logistic regression models, to compensate for under representation of persons with characteristics associated with death or drop-out. Individual probabilities are calculated from separate logistic models (eMethods 1 and eTable 1 in the Supplement)using information from visits and annual telephone calls. Weights are calculated as the inverse of the product of these probabilities, stabilized,[26] and applied to our generalized estimating equation models.

We also account for informative attrition by assigning cognitive scores to persons missing cognitive data but who had hospitalizations with discharge codes for dementia. A previous report[27] found strong associations of these cases with hypertension[6] and prior low cognitive performance. Participants without hospitalizations and with dementia codes had nearly identical scores at visits 2 and 4, but those participants hospitalized with dementia about 2 years after visit 4 had z scores 1.33 units lower than at visit 2;[27] using this value we corrected scores otherwise expected for all individuals hospitalized with dementia discharge codes but who did not attend subsequent visits(eMethods 2 in the Supplement).

Results

A total of 13,476 participants contributed data to this analysis, of whom 3,229 were African-American. Compared with participants with normal BP (Table 1), those with hypertension participants were older, were more likely to have diabetes mellitus and stroke, and had lower educational levels and baseline cognitive scores. Individuals with baseline hypertension were twice as likely to die before visit 5 than individuals without hypertension, and 53.9% of individuals with SBP of at least 160 mm Hg at visit 2 died before visit 5; 58.6% in African-Americans. Maximum follow-up was 23.5 years; of the 80.8% of participants with at least one visit beyond visit 2, the median follow-up time was 19.1 (intraquartile range, 6.0, 20.8) years. Of the original visit 2 ARIC cohort, participants completing 20-year follow-up were younger and healthier, and had higher cognitive performance compared with those who died before visit 5 and those who were alive but did not attend visit 5 (eTable 2 in the Supplement).

Hypertension versus no hypertension was associated with steeper 20-year cognitive decline by 0.056 *z* score units for global cognition (Table 2). Similar associations were observed for

the DSST and WFT. Pre-hypertension was also significantly associated with DSST decline. The amount of decline in the global cognitive *z* score during 20 years observed for individuals with prehypertension was 4.8% greater, and for those with hypertension, 6.5% greater, than in individuals with normal BP. An average ARIC participant with normal BP at baseline had a decline of 0.840 global cognitive *z* score points during 20 years, compared with 0.880 global *z* score points for participants with prehypertension and 0.896 global *z* score points for participants with hypertension. On the DSST, hypertension was associated with 11.206 (95% CI, 10.831, 11.580) fewer symbols during 20 years, compared with only 10.100 (95% CI, 9.766, 10.433) fewer symbols for normal BP.

Effect of antihypertensives and interim stroke

Individuals with hypertension who used medications had a nearly identical mean SBP (at visit 2) as those with pre-hypertension (eTable 3 in the Supplement). Their 20-year decline was intermediate between that of the pre-hypertensive group and the hypertensive group who did not use medications. The latter group had the steepest decline, especially in white participants. Untreated hypertension in African-Americans was significantly associated with decline on the DSST.

Omitting cognitive test scores after a stroke resulted in 359 fewer scores. Associations of prehypertension and hypertension with cognitive change were similar to those in the primary analysis.

BP categories reflecting 2014 guidelines

Individuals with an indication for antihypertensive treatment, based on the 2014 JNC 8 recommendations (Table 3),[23] had a greater 20-year cognitive decline than individuals without an indication for treatment. Effect sizes were slightly lower than those for participants with hypertension (Table 2), but the comparison is difficult because very few individuals (n=189) underwent reclassification with the JNC-8 criteria.

Visits 2 and 5 BP

Baseline continuous SBP values were significantly associated with decline in white (Figure 2; a decline of 0.048 more global cognitive *z* points per 20-mm Hg SBP increment [95% CI −0.074, −0.022]) but not black (eFigure 1 in the Supplement; a decline of 0.020 fewer points[95% CI −0.026, 0.066]) participants. Visit 5 SBP, however, was not associated with the prior 20-year cognitive change in either race: the coefficient for each 20 mm Hg increment was −0.020 global cognitive *z* points decline (p=0.09) in white and −0.028 global cognitive z points in African Americans (p=0.21). We found no evidence of a J-shaped association, noting lesser, not greater, amounts of decline at the lowest SBP category at visits 2 and 5. Blood pressures at visit 5, when participants were 20 years older, were higher than at visit 2. Associations of DBP with cognitive change were similar to those for SBP (eFigures 2 and 3 in the Supplement).

