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The relationship of hypertension in the elderly to AD, vascular dementia, and cognitive function

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Abstract—Background: Hypertension at the age of 45 to 50 years may predispose to AD later in life. It is not known whether hypertension after age 65 years also contributes to AD risk, and its effect on cognitive function is also not fully understood. **Methods:** Data were analyzed from 1,259 Medicare recipients free of dementia in a longitudinal study covering a 7-year period (1991 to 1998). The effect of hypertension was first examined in relationship to the risk for incident AD and then to incident vascular dementia (VaD) using Cox proportional hazards models. Changes in performance over time on tasks of memory, language, and visuospatial/cognitive function were compared in those with and without hypertension using generalized estimating equations. **Results:** Of the 1,259 subjects, 731 (58.1%) had a history of hypertension associated with diabetes, stroke, and heart disease. A history of hypertension was not associated with an increased risk for AD (rate ratio [RR] 0.9, 95% CI 0.7 to 1.3) but was associated with an increased risk for VaD (1.8 [1.0 to 3.2]). Hypertension was not associated with changes in memory, language, and general cognitive function in normal individuals over time. Compared with individuals with neither hypertension nor heart disease, those with hypertension or heart disease alone had no increase in risk for VaD. However, when both were present, there was a threefold increase in risk for VaD. A sixfold increase in risk was observed when both hypertension and diabetes were present. **Conclusions:** Hypertension after age 65 years is not associated with AD and does not adversely affect memory, language, or general cognitive function. A history of hypertension may be an antecedent to VaD, particularly in the presence of heart disease or diabetes.

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Hypertension has been associated with the later development of AD and vascular dementia (VaD),^{1–6} though this is disputed.⁷ Hypertension is thought to act over years by decreasing the elasticity of vessels,

increasing resistance, and reducing responsiveness to momentary changes in tissue demands.^{3,8,9} Atherosclerosis is one of the mechanisms that give rise to increased vascular wall tension. Atherosclerosis, mea-

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sured directly by carotid ultrasound, may be related to peripheral blood pressure and has been associated with both AD and VaD.¹⁰ Because hypertension is frequent in the elderly, we hypothesized that it might also be a risk factor for AD or VaD.

Methods. *Study population.* Data were derived from participants in the Washington Heights–Inwood Columbia Aging Project identified from a random sample of healthy Medicare beneficiaries 65 years or older residing in northern Manhattan between 1991 and 1996. The sampling procedures have been described elsewhere.¹¹ Participants underwent an in-person, structured interview of health and function at the time of study entry, followed by a standard medical history, physical and neurologic examination, and neuropsychological battery. Participants were followed at approximately 18-month intervals, repeating the evaluations used at baseline at each follow-up. Only individuals who completed at least one follow-up were included in the analyses.

Of the 2,126 individuals who underwent baseline assessment, 327 (15.4%) were demented and excluded from the subsequent analysis. Data were not available for 540 (25.4%) of the cohort: 142 (6.7%) died before follow-up, 396 (18.9%) either refused further involvement with the study or moved out of the area, and 2 (0.09%) had missing hypertension history data. These 540 individuals were similar to the study sample in sex, education, distribution of *APOE* genotype, and frequency of a history of stroke, hypertension, and smoking. Those who remained in the study were younger: 75.7 vs 77.0 years old ($p < 0.001$). There were also more Hispanics than whites or African Americans remaining in the study. Those who remained were less likely to have diabetes (13.3% vs 20.2%; $p = 0.0005$) or heart disease (21.8% vs 26.0%; $p = 0.05$). The remaining sample included 1,259 (59.2%) that were available for longitudinal analysis. The Columbia University Institutional Review Board reviewed and approved this project. All individuals provided written informed consent.

