Published in final edited form as:

Am J Geriatr Psychiatry. 2012 February ; 20(2): 179–187. doi:10.1097/JGP.0b013e31820ee833.

Hypertension is Associated With Cognitive Decline in Elderly People at High Risk for Dementia

Michael Wysocki, B.S., Xiaodong Luo, Ph.D., James Schmeidler, Ph.D., Karen Dahlman, Ph.D., Gerson T. Lesser, M.D., Hillel Grossman, M.D., Vahram Haroutunian, Ph.D., and Michal Schnaider Beer, Ph.D.

Departments of Psychiatry (MW, XL, JS, KD, HG, VH, MSB) and Geriatrics and Adult Development (GTL), Mount Sinai School of Medicine; Jewish Home & Hospital (GTL); and JJ Peters Veterans Affairs Medical Center, Bronx (HG, VH), New York

Abstract

Cardiovascular risk factors including hypertension (HTN) have been shown to increase the risk of Alzheimer disease. The current study investigated whether individuals with HTN are more susceptible to increased cognitive decline and whether the influence of HTN on cognitive decline varied as a function of dementia severity. A total of 224 nursing home and assisted living residents, with a mean age of 84.9 (± 7.6) years, were assessed longitudinally with Mini Mental State Exams (MMSE) and Clinical Dementia Ratings (CDR). Baseline dementia status was defined by the CDR score. As described in Table 2, MMSE scores in persons with HTN and questionable dementia (CDR = 0.5) declined significantly faster than nonhypertensive questionably demented persons. Hypertensive participants did not decline significantly faster than nonhypertensive participants in persons with intact cognition (CDR = 0) or frank dementia (CDR ≥ 1). These results suggest an increased risk of subsequent cognitive decline in hypertensive individuals who are especially vulnerable to developing dementia and raises the possibility that avoiding or controlling HTN might reduce the rate of cognitive decline in cognitively vulnerable individuals, potentially delaying their conversion to full-fledged dementia.

Keywords

Alzheimer disease; cardiovascular risk factors; cognitive impairment; dementia; elderly people; hypertension; mild cognitive impairment

OBJECTIVES

Cardiovascular (CV) disease and dementia are disorders common in the geriatric population.

¹ Although the link between CV risk factors and vascular dementia has been observed for some time,^{2–4} links between CV risk factors and cognitive impairment due to nonvascular causes, including Alzheimer disease (AD) have also been noted.^{5–8}

Hypertension (HTN) is a CV disease risk factor that affects 65% of the population age 65 and older⁹ and nonvascular dementia (e.g., AD) affects nearly 5 million people in the United States.¹⁰ A possible relationship between HTN and cognitive impairment has been the focus of increased attention in recent years because lifestyle factors associated with HTN (such as alcohol, tobacco, and sodium consumption, as well as obesity and amount of exercise) are

potentially modifiable. Reducing these lifestyle risk factors, in conjunction with early detection and pharmacological treatment of HTN, may reduce the risk or severity of cognitive impairment and rate of decline.

Although the amount of research examining the relationship between HTN and cognitive function has increased recently, findings have been inconsistent.¹¹ Several studies have found that a diagnosis of HTN is predictive of late life cognitive impairment.^{12–15} Importantly, this association is not limited to midlife HTN,^{12,13} because late life HTN^{12,14,15} has also been associated with dementia. Individuals with increased diastolic blood pressure (BP) at age 70 were significantly more likely to develop AD by age 75. Some findings suggest that associations between HTN and dementia are more subtle, possibly more complex or less direct than originally theorized.^{16,17} These results may have been affected by factors such as small sample size, reliance on an inadequate number of concurrent BP measures, and relatively young age of the studied samples. The latter factor is especially germane in light of the possibility of an age-dependent association between BP and cognitive function; that is, these relationships are stronger in older samples.^{18–20}

The majority of these studies have examined the association of HTN with prevalent or incident dementia or the presence of cognitive impairment in the context of vascular dementia. Because HTN is unlikely to be a primary cause of nonvascular dementia, its effects are likely to be important, but more subtle, influencing parameters such as rate of cognitive decline, severity of cognitive compromise, and/or specific domains of cognitive function. Fewer studies have looked at the association between HTN and the rate of cognitive decline²¹ in individuals in different stages of dementia. The current study investigated whether individuals with HTN were more susceptible to accelerated cognitive decline than nonhypertensive individuals and whether the influence of HTN on cognitive decline varied as a function of dementia severity.