Analyses using IPAW

The magnitude of the effect of categorized hypertension was increased (steeper cognitive decline of 0.091 global cognitive *z* score units during 20 years, compared with 0.056 in the

primary analysis) after accounting for drop-out and death using IPAW methods (eTable 4 in the Supplement). After IPAW modeling, the DSST association with hypertension in African Americans reached statistical significance and was of similar magnitude to that in whites (−0.084 and −0.105, respectively; eTable 4 in the Supplement).

Adding IPAW to the models evaluating the treatment indication for hypertension increased the effect estimate for the overall sample (−0.084 for the global cognitive *z* score vs −0.044) and in whites (−0.056) but not in African-Americans (−0.100).

Expanded measurement

Using expanded measurement for missing scores for individuals with hospitalizations with dementia (eMethods 2 in the Supplement) led to stronger coefficients for hypertension(−0.086 global cognitive z units for 20-year change (overall)compared with −0.056 without this expanded measurement), with similar strengthening of results for pre-hypertension and by race.

Discussion

In our study of 13,476 individuals followed up for as long as 23 years with rigorous BP and covariate measurement and standardized cognitive assessment, hypertension in midlife was independently associated with a steeper decline in cognitive performance. As hypothesized, hypertension was most consistently associated with the DSST score, the test reflecting domains most typically affected by vascular disease.[28] Although other studies have suggested that lower BP might lead to hypoperfusion and thus *worse* cognitive outcomes in older persons,[29,30] we did not find support for this suggestion based on midlife BP. In contrast to studies supporting a J-shaped curve from midlife BP(with worse outcomes at very low BP, for cognition,[31] cardiovascular disease,[32] stroke,[33] and brain white matter hyperintensities (in older persons)[34]), we found a nearly continuous effect of midlife SBP, with steeper cognitive decline as BP increased in whites only.

The lack of an association between current (late-life) BP and prior cognitive change in our study, in combination with other clinical trials failing to show improvement in cognitive function among elderly individuals treated to lower BP targets[35] supports the view that, at the population level, higher BP in later life may be less detrimental, perhaps because hypertension at a later age reflects new conversion,[36] or because of reverse causation (lower BP in individuals who are already experiencing neurodegeneration).[37] Evidence considered in the recently published JNC-8 guidelines for hypertension[23] led to a recommendation for less tight control in persons older than 60 years. Our results suggest that those participants with an indication for treatment under these guidelines have more decline than individuals without an indication for treatment. However, results were very similar to those seen for the classically defined hypertension categories, likely due to significant overlap of the persons categorized into the JNC-7 “hypertension” category and the JNC-8 “indication for treatment” category.

Evaluation of cognitive *change* instead of dementia or cognitive performance at a single point allows for a reduction of the influence of confounding factors such as cultural factors

or inherited cognitive ability. The utility of this approach is demonstrated by previous findings in the ARIC Study that educational level, although strongly associated with cognitive performance at any single visit, is not an important predictor of cognitive *change*.[38,39]

The additional effect of hypertension beyond that of aging alone appears to be relatively modest (6.5% more decline after 20 years). A primary limitation of our study that may account for the relatively modest effect sizes involves the attrition observed in individuals not only with the worst cognition but also the highest baseline BP. However, as shown by our sensitivity analyses, our estimates of the BP/ cognitive change relationship are likely to be conservative. The IPAW modeling increased the estimate of the hypertension-associated change in 20-year race-combined global cognitive *z* scores by almost 70%, from −0.056 to −0.091. Furthermore, consideration of scores for patients hospitalized with dementia also increased our estimated hypertension-associated declines; these effects may be supplementary to the effects of adjusting for attrition. We believe the bias due to attrition is a primary reason for the relative lack of an observed association between hypertension and cognitive decline in African American participants, with the smaller sample size further reducing power. Proportionately more African American than white participants died before visit 5 across all hypertension strata, and the highest BPs at baseline associated with the highest mortality rates, were seen most frequently in African-Americans. Systolic BP also increases stroke risk 3-fold more for African Americans than for whites,[40] possibly further increasing disproportionate attrition. These patterns could lead to dilution of an association and explain our lack of an association in African Americans. Treatment decisions are also likely to affect attrition; individuals with better BP management in midlife may be less likely to die or to experience cognitive impairment, and thus less attrition would be noted in these individuals. In addition, many vascular risk factors co-occur, and hypertension, in combination with other vascular risk factors such as diabetes mellitus or smoking, may have additive effects on cognitive change and on attrition.