Clinical assessments. Physicians completed standardized medical and neurologic histories and examinations, and subjects underwent a standardized neuropsychological test battery testing multiple domains in either Spanish or English. Orientation was evaluated using parts of the modified Mini-Mental State Examination.¹² Language was assessed using the Boston Naming Test,¹³ the Controlled Word Association test,¹⁴ category naming, and the Complex Ideational Material and Phrase Repetition subtests of the Boston Diagnostic Aphasia Evaluation.¹⁵ Abstract reasoning was tested using the Abstract Reasoning and Similarities subtests from the Wechsler Adult Intelligence Scale–Revised (WAIS-R),¹⁶ the nonverbal Identities and Oddities subtest of the Mattis Dementia Rating Scale,¹⁷ the Rosen Drawing Test,¹⁸ and a matching version of the Benton Visual Retention Test.¹⁹ Memory was evaluated using the multiple-choice version of the Benton Visual Retention Test¹⁹ and seven subtests of the Selective Reminding Test²⁰: total recall, long-term recall, long-term storage, continuous long-term storage, words recalled on last trial, delayed recall, and delayed recognition. This neuropsychological battery had been validated in the same geographic area.^{21,22}

Results of these examinations were reviewed by a group

of physicians and neuropsychologists who reached consensus regarding the presence or absence of dementia using published criteria for probable and possible AD²³ and VaD.²⁴ Severity of AD was rated using the Clinical Dementia Rating Scale (CDR).²⁵ Only those individuals with CDR scores of ≥ 1.0 were considered as cases for the initial analyses. Individuals who had CDR ratings of ≤ 0.5 remained in the comparison group.

Brain imaging was available in 85% of cases with a history of stroke; in the remainder, stroke was defined by World Health Organization criteria.²⁶ Subjects without dementia at baseline, but with stroke, were included in the analyses.

Ethnic group. At baseline, ethnic group was documented by self-report using the format of the 1990 US Census.²⁷ Individuals were first asked to indicate their racial group and then whether or not they were of “Hispanic origin.”

Hypertension. At baseline, all participants were asked whether or not they had a history of hypertension (high blood pressure) at any time during their life. If affirmative, they were asked whether or not they were under treatment and the specific type of treatment. Blood pressure was also recorded at each visit using the Dinamap Pro 100 (Critikon Co., Tampa, FL). The blood pressure cuff was placed on the right arm while the individual was seated, and a recording was obtained every 3 minutes over 9 minutes. The third measurement was recorded in the database. Values above 140 mm Hg (systolic) and 90 mm Hg (diastolic) were used as criteria for hypertension.²⁸ For analytic purposes, we reclassified measured blood pressure using the guidelines suggested in the Sixth Report of the National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.²⁹

Other medical information. At the baseline interview, all participants received a standardized interview concerning a history of medical illnesses (e.g., diabetes, cancer) at any time during their lives. If affirmative, they were asked about the type of treatment received.

APOE genotype. Genotypes were obtained by amplification of genomic DNA with PCR subjected to *CfoI* restriction analysis using *APOE* primers and conditions similar to those described by Hixson and Vernier³⁰ and modified by Maestre et al.³¹

Data analysis. Continuous variables were compared using analysis of variance, and categorical variables were compared using χ^2 tests. Cox regression models were used with the exposure being a history of hypertension and the outcome either AD or VaD. Patients who met criteria for possible AD with a history of stroke were classified as possible AD for the analyses regarding AD and as VaD for the studies regarding that outcome. Baseline information was used for all covariates including age, education, and a history of diabetes or heart disease. Heart disease was defined as a history of myocardial infarction, congestive heart failure, or angina. For these regression analyses, we set $\alpha = 0.05$ and $\beta = 0.20$. With a fixed sample size of 1,259, the exposure of hypertension and the confounders of diabetes and heart disease, the lowest detectable risk ratio (RR) for AD was 1.68 and for VaD 2.5. To assess for effect modification by other vascular diseases, dummy variables were created and used in Cox regression models.