METHODS

Participants

The sample consisted of 224 residents of the Jewish Home and Hospital (JHH), Bronx and Manhattan divisions, both skilled nursing facilities, and Kittay House, an assisted living facility affiliated with the JHH. Residents of these nursing homes and assisted living facilities comprised persons who are unable to live independently for a variety of reasons including financial (inability to afford home health care), physical (e.g., hip fracture leading to reduced mobility), frailty due to medical illness (e.g., arthritis), or cognitive compromise. Residents of such institutions constitute a growing proportion of the elderly people---about 40% of Americans older than 85 years.²² Exclusion criteria included persons in need of acute medical or psychiatric care and those with a diagnosis of cerebrovascular disease or cerebrovascular accident. The Mount Sinai School of Medicine(MSSM) and the Clinical and Biologic Studies of Early AD research program have been academically affiliated with the JHH for more than 20 years. Each participant received complete medical care by JHH and Mount Sinai staff. As part of this affiliation, each new long-term resident admitted to the Jewish Home was administered a Mini Mental State Exam (MMSE) and assessed for further voluntary participation in clinical, biological, and longitudinal studies of cognition. Participants were included if their baseline MMSE score was between 10 and 30, and there had been at least one follow-up MMSE and assessment. Medical records were available for review of HTN status, along with complete data on age, sex, race, and education. Participants with histories of cerebrovascular disease or cerebrovascular accident were excluded. The total number of annual assessments among the 224 participants was 929 (mean assessments per participant = 4.15; SD: 2.21; range: 2–12). Participants with baseline MMSE score below 10 were excluded to minimize floor effects. Follow-up assessments

after a participant reached a score of 0 in the MMSE were also excluded. All assessments were approved by the institutional review boards of MSSM and JHH.

ASSESSMENT PROCEDURES

Mini Mental State Exam

Each participant was serially assessed at approximately annual intervals with a Mini Mental State Exam (MMSE). The MMSE is a commonly used 30-point scale for assessing cognitive function in the areas of orientation, registration, attention and calculation, recall, language, and praxis.²³ MMSE administration was performed according to existing standards.²¹ The spelling of the word “world” backwards was used exclusively for the “Attention and Calculation” domain, as opposed to the alternative serial 7s.

Clinical Dementia Rating

The Clinical Dementia Rating (CDR) scale was administered to each participant at the time of the baseline MMSE, and then concurrently with subsequent annual MMSE administrations. The CDR is an established instrument for assessment of cognitive function and performance on a 5-point scale in both clinical and research settings in the following six domains: Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care.²⁴ A score for each domain is established through semistructured interviews with the participant, as well as a separate informant interview with an individual familiar with the participant (usually a family member, nurse, or certified nursing assistant). The overall score is derived by an algorithm based primarily on the Memory domain score, and secondarily on the scores of the remaining 5 domains. Scores range from 0 (nondemented), 0.5 (questionable dementia), 1 (mild dementia), 2 (moderate dementia), to 3 (severe dementia). The use of nursing staff (nurses and certified nursing assistants) for information regarding a participant’s cognitive status or change in status provides a reliable gauge of that participant’s current status, but it is less useful for assessing change from a more distant state, especially the participant’s state prior to facility admission. However, family and friends are used as additional informants whenever possible. Furthermore, although we do not have firm supporting documentation, our experience suggests that in this population, when misclassification errors occur, they are likely in the direction of classifying persons with compromised “native abilities” as cognitively impaired, that is, assigning a CDR of 0.5 when the true CDR score is 0. There is, however, the possibility that participants with some minimal amount of impairment are infrequently categorized as CDR 0 instead of CDR 0.5 because the loss is subtle enough to escape detection at the time of testing or the informant is not familiar enough with the participant to detect questionable impairment. These limitations are minimized through the comprehensive review of each participant’s medical record by a study physician. For the purposes of the present analysis, participants were stratified by dementia severity, that is, nondemented (CDR = 0), questionably demented (CDR = 0.5), and demented (CDR ≥ 1), and the MMSE (not the CDR), was the dependent variable. The term “Questionably Demented” was used to describe the CDR = 0.5 group instead of “Mild Cognitive Impairment” as this was the original CDR category title,²¹ and the cognitive grouping was defined solely by the participants’ CDR scores.