In the Honolulu-Asia Aging Study, use of beta-blockers was associated with a lower risk for cognitive impairment, independent of BP level;[41] data from this study were also used to attribute 27% of dementia cases among persons not taking antihypertensives in midlife to SBP elevations.[42] Our results also suggest that medication reduces the decline attributable to hypertension, but analysis of antihypertensive treatment is vulnerable to healthy user and indication biases. Users may be more adherant, follow physicians' orders, or have better access to care and healthier habits. However, antihypertensives are given to people with higher BPs, possibly decreasing any observed antihypertensive-induced reduction in cognitive decline, but we see less decline in people using antihypertensives despite this decrease. Antihypertensive use also changes over time, with initiation of treatment in later years in many initially untreated participants.

Although evidence of a definitive benefit of antihypertensive treatment would require a randomized clinical trial (such as the ongoing Systolic Blood Pressure Intervention Trial-Memory and Cognition in Decreased Hypertension [SPRINT-MIND]), existing clinical trials may not be of long enough duration to demonstrate a benefit. Thus, studies like the ARIC Neurocognitive Study are necessary to observe effects occurring during decades of

exposure. Although we note a relatively modest additional decline associated with hypertension, lower cognitive performance increases the risk for future dementia, and a shift in the distribution of cognitive scores, even to this degree, is enough to increase the public health burden of hypertension and pre-hypertension significantly. Initiating treatment in late life might be too late to prevent this important shift. Epidemiological data, including our own study, support midlife BP as a more important predictor of—and possibly target for prevention of— late-life cognitive function than is later-life BP.

Conclusions

Midlife hypertension, by several definitions, and elevated midlife, but not late-life, SBP were associated with more cognitive decline during the 20-year ARIC Study. Greater linear decline is found with higher midlife BP in white than in African American participants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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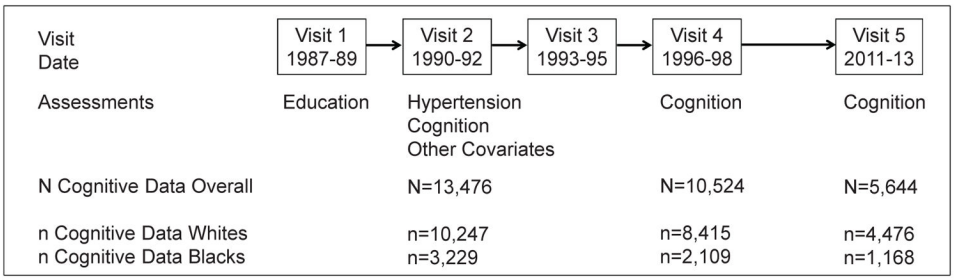

Figure 1.

Timeline for the Atherosclerosis Risk in Communities (ARIC) Study. Visits, assessments, and numbers of participants are tabulated.