A factor analysis was performed using data from the

Table 1 Baseline characteristics of individuals who did and did not develop dementia

Demographic characteristics	Incident AD	Incident vascular dementia	Remained free of dementia
n	157	56	1,043
Age (SD), y	79.3 (6.7)	77.9 (6.2)	75.0 (5.6)
Education (SD), y	7.1 (4.5)	8.2 (4.4)	8.9 (4.6)
Sex			
Women, n = 868, n (%)	108 (12.4)	41 (4.7)	721 (83.1)
Men, n = 391, n (%)	49 (12.5)	15 (3.8)	322 (82.4)
Ethnic group			
African American, n = 408, n (%)	62 (15.2)	22 (5.4)	328 (80.4)
Hispanic, n = 560, n (%)	71 (12.7)	25 (4.5)	458 (81.8)
White, n = 282, n (%)	23 (8.2)	9 (3.2)	249 (88.3)
Other, n = 9, n (%)	1 (11.1)	0	8 (88.9)
APOE-ε4 genotype, %	32.9	31.9	27.1
Heart disease, %	29.9	35.7*	28.4
Diabetes, %	21.7	41.4*	18.9
Hypertension, %	54.5	69.9	57.9
Stroke, %	10.3	100	8.1
Never smoked, %	56.4	55.3	50.1
Past smoker, %	25.6	31.9	34.6
Current smoker, %	18.0	12.6	15.3

Nineteen patients with other dementia are not shown. There is overlap in the vascular dementia category as 16 patients met criteria for possible AD and vascular dementia. Their data are included in both columns and analyses.

* $p < 0.05$.

entire cohort with the 15 neuropsychological measures using a principal component analysis with varimax rotation and Kaiser normalization.³² This analysis yielded three factors: 1) a memory factor, where the seven subtests of the Selective Reminding Test were the main contributors; 2) a visuospatial/cognitive factor, in which visuospatial and tests of reasoning were the main contributors; and 3) a language factor, where language measures from the Boston Naming Test,¹³ Controlled Oral Word Association test,¹⁴ and the WAIS-R Similarities¹⁶ were the main contributors. Component scores for each participant at each visit were calculated by adding the scores of the measures that contributed most to each factor. Each factor score was normally distributed (skewness: memory 0.8, language -0.6, visuospatial/cognitive 0.7).

Generalized estimation equations (GEE)³³ were used to examine changes in each neuropsychological domain over time. The dependent variables were the factor scores, and

the independent variables were baseline history of hypertension and time, included as a continuous variable. The GEE analyses yield β values that represent the strength of the associations between factor scores and variables included in the model. A significant group effect indicates a difference between two groups at the baseline or at any subsequent interval. A positive value for β indicates that the group with a specific variable performed better than the group without that variable. A significant time effect indicates a change in a factor score over the total duration of follow-up. A significant interaction effect indicates a difference in the rate of change in a factor score depending on the presence of the covariate.

Results. Of the initial 1,259 participants, 731 (58.1%) reported a history of hypertension at baseline. Compared with individuals without hypertension, those with hypertension were more likely to report a history of heart dis-

Table 2 Proportional hazards model to assess risk for AD or vascular dementia (VaD) by history of hypertension

Hypertension	Total at risk	Developed AD, n (%)	AD, RR (95% CI)	Developed VaD, n (%)	VaD, RR (95% CI)
Present	731	84 (11.5)	0.9 (0.7–1.3)	39 (5.3)	1.8 (1.0–3.2)*
Absent	528	73 (13.8)	1.0 (reference)	17 (3.2)	1.0 (reference)

Unadjusted risk ratio (RR) and 95% CI are shown. When AD model was repeated adjusting for age, education, ethnic group, and history of heart disease, the RR decreased to 0.8 (95% CI, 0.6–1.1). Similarly, the RR decreased to 1.6 (0.9–2.9) for the VaD model when it was adjusted for these factors. The RR did not change when stratified by treatment.

* $p = 0.05$.

Table 3 Risk for AD or vascular dementia (VaD) by direct measurement of blood pressure