HYPERTENSION STATUS

Comprehensive medical records since the time of facility admission were available for each participant. HTN status was obtained through the review of each participant’s medical record by a geriatrician or licensed nurse with a geriatric specialization. A participant was considered hypertensive if he or she was admitted to the facility with an existing diagnosis

of HTN, or a diagnosis was made upon, or after, admission. The HTN diagnostic criteria used was the American Heart Association definition of systolic BP of 140 mm Hg or higher and/or a diastolic pressure of 90 mm Hg or higher.²⁵ Because the diagnostic criteria for HTN have changed over the years, elderly participants who had been diagnosed in midlife would have been diagnosed by different, less conservative criteria than the current AHA definition. Therefore, preadmission diagnoses may have been based on criteria that were in effect as standard of care at the time of diagnosis. Information on preadmission HTN onset and treatment was not consistently available.

If a participant did not have an existing diagnosis of HTN at the time of initial cognitive assessment but received this diagnosis during the period of study, it was uncertain whether the onset of HTN was recent, or whether an earlier diagnosis had not been reported. In this case, only cognitive assessments following the HTN diagnosis were considered for analysis. All other participants had no diagnosis of HTN and no record of measured BP that met the HTN criteria cited earlier at any preadmission or postadmission time and were considered nonhypertensive. By this definition, no participant's HTN status changed during the study.

DATA ANALYSIS

Advanced age, female, nonwhite, and lower education have been shown to be associated with increased dementia risk.^{26–28} Therefore age, sex, race (Caucasian versus non-Caucasian), and years of education (continuous for descriptive purposes and trichotomized to <8, 8–12, and >12 for the mixed regression models described later) were used as covariates due to their known associations with cognitive performance and impairment.

Table 1 presents descriptive statistics for the study sample. For the primary analyses, the 224 subjects were stratified into 3 groups according to their baseline CDR scores: nondemented (CDR = 0, N = 55), questionably demented (CDR = 0.5, N = 63), and demented (CDR ≥ 1, N = 106).

Linear mixed models were used to examine the raw MMSE scores over time for CDR observations equal to the baseline CDR group for each subject. These models are especially suited to the current study design because the number of follow-up occasions varied from 1 to 11 and the mean of the number of follow-up assessments was 3.15 (SD: 2.21).

The linear mixed models used the MMSE scores (at baseline and at successive follow-up time points) as dependent variables. The HTN status at baseline, the follow-up time from baseline, and the interaction between the follow-up time and HTN status were entered as independent variables. The analysis controlled for age at baseline, sex, race, and education. All the linear mixed model analyses included a random intercept and random decline, to represent each subject's estimated baseline value and rate of decline from the baseline through the follow-up period. SAS GLIMMIX (SAS Institute, Inc., Cary, NC) was used to fit the linear mixed models.

For the primary analyses, a separate linear mixed model was fitted for each of the CDR groups. Observations were included in an analysis until a later CDR score differed from the baseline CDR score. In the event that a different CDR score was obtained in the middle of a consecutive string of similar scores (e.g., a sequence of five CDR observations, for which the first two and last two fell into the same CDR group as the baseline, but the middle CDR score differed), all MMSE values in the string were included in the analysis. The consistency of the consecutive string of similar observations was sufficient to disregard the apparent exception in the middle. Because the main goal was to compare the rates of cognitive decline of participants with and without HTN separately within each CDR

category, MMSE scores recorded after a participant changed from one CDR category to a new CDR category were disregarded.

RESULTS

Of the 224 participants (Table 1), 134 had a diagnosis of HTN (59.82%; mean age = 84.35 [SD: ± 7.8], mean years of education = 11.34 [SD: ± 3.4]), and 90 were nonhypertensive (mean age = 85.71 [SD: ± 7.26], mean years of education = 11.96 [SD: ± 3.7]). The mean age of the entire sample was 84.89 (SD: ± 7.6) at baseline, and the age range was 60.89–104.52. Mean education level was 11.59 years (SD: ± 3.5). The sample was stratified by CDR score at baseline and further subdivided into groups by HTN status at baseline. The six groups did not differ significantly in age, level of education, or race, but they did differ in gender ($\chi^2 = 11.36$, $df = 5$, $p = 0.045$) after applying the Scheffe post-hoc procedure²⁹ for multiple comparisons to the χ^2 test. The nondemented nonhypertensive group had nominally fewer female participants than the other groups, but this comparison was not significant.