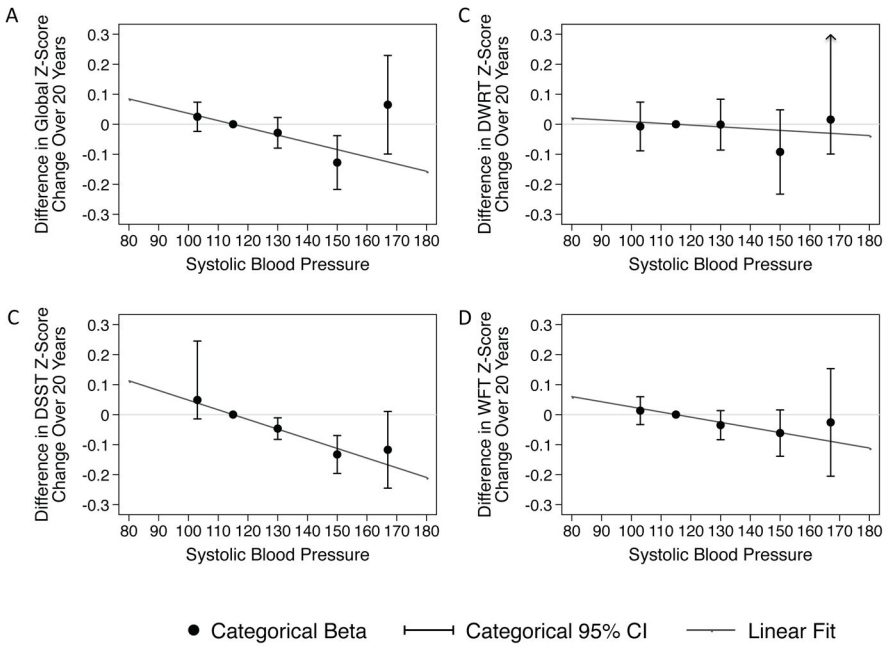

Figure 2.

Adjusted association of visit 2 (1990–1992) systolic blood pressure categories and linear systolic blood pressure with 20-year cognitive change among Whites.

Model adjusted for age, age^2, gender, center (whites, North Carolina; Minnesota; Maryland, blacks, North Carolina; Mississippi), education (<high school; high school, GED or vocational school; college, graduate or professional school) body mass index (BMI [calculated as weight in kilograms divided by height in meters squared]; <25, 25-<30, ≥30), diabetes mellitus, alcohol consumption (never; former; current), smoking status (never; former; current), apolipoprotein E (APOE) ε4 genotype (0, 1, or 2 alleles), history of stroke, time as a linear spline with knot at 6 years, age by time spline terms, squared age by time spline terms, gender by time spline terms, center by time spline terms, education by time spline terms, BMI by time spline terms, diabetes mellitus by time spline terms, smoking status by time spline terms, and APOE ε4 genotype by time spline terms. Systolic BP categories are defined as: <110 mmHg; 110-<120 mmHg; 120-<140 mmHg; 140-<160 mmHg; ≥160 mmHg. 110–120 mm Hg (represented by the 2nd data marker) is the reference group. Data points are shown at the midpoint of the categories for the 110–120, 120–140, and 140–160 mm Hg groups (115, 130, and 150 mm Hg, respectively), but at the median values for the two extreme groups (<110 and ≥160 mmHg), because of the large range of values seen in each of these groups. A: Global *z* Score, B: Delayed Word Recall Test (DWRT) *z* Score, Panel C: Digit Symbol Substitution Test (DSST) *z* Score, Panel D: Word Fluency Test (WFT) *z* Score). Data markers indicate categorical β values; lines, linear fit; error bars, categorical 95% confidence intervals.

Table 1

ARIC participant characteristics by race and BP category at Visit 2 (1990–1992).