Blood pressure values	mm Hg	Total at risk	Developed AD		Developed VaD		Developed AD or VaD	
			n (%)	RR (95% CI)	n (%)	RR (95% CI)	n (%)	RR (95% CI)
SBP								
Normal	<130	171	27 (15.8)	1.0 (reference)	6 (3.5)	1.0 (reference)	30 (17.5)	1.0 (reference)
High-normal	130–139	245	27 (11.0)	0.8 (0.5–1.3)	10 (4.1)	1.3 (0.5–3.5)	34 (13.9)	0.9 (0.5–1.4)
Stage 1	140–159	440	50 (11.4)	0.8 (0.5–1.2)	21 (4.8)	1.4 (0.5–3.4)	63 (14.3)	0.9 (0.6–1.3)
Stage 2	160–179	220	29 (13.2)	0.8 (0.5–1.3)	6 (2.7)	0.8 (0.2–2.3)	33 (15.0)	0.8 (0.5–1.3)
Stage 3	≥180	133	18 (13.5)	0.8 (0.4–1.4)	9 (6.8)	1.7 (0.6–4.8)	23 (17.3)	0.9 (0.5–1.5)
DBP								
Normal	<85	906	113 (12.5)	1.0 (reference)	35 (3.9)	1.0 (reference)	134 (14.8)	1.0 (reference)
High-normal	85–89	116	19 (16.4)	1.1 (0.7–1.8)	3 (2.6)	0.6 (0.2–2.0)	21 (18.1)	1.1 (0.7–1.7)
Stage 1	90–99	115	11 (9.6)	0.7 (0.4–1.4)	8 (7.0)	1.8 (0.8–4.0)	15 (13.0)	0.9 (0.5–1.5)
Stage 2	100–109	41	2 (4.9)	0.3 (0.1–1.4)	1 (2.4)	0.6 (0.1–4.6)	3 (7.3)	0.4 (0.1–1.4)
Stage 3	≥110	30	6 (20.0)	1.8 (0.8–4.0)	5 (16.7)	4.6 (1.8–11.9)*	10 (33.3)	2.5 (1.3–4.7)†

Direct measurement of blood pressure was classified by the Sixth Report of the National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.²⁹

* $p = 0.001$.

† $p = 0.006$.

RR = rate ratio; SBP = systolic blood pressure; DBP = diastolic blood pressure.

ease (13.5% vs 27.8%; $p < 0.0001$), diabetes (15% vs 23.9%; $p < 0.0001$), or stroke (7.3% vs 12.8%; $p < 0.006$). Those without hypertension more frequently were smokers than those with hypertension (19.1% vs 12.8%; $p < 0.01$).

A history of hypertension was validated by direct measurement of blood pressure. The average systolic blood pressure for those without a history of hypertension was 143 mm Hg and diastolic 73 mm Hg, whereas those with a history of hypertension, either treated or untreated, had average blood pressures of 154 mm Hg systolic and 78 mm Hg diastolic. With use of the criteria for hypertension,²⁸ the sensitivity and specificity were 76 and 48% for systolic hypertension and 85 and 35% for diastolic hypertension. The values for sensitivity and specificity did not differ for those with and without AD.

Over the 7 years of follow-up, AD developed in 157 (12.5%) of the 1,259 participants. The proportion of males and females who developed AD was similar, but AD was more frequent in African Americans than Hispanics or whites. Compared with those who remained free of dementia, those who developed AD had fewer years of education. At baseline, neither a history of hypertension, diabetes, heart disease, or stroke nor the presence of the *APOE*- $\epsilon 4$ genotype differentiated who would develop AD with CDR of >1 (table 1).

VaD developed in 56 (4.4%) of the 1,259 study participants during the 7 years of follow-up. The proportion of males and females who developed VaD was similar, as were the proportion of whites, African Americans, and Hispanics, though the numbers in each group were small. Compared with those who remained free of dementia, those with a baseline history of heart disease or diabetes were more likely to develop VaD. Neither age nor the presence of the *APOE*- $\epsilon 4$ genotype nor prior smoking history differentiated who would develop VaD (see table 1).

A history of hypertension was not associated with an

increased risk for AD (table 2). The incidence rate of AD without a history of hypertension was 2.9%/person-year, and with a history of hypertension it was 3.1%/person-year. Adjustment for age, education, heart disease, and ethnic group had no effect on the relationship. No additive or synergistic effects were found between hypertension and other vascular risk factors and the relationship to AD risk. Treatment of hypertension did not affect risk estimates for AD (no treatment: RR 0.96, 95% CI 0.6 to 1.5; treated: 0.86, 0.6 to 1.2).