In the CDR = 0 group, there were no differences in MMSE at baseline, or difference in rate of change in MMSE over time, in participants with or without HTN (Table 1). MMSE did not significantly change over time in this group ($p = 0.11$). In the CDR = 0.5 group, participants with HTN scored 3.9 points higher on MMSE at baseline ($p = 0.001$) but had a greater rate of decline in MMSE over time compared to the nonhypertensives (hypertensives had an MMSE decrease of 0.78 per year, compared to an increase of 0.76 per year in the nonhypertensives, $p = 0.006$). In the CDR ≥ 1 group, there was no difference in MMSE at baseline between hypertensive and nonhypertensives; the MMSE declined by 2.04 points per year ($p < 0.001$) with no evidence for a different rate of change in hypertensives compared to nonhypertensives ($p = 0.83$).

HTN has been associated with dementia in a relatively consistent manner, but, to the best of our knowledge, no study examined whether this relationship is driven by specific periods during the dementia course. We hypothesized that in each of the three dementia periods examined in this study, hypertensive subjects will decline faster than nonhypertensive subjects. Table 2 presents the primary results of this study and includes the coefficients of the linear mixed model covariates (age, sex, education, race, time, HTN, and HTN/time interaction) for the primary linear mixed model analyses for the three CDR groups. In the CDR = 0 group, none of the covariates was significant. In the CDR = 0.5 group, participants with HTN had higher MMSE scores at baseline. However, there was an interaction of HTN with time, with a significantly steeper MMSE decline in participants with HTN (Table 2). In the CDR ≥ 1 group, only decline in MMSE over time was significant (Table 2).

CONCLUSIONS

For HTN participants with questionable dementia, the rate of cognitive decline was significantly more rapid relative to nonhypertensive participants, averaging 0.7824 points per year versus -0.7552 in non-HTN persons with questionable dementia. HTN status was not associated with rate of cognitive decline for participants with no dementia at initial baseline assessment, nor for participants with mild to severe dementia at baseline. These findings suggest that HTN is associated with increased rate of cognitive decline specifically in vulnerable individuals at the earliest stages of dementia, but once the cognitive decline process has been triggered, additional contributions to cognitive decline by HTN diminish. These results are consistent with the existing literature showing positive associations between BP values and risk of dementia.^{11–17} The present results emphasize the imminent increased risk of cognitively vulnerable individuals who are also hypertensive. In studies

that found no associations between HTN and cognitive decline, dementia stage was not taken into account and might be one reason for their negative results.

For cognitively intact individuals, it is possible that the MMSE is not sufficiently sensitive to detect subtle neuropsychological effects of CV risks such as HTN, as suggested by the very low variation among participants' slopes. In contrast, both the CDR = 0.5 and CDR > 1 groups had substantial variation among participants' slopes, permitting detection of an HTN interaction if present. Because an interaction of HTN with MMSE change over time was not found for the CDR > 1 group despite its considerable variation, this suggests a window of cognitive vulnerability to HTN. Another possible explanation for the lack of HTN effects or variation in the CDR = 0 group is that in cognitively intact individuals, there is sufficient cognitive reserve³⁰ to compensate fully for the potentially deleterious effects of HTN such that no evidence of cognitive change could be observed. However, the education level of the current sample did not vary significantly across the CDR groups, and measures of premorbid intelligence/IQ were not commonly available. Conversely, in individuals with frank but even moderate dementia, the brain might be sufficiently compromised by neuropathology for any additive cognitive effects of HTN to be overshadowed or to be relatively inconsequential.³¹ The reduction of cerebral blood flow via any one of the events noted earlier could result in cognitive impairment, but hypertensive individuals who are already cognitively vulnerable might suffer exacerbation of cognitive deficits when these conditions are compounded.

While the mechanism(s) affecting the association of cognitive decline rate and HTN remains unknown, several potential explanations have been presented.