	Racial Group, BP category[a]					
	White			African American		
	Normal (n=4322)	Prehypertension (n=2274)	Hypertension (n=3651)	Normal (n=779)	Prehypertension (n=601)	Hypertension (n=1849)
Age (years), mean (SD)	56 (6)	58 (6)	59 (6)	55 (6)	56 (6)	57 (6)
Female	2,453 (56.8)	1,104 (48.5)	1,862 (51.0)	455 (58.4)	383 (63.7)	1,237 (66.9)
Center						
Minneapolis, MN	1,450 (33.5)	920 (40.5)	1,245 (34.1)	0	0	0
Washington County, MD	1,374 (31.8)	708 (31.1)	1,424 (39.0)	0	0	0
Forsyth County, NC	1,498 (34.7)	646 (28.4)	982 (26.9)	93 (11.9)	62 (10.3)	209 (11.3)
Jackson, MS	0 (0)	0	0	686 (88.1)	539 (89.7)	1,640 (88.7)
Educational level[b]						
<High school	525 (12.1)	375 (16.5)	733 (20.1)	243 (31.2)	202 (33.6)	791 (42.8)
High school, GED, or vocational school	1,956 (45.3)	1,022 (44.9)	1,712 (46.9)	233 (29.9)	183 (30.4)	512 (27.7)
College, graduate, or professional school	1,841 (42.6)	877 (38.6)	1,206 (33.0)	303 (38.9)	216 (35.9)	546 (29.5)
Smoking status						
Never	1,633 (37.8)	888 (39.1)	1,380 (37.8)	348 (44.7)	262 (43.6)	866 (46.8)
Former	1,629 (37.7)	932 (41.0)	1,600 (43.8)	221 (28.3)	182 (30.3)	536 (29)
Current	1,060 (24.5)	454 (20.0)	671 (18.4)	210 (27.0)	157 (26.1)	447 (24.2)
Alcohol consumption						
Never	749 (17.3)	414 (18.2)	732 (20.0)	263 (33.8)	217 (36.1)	673 (36.4)
Former	693 (16.0)	375 (16.5)	749 (20.5)	231 (29.7)	167 (27.8)	604 (32.7)
Current	2,880 (66.6)	1,485 (65.3)	2,170 (59.4)	285 (36.6)	217 (36.1)	572 (30.9)
BMI						
<25	1,952 (45.2)	717 (31.5)	901 (24.7)	228 (29.3)	129 (21.5)	283 (15.3)
25 to<30	1,767 (40.9)	949 (41.7)	1,473 (40.3)	313 (40)	233 (38.8)	629 (34.0)
≥30	603 (14.0)	608 (26.7)	1,277 (35.0)	238 (31)	239 (39.8)	937 (50.7)
Diabetes mellitus	239 (5.5)	255 (11.2)	720 (19.7)	114 (15)	124 (20.6)	567 (30.7)
Prevalent stroke	26 (0.6)	19 (0.8)	104 (2.8)	9 (1.2)	3 (0.5)	75 (4.1)

	Racial Group, BP category[a]					
	White			African American		
	Normal (n=4322)	Prehypertension (n=2274)	Hypertension (n=3651)	Normal (n=779)	Prehypertension (n=601)	Hypertension (n=1849)
Hypertension medication use[c]	0	0	2,874 (78.7)	0	0	1,520 (82.2)
Beta-blockers	0	0	1,030 (28.2)	0	0	316 (17.1)
Calcium channel blockers	0	0	668 (18.3)	0	0	301 (16.3)
ACE-I/ARB	0	0	590 (16.2)	0	0	210 (11.4)
Diuretics	0	0	1,314 (36.0)	0	0	804 (43.5)
Combination Therapy	0	0	178 (4.9)	0	0	117 (6.3)
Other	0	0	42 (1.2)	0	0	89 (4.8)
APOE ε4 alleles						
0	3,086 (71.4)	1,634 (71.9)	2,692 (73.7)	452 (58.0)	377 (62.7)	1,094 (59.2)
1	1,147 (26.5)	583 (25.6)	896 (24.5)	290 (37.2)	196 (32.6)	676 (36.6)
2	89 (2.1)	57 (2.5)	63 (1.7)	37 (4.7)	28 (4.7)	79 (4.3)
Visit 2 cognitive test scores, mean (SD)						
DWRT, No. of words	6.92 (1.42)	6.73 (1.49)	6.63 (1.42)	6.34 (1.65)	6.19 (1.62)	6.00 (1.65)
DWRT, *z* score	0.20 (0.94)	0.07 (0.98)	0.01 (0.93)	−0.18 (1.08)	−0.28 (1.02)	−0.41 (1.08)
DSST, No. of symbols	50.6 (11.3)	48.9 (11.6)	46.9 (11.5)	34.1 (14.2)	32.1 (12.7)	29.6 (12.9)
DSST, *z* score	0.42 (0.80)	0.30 (0.81)	0.16 (0.81)	−0.74 (1.00)	−0.88 (0.90)	−1.06 (0.91)
WFT, No. of words	35.6 (11.8)	34.7 (11.8)	34.2 (11.9)	30.5 (13.5)	28.6 (12.8)	26.6 (12.8)
WFT, *z* score	0.19 (0.95)	0.12 (0.94)	0.08 (0.95)	−0.22 (1.08)	−0.37 (1.02)	−0.53 (1.02)
Global *z* score	0.35 (0.86)	0.21 (0.88)	0.11 (0.86)	−0.49 (1.06)	−0.66 (1.00)	−0.86 (1.02)
Visit 5 attendance status						
Attended	2,377 (55.0)	968 (42.6)	1,131 (31.0)	358 (46.0)	254 (42.3)	556 (30.1)
Alive but did not attend	1,187 (27.5)	742 (32.6)	1,145 (31.4)	262 (33.6)	186 (30.9)	562 (30.4)
Died	758 (17.5)	564 (24.8)	1,375(37.7)	159 (20.4)	161 (26.8)	731 (39.5)