The incidence of VaD among those without a history of hypertension was 4.2%/person-year, but with a history of hypertension, it increased to 8.6%. Compared with those without hypertension, the relative risk for VaD among persons with a history of hypertension was nearly twofold higher (see table 2). Adjustments for age, education, sex, ethnicity, *APOE*- $\epsilon 4$ status, and history of heart disease or smoking diminished this relationship (see table 2). Treatment of hypertension again did not affect risk estimates for VaD (no treatment: RR 1.7, 95% CI 0.8 to 3.6; treated: 1.7, 0.9 to 3.2). We repeated this analysis, excluding patients with AD and stroke classified as VaD, and the RR increased (RR 2.1, 95% CI 1.0 to 4.6, $p = 0.05$). Adjustment for confounders, diabetes, and heart disease again decreased the association (RR 1.8, 95% CI 0.8 to 3.9). Diabetes was strongly associated with VaD (RR 2.7, 95% CI 1.3 to 5.6, $p = 0.007$) in the model.

The sensitivity and specificity for a history of hypertension were 76 and 48% (systolic hypertension) and 85 and 35% (diastolic hypertension). We analyzed the association between hypertension and dementia in two ways. Using the classification of high blood pressure suggested by the Sixth Report of the National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure,²⁹ we examined the baseline systolic and diastolic blood pressure measurements. There was no relationship

Table 4 Independent effects of history of hypertension and two vascular risk factors (heart disease and diabetes) on risk for AD

History at baseline			At risk, n (%)	Developed AD, n (%)	OR (95% CI)
Hypertension	Heart disease	Diabetes			
No	No		370 (88)	53 (12)	1.0 (reference)
Yes	No		403 (91)	38 (9)	0.9 (0.6–1.4)
No	Yes		85 (83)	17 (17)	1.0 (0.6–1.8)
Yes	Yes		242 (84)	46 (16)	1.3 (0.9–2.0)
No		No	386 (87)	60 (13)	1.0 (reference)
Yes		No	495 (89)	60 (11)	1.0 (0.7–1.5)
No		Yes	69 (87)	10 (13)	1.3 (0.7–2.6)
Yes		Yes	150 (86)	24 (14)	1.6 (1.0–2.6)*

* Significant at $p < 0.05$.

between any stage of high blood pressure and either AD or VaD, with a single exception. A relationship between measured diastolic blood pressure values of ≥ 110 mm Hg and incident VaD was found (RR 4.6, 95% CI 1.8 to 11.9, $p = 0.001$) (table 3). However, there were only 30 individuals who had diastolic blood pressure values of ≥ 110 mm Hg, and only 5 of these developed VaD. Because many individuals reported both hypertension and other vascular diseases, we also investigated the independent and joint effects of hypertension and other vascular-related disorders on either AD or VaD (tables 4 and 5). Compared with individuals without hypertension or other vascular disorders, there was no increased risk for either AD or VaD among those with hypertension, heart disease, or diabetes. However, when hypertension and heart disease were reported together, the risk for VaD was greatly increased (RR 3.3, 95% CI 1.7 to 6.6, $p = 0.0007$). The joint effects of diabetes and hypertension on VaD risk were also greatly increased (RR 6.2, 95% CI 2.9 to 13.5, $p < 0.0001$). There was only a weak joint effect of hypertension and diabetes on AD risk.

GEE analysis in those without dementia revealed that the presence or absence of hypertension did not influence memory, language, or cognition performance over the follow-up period. The differences in slope were 0.19 (–3.2 to 3.6; $p = 0.46$) for memory, 0.10 (–0.14 to 0.35; $p = 0.41$)

for language, and 0.45 (–0.88 to 1.8; $p = 0.51$) for general cognition.

Discussion. This prospective study of 1,259 participants over 7 years found no association between a history of hypertension and the development of AD. When hypertension was classified using measured blood pressure, no evidence of association with AD existed. Moreover, hypertension did not affect memory, language, or general cognitive function over time.

Though there was an association between hypertension and VaD, it was weak and may have been confounded by other variables. A significant relationship was found only when the diastolic blood pressure exceeded 110 mm Hg, which occurred in only a small number of individuals. Although it is possible that this finding was the result of a type 1 error from multiple comparisons, the association reached significance even after Bonferroni correction for 12 subcategories of high blood pressure ($p = 0.004$). The RR for the other categories of measured diastolic and systolic blood pressures were not consistent. Nonetheless, a weak association between elevated diastolic blood pressure and VaD could not be excluded.