Midlife HTN has been associated with greater burden of neuritic plaques and neurofibrillary tangles at autopsy.³² This suggests the possibility of direct links between HTN and processes leading to AD pathology. The relationship between HTN and AD neuropathology may additionally be modified by the presence or absence of hypertensive treatment, as one study suggested that less AD neuropathology was found in treated hypertensives compared to nonhypertensives.³³

Compromised cerebral perfusion has been suggested as a possible factor.³⁴ Hypertensive geriatric participants' evidence reduced cerebral blood flow in prefrontal, anterior cingulate, and occipital areas. These findings suggest that the chronic suboptimal blood flow associated with HTN could result in late life cognitive impairment.^{35,36} If this is the case, any effect of antihypertensive pharmacologic treatment upon cognitive preservation may depend on how soon HTN is detected after onset and how closely an individual modifies his or her risk factors and follows a prescribed antihypertensive treatment regimen. This possibility is consistent with recent findings suggesting that the pharmacologic treatment of HTN is significantly associated with lessened severity of the hallmark neuropathological lesions of AD,³³ and findings that indicate increased AD neuropathology in persons with autopsy confirmed coronary artery disease.³⁷ Other possible mechanisms affecting cognition through cerebral hypoperfusion include impairment of blood--brain permeability in chronic HTN.³⁶ This has been shown to be associated with increased hippocampal and cortical amyloid β peptide and oligomer levels that have been implicated in neurotoxicity and involvement in AD memory loss.³⁸ Observations of impaired endothelium,³⁹ as well as impaired glucose metabolism and protein synthesis as a result of HTN, have been also proposed as potential mechanisms for the association of HTN with dementia.³⁴ HTN is also a significant risk factor for silent brain infarcts and white matter lesions.⁴⁰ This, in turn, could have contributed to the decline in MMSE score observed in the study. Because MRI data was not readily available for the current sample, this possibility was not explored. However, stroke was an exclusion criteria for the study, diminishing the potential confounding effect of cerebrovascular disease on the results.

The sizable number of follow-up assessments in the current study offers a more comprehensive longitudinal view of the study participants' cognitive states over time relative to existing studies with larger samples, but shorter periods of follow-up assessment. Although the establishment of HTN status in the current study allowed for a reliable gauge of HTN status at the time of study, our study was limited in that age of HTN onset was unavailable due to the lack of, or judged unreliability of, midlife medical histories. Also, records of BP measures and antihypertensive pharmacologic treatment information prior to study enrollment, both of which may modulate the association between HTN and cognitive decline, were not available for all participants. The question of exactly how well HTN is controlled is of potential interest, but addressing the influence of the degree of this control on cognitive function requires appreciably larger sample sizes than those available and should include an untreated hypertensive group not available in an observational study environment. If inaccuracies in the measurement of HTN do exist, we believe they would tend to be of underdiagnosis rather than overdiagnosis. If this is the case, and underdiagnosed HTN patients were included in the HTN group, the results would have been even stronger.

The apparent increase in MMSE scores over time in the questionably demented, nonhypertensive group (Figure 2) might reflect the heterogeneity of the group. It is not unusual for some subjects in this "questionable" group to be in the early stages of decline, which will lead to dementia, whereas others might have some mild cognitive impairment (MCI), but be stable or fluctuate slightly over time.

A number of studies have suggested an association between midlife HTN and late life dementia;^{11,12} other studies have demonstrated that both systolic and diastolic BP values decline in older individuals with dementia.^{15,18} Thus, the longitudinal association between midlife and late life HTN and the longitudinal course of cognitive function and decline is often difficult to assess. It is possible that this relationship may not be linear and could be influenced by additional lifestyle factors, such as smoking history, diabetes, level of activity/exercise, etc. There is also the possibility that the relationship between HTN and cognitive decline is noncausal, and that one of these additional lifestyle factors is influencing both. Comprehensive data spanning from the time of initial diagnosis of midlife HTN, including antihypertensive pharmacologic treatment regimens, through late life onset of dementia, is not commonly available, and this question was not addressed. Antihypertensive pharmacologic treatment status was also not addressed because detailed medical histories prior to study enrollment were not available for all participants. Participants of the present study are residents of academically guided skilled nursing and assisted living facilities. Current medication regimens are closely monitored (and virtually all individuals with HTN diagnoses receive HTN medication), and therefore results are less likely to be affected by a participant's impaired cognitive abilities interfering with maintaining an antihypertensive medication regimen. There is a need to be cautious when generalizing to the noninstitutionalized population, but according to the U.S. Department of Health and Human Services 2005 65+ report, 43% (older than 85 years) of the elderly people live in NH or AL facilities.²² Thus, these data are directly relevant to this growing population.