*Blood pressure categories are defined as:
Normal blood pressure: systolic blood pressure <120 mmHg and diastolic blood pressure <80 mmHg and no hypertension medication use.
Pre-Hypertension: systolic blood pressure ≥120 mmHg and <140 mmHg or diastolic blood pressure ≥80 mmHg and <90 mmHg and no hypertension medication use.
Hypertension: systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or hypertension medication use.

**Education assessed at ARIC visit 1 (1987–1989).

[***] Some participants were on multiple HTN medications.

Abbreviations: ACE-I: angiotensin-converting-enzyme inhibitor; APOE: apolipoprotein E; ARB: angiotensin receptor blocker; ARIC: Atherosclerosis Risk in Communities; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP:blood pressure; GED: general educational development; DWRT, delayed word recall test; DSST, digit symbol substitution test; WFT, word fluency test.

[a] Normal BP is defined as systolic BP (SBP) of less than 20 mm Hg, diastolic BP (DBP) of less than 80 mm Hg, and no antihypertensive use; prehypertension, SBP of 120 to less than 140 mm Hg or DBP of 80 to less than 90 mm Hg and no antihypertensive use; and hypertension, SBP of 140 mm Hg or more, DBP of 90 mm Hg or more, or antihypertensive use. Unless otherwise indicated, data are expressed as number (percentage) of participants.

[b] Assessed at ARIC visit 1 (1987–1989).

[c] Some participants received multiple antihypertensives.

Table 2

Additional adjusted 20-year cognitive change associated with ARIC visit 2 (1990–1992) BP categories

Measure	Cognitive Change (95% CI)[a]		
	Normal BP	Prehypertension	Hypertension
All participants[b]			
	(N=5,101)	**n=2,875**	**n=5,500**
Global z score	0 (reference)	−0.040 (−0.085, 0.005)	**−0.056 (−0.100, −0.012)**
DWRT z score	0 (reference)	−0.024 (−0.097, 0.050)	−0.008 (−0.079, 0.063)
DSST z score	0 (reference)	**−0.046 (−0.077, −0.014)**	**−0.079 (−0.110, −0.048)**
WFT z score	0 (reference)	−0.040 (−0.081, 0.002)	**−0.057 (−0.097, −0.017)**
DWRT raw score, No. of words	0 (reference)	−0.036 (−0.148, 0.077)	−0.012 (−0.120, 0.096)
DSST raw score, No. of symbols	0 (reference)	**−0.650 (−1.100, −0.202)**	**−1.124 (−1.563, −0.685)**
WFT raw score, No. of words	0 (reference)	−0.493 (−1.013, 0.026)	**−0.780 (−1.208, −0.212)**
Whites[c]			
	4,322	2, 274	3,651
Global z score	0 (reference)	−0.036 (−0.085, 0.014)	**−0.063 (−0.112, −0.014)**
DWRT z score	0 (reference)	0.004 (−0.077, 0.084)	−0.019 (−0.100, 0.062)
DSST z score	0 (reference)	**−0.046 (−0.080, −0.011)**	**−0.086 (−0.121, −0.051)**
WFT z score	0 (reference)	−0.045 (−0.091, 0.001)	**−0.066 (−0.111, −0.020)**
DWRT raw score, No. of words	0 (reference)	0.005 (−0.117, 0.128)	−0.029 (−0.151, 0.094)
DSST raw score, No. of symbols	0 (reference)	**−0.650 (−0.141, −0.159)**	**−1.220 (−1.719, −0.721)**
WFT raw score, No. of words	0 (reference)	−0.565 (−1.141, 0.012)	**−0.820 (−1.390, −0.250)**
African Americans[c]			
	779	601	1,849
Global z score	0 (reference)	−0.034 (−0.145, 0.077)	−0.016 (−0.113, 0.082)
DWRT z score	0 (reference)	−0.104 (−0.287, 0.079)	0.032 (−0.121, 0.184)
DSST z score	0 (reference)	−0.023 (−0.101, 0.056)	−0.044 (−0.111, 0.022)
WFT z score	0 (reference)	0.006 (−0.090, 0.101)	−0.013 (−0.096, 0.069)
DWRT raw score, No. of words	0 (reference)	−0.158 (−0.435, 0.120)	0.048 (−0.183, 0.280)