When analyzed independently and jointly, an in-

Table 5 Independent effects of history of hypertension and two vascular risk factors (heart disease and diabetes) on risk for vascular dementia (VaD)

History at baseline			At risk, n (%)	Developed VaD, n (%)	OR (95% CI)
Hypertension	Heart disease	Diabetes			
No	No		409 (97)	14 (3)	1.0 (reference)
Yes	No		430 (98)	11 (2)	1.1 (0.5–2.4)
No	Yes		99 (97)	3 (3)	0.8 (0.2–2.8)
Yes	Yes		260 (90)	28 (10)	3.3 (1.7–6.6)*
No		No	434 (97)	12 (3)	1.0 (reference)
Yes		No	534 (96)	21 (4)	1.9 (0.9–4.0)
No		Yes	74 (94)	5 (6)	3.2 (1.1–9.2)*
Yes		Yes	156 (90)	18 (10)	6.2 (2.9–13.5)*

* Significant at $p < 0.05$.

teraction between hypertension and heart disease on VaD risk was found. Concurrent diabetes and hypertension appeared to have additive effects on VaD risk. Because heart disease, diabetes, and hypertension are common ailments in the elderly, the joint effects on the risk for VaD in the elderly need to be further investigated. However, in the absence of heart disease and diabetes, the relationship between VaD and hypertension remains tenuous.

The evidence favoring an association between hypertension and dementia, including AD and VaD, has been most compelling for hypertension during middle age.^{2,34-37} Perhaps this is when other vascular-related diseases are developing and the combined effects of these changes in the vasculature are becoming evident. Complications of hypertension, such as stroke, may trigger the onset of AD,³⁸ though our results do not suggest the existence of an interaction between hypertension and stroke on AD risk. Treatment of hypertension may decrease AD risk in men,² and the strength of the relationship between dementia and hypertension may vary with the severity of hypertension during middle age.⁴ Not all studies have verified a relationship between hypertension and AD.⁷

Skoog et al.⁶ found an association between hypertension at age 70 years and dementia 10 to 15 years later in a smaller cohort of 382, where <10% of the people became demented. Two hypertension treatment trials failed to reduce the incidence of cognitive decline,³⁹⁻⁴¹ though differential dropout⁴² or the choice of drug may have contributed to the outcome.⁴³ The Canadian Study of Health and Aging⁴⁴ examined 105 patients who developed VaD over 5 years and found that hypertension was a significant risk factor only for females, but not males. Thus, it is possible that with longer follow-up of our cohort, a more definitive result would have emerged with regard to the association between hypertension and VaD. However, an earlier study⁴⁵ using data from this same cohort showed that only diabetes was associated with the development of VaD and that there was no association between traditional vascular risk factors and AD, thereby eliminating the possibility of confounding by these variables. Our finding of synergistic or additive effects on the risk for VaD between hypertension and either heart disease or diabetes has not been previously described.

A study of experimental hypertension in nonhuman primates revealed an association between cognitive and behavioral abnormalities and extravasation from vessels with impaired blood-brain barrier function.⁴⁶ Although this might also be true in humans, the effects are acute. Further research needs to be done to clarify the relationship between each of the vascular risk factors and cerebral vessel dysfunction, especially because these effects may take time to develop.

We found no relationship between hypertension and changes in memory, language, or general cognitive function over follow-up of cognitively normal

participants. Prior studies have used less detailed assessments of neuropsychological function^{3,5,47-49} or were cross-sectional in nature.^{47,49,50} Our use of GEE to evaluate longitudinal data provides the ability to measure the slope of performance as an indicator of change in each cognitive domain over the study period. There were no differences in the slopes for memory, language, and visuospatial/general cognition function in those with, compared with those without, hypertension.

A history of hypertension at age 65 years, treated or untreated, does not contribute to the development of AD and does not predispose to a decline in cognition, even without the development of dementia as people age. The association between hypertension and VaD is weak and may be related to concurrent vascular-related disorders so prevalent among the elderly.

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