Measure	Cognitive Change (95% CI)[a]		
	Normal BP	Prehypertension	Hypertension
DSST raw score, No. of symbols	0 (reference)	−0.322 (−1.434, 0.790)	−0.626 (−1.571, 0.318)
WFT raw score, No. of words	0 (reference)	0.070 (−1.124, 1.264)	−0.167 (−1.201, 0.867)

Abbreviations: ARIC, Atherosclerosis Risk in Communities; BP, blood pressure; DWRT: delayed word recall test; DSST: digit symbol substitution test; WFT: word fluency test.

[a] Normal BP is defined as systolic BP (SBP) of less than 20 mm Hg, diastolic BP (DBP) of less than 80 mm Hg, and no antihypertensive use; prehypertension, SBP of 120 to less than 140 mm Hg or DBP of 80 to less than 90 mm Hg and no antihypertensive use; and hypertension, SBP of 140 mm Hg or more, DBP of 90 mm Hg or more, or antihypertensive use. Unless otherwise indicated, data are expressed as number (percentage) of participants.

[b] Adjusted for age, square of age, gender, race/center (Minnesota whites; Maryland whites; North Carolina whites; North Carolina blacks; Mississippi blacks), educational level (less than high school; high school, General Educational Development Test [GED], or vocational school; college, graduate or professional school) body mass index (BMI [calculated as weight in kilograms divided by height in meters squared] <25, 25 to <30, or ≥30), diabetes mellitus, alcohol consumption (never; former; current), smoking status (never; former; current), APOE ε4 genotype (0, 1, or 2 alleles), history of stroke, time as a linear spline with knot at 6 years, age by time spline terms, square of age by time spline terms, gender by time spline terms, center by time spline terms, education by time spline terms, BMI by time spline terms, diabetes mellitus by time spline terms, smoking status by time spline terms, APOE ε4 genotype by time spline terms, BP category by time spline terms, and BP category by race/center interactions. Boldface data represent $p<0.05$.

[c] Adjusted for age, square of age, gender, center (whites, North Carolina; Minnesota; Maryland, blacks, North Carolina; Mississippi), education (<high school; high school, GED or vocational school; college, graduate or professional school) body mass index (<25 kg/m^2, 25–<30 kg/m^2, ≥30 kg/m^2) diabetes mellitus, alcohol consumption (never; former; current), smoking status (never; former; current), APOE ε4 genotype (0, 1, or 2 alleles), history of stroke, time as a linear spline with knot at 6 years, age by time spline terms, square of age by time spline terms, gender by time spline terms, center by time spline terms, education by time spline terms, BMI by time spline terms, diabetes mellitus by time spline terms, smoking status by time spline terms, APOE ε4 genotype by time spline terms, and BP category by time spline terms.

Table 3

Additional adjusted 20-year cognitive change for the association of visit 2 (1990–1992) with recommended treatment category by JNC 8 criteria

	Cognitive Change (95% CI)	
	HTN Treatment Not Indicated[a]	**HTN Treatment Indicated[b]**
All Participants[c]		
	(n=8,165)	(n=5,311)
Global *z* score	0 (reference)	**−0.044 (−0.085, −0.003)**
DWRT *z* score	0 (reference)	−0.008 (−0.074, 0.058)
DSST *z* score	0 (reference)	**−0.064 (−0.093, −0.035)**
WFT *z* score	0 (reference)	**−0.042 (−0.079, −0.005)**
DWRT raw score, No. of words	0 (reference)	−0.012 (−0.112, 0.088)
DSST raw score, No. of symbols	0 (reference)	**−0.909 (−1.319, −0.498)**
WFT raw score, No. of words	0 (reference)	**−0.520 (−0.982, −0.058)**
Whites[d]		
	6,755	3,492
Global *z* score	0 (reference)	**−0.056 (−0.102, −0.009)**
DWRT *z* score	0 (reference)	−0.033 (−0.109, 0.043)
DSST *z* score	0 (reference)	**−0.074 (−0.108, −0.041)**
WFT *z* score	0 (reference)	**−0.049 (−0.092, −0.006)**
DWRT raw score, No. of words	0 (reference)	−0.050 (−0.165, 0.066)
DSST raw score, No. of symbols	0 (reference)	**−1.052 (−1.529, −0.575)**
WFT raw score, No. of words	0 (reference)	**−0.616 (−1.155, −0.077)**
African Americans[d]		
	1,410	1,819
Global *z* score	0 (reference)	−0.001 (−0.083, 0.081)
DWRT *z* score	0 (reference)	0.075 (−0.055, 0.205)
DSST *z* score	0 (reference)	−0.031 (−0.087, 0.025)
WFT *z* score	0 (reference)	−0.017 (−0.089, 0.054)

	Cognitive Change (95% CI)	
	HTN Treatment Not Indicated[a]	**HTN Treatment Indicated[b]**
DWRT raw score, No. of words	0 (reference)	0.114 (−0.083, 0.311)
DSST raw score, No. of symbols	0 (reference)	−0.441 (−1.238, 0.357)
WFT raw score, No. of words	0 (reference)	−0.218 (−1.108, 0.6734)

Abbreviations: ARIC, Atherosclerosis Risk in Communities; DWRT, delayed word recall test; DSST, digit symbol substitution test; WFT, word fluency test; JNC-8, Eighth Joint National Committee.

[a]Treatment was not indicated for the following categories: (1) 60 years or older, systolic BP (SBP) of less than 150 mm Hg and diastolic BP (DBP) of less than 90, and no antihypertensive use; (2) younger than 60 years, SBP of less than 140 mm Hg and DBP of less than 90 mm Hg, and no antihypertensive use; (3) diabetes mellitus at visit 2, SBP of less than 140 mm Hg and DBP of less than 90 mm Hg, and no antihypertensive use; and (4) chronic kidney disease (CKD) at visit 2 (defined as estimated glomerular filtration rate of <60 mL/min/1.73 m^2), SBP of less than 140 mm Hg and DBP of less than 90 mm Hg, and not taking antihypertensive medications.

[b]Treatment was indicated for the following categories: (1) 60 years or older and SBP of at least 150 mm HG or DBP of at least 90 mm Hg; (2) younger than 60 years and SBP of at least 140 mm Hg or DBP of at least 90 mm Hg; (3) antihypertensive use; (4) diabetes mellitus at visit 2 and SBP of at least 140 mm Hg or DBP of at least 90 mm Hg; and (5) CKD at visit 2 and SBP of at least 140 mm Hg or DBP of at least 90 mm Hg.

[c]Adjusted for age, square of age, gender, race/center (Minnesota whites; Maryland whites; North Carolina whites; North Carolina blacks; Mississippi blacks), educational level (<high school; high school, General Educational Development Test [GED], or vocational school; college, graduate or professional school) body mass index (BMI [calculated as weight in kilograms divided by height in meters squared] <25 k, 25 to<30, or ≥30), diabetes mellitus, alcohol consumption (never; former; current), smoking status (never; former; current), APOE ε4 genotype (0, 1, or 2 alleles), history of stroke, time as a linear spline with knot at 6 years, age by time spline terms, square of age by time spline terms, gender by time spline terms, center by time spline terms, education by time spline terms, BMI by time spline terms, diabetes mellitus by time spline terms, smoking status by time spline terms, APOE ε4 genotype by time spline terms, BP category by time spline terms, and BP category by race/center interactions. Boldface data represent p<0.05.

[d]Adjusted for age, square of age, gender, center (whites, North Carolina; Minnesota; Maryland, blacks, North Carolina; Mississippi), educational level (<high school; high school, General Educational Development Test [GED], or vocational school; college, graduate or professional school), BMI, diabetes mellitus, alcohol consumption (never; former; current), smoking status (never; former; current), APOE ε4 genotype (0, 1, or 2 alleles), history of stroke, time as a linear spline with knot at 6 years, age by time spline terms, square of age by time spline terms, gender by time spline terms, center by time spline terms, education by time spline terms, BMI by time spline terms, diabetes mellitus by time spline terms, smoking status by time spline terms, APOE ε4 genotype by time spline terms, and BP category by time spline terms. Boldface data represent p<0.05.