Although the present study does not address time of onset of HTN or its treatment, it does suggest that a lifetime diagnosis of HTN is likely to influence the course of cognitive decline once the process of cognitive compromise has been initiated.

These results demonstrate an increased risk of subsequent cognitive decline in hypertensive individuals who are especially vulnerable to developing dementia. This raises the possibility that avoiding or controlling HTN may reduce the rate of cognitive decline in cognitively vulnerable individuals, thus delaying their conversion to full-fledged dementia. While early

HTN detection and treatment are essential to minimize the direct CV risks, the present findings emphasize an additional incentive, cognitive preservation, for early HTN detection and consistent, effective long-term treatment.

Acknowledgments

This study was supported by NIA grant AG02219, Berkman Charitable Trust, and Dextra Baldwin McGonagle Foundation.

References

1. Messerli FH, Williams B, Ritz E. Essential hypertension. *Lancet*. 2007; 370(9587):591–603. [PubMed: 17707755]
2. Elias MF, Wolf PA, D'Agostino RB, et al. Untreated blood pressure level is inversely related to cognitive functioning: the Framingham Study. *Am J Epidemiol*. 1993; 138(6):353–364. [PubMed: 8213741]
3. Hachinski V. Preventable senility: a call for action against the vascular dementias. *Lancet*. 1992; 340(8820):645–648. [PubMed: 1355217]
4. Farmer ME, Kittner SJ, Abbott RD, et al. Longitudinally measured blood pressure, antihypertensive medication use, and cognitive performance: the Framingham Study. *J Clin Epidemiol*. 1990; 43(5):475–480. [PubMed: 2324788]
5. Reitz C, Tang MX, Manly J, et al. Hypertension and the risk of mild cognitive impairment. *Arch Neurol*. 2007; 64(12):1734–1740. [PubMed: 18071036]
6. Honig LS, Kukull W, Mayeux R. Atherosclerosis and AD: analysis of data from the US National Alzheimer's Coordinating Center. *Neurology*. 2005; 64(3):494–500. [PubMed: 15699381]
7. Maalikjy AN, Borroni B, Agosti C, et al. Volume cerebral blood flow reduction in pre-clinical stage of Alzheimer disease: evidence from an ultrasonographic study. *J Neurol*. 2005; 252(5):559–563. [PubMed: 15726249]
8. Kalaria RN. Vascular factors in Alzheimer's disease. *Int Psychogeriatr*. 2003; 15(suppl 1):47–52. [PubMed: 16191216]
9. Bergmann C, Sano M. Cardiac risk factors and potential treatments in Alzheimer's disease. *Neurol Res*. 2006; 28(6):595–604. [PubMed: 16945210]
10. Alzheimer's Association. Basics of Alzheimer's Disease. Alzheimer's Association; Jan 7. 2005
11. Anson O, Paran E. Hypertension and cognitive functioning among the elderly: an overview. *Am J Ther*. 2005; 12(4):359–365. [PubMed: 16041200]
12. Launer LJ, Ross GW, Petrovitch H, et al. Midlife blood pressure and dementia: the Honolulu-Asia aging study. *Neurobiol Aging*. 2000; 21(1):49–55. [PubMed: 10794848]
13. Kilander L, Nyman H, Boberg M, et al. Hypertension is related to cognitive impairment: a 20-year follow-up of 999 men. *Hypertension*. 1998; 31(3):780–786. [PubMed: 9495261]
14. Tzourio C, Dufouil C, Ducimetiere P, et al. Cognitive decline in individuals with high blood pressure: a longitudinal study in the elderly. EVA Study Group. *Epidemiology of Vascular Aging. Neurology*. 1999; 53(9):1948–1952. [PubMed: 10599763]
15. Cacciatore F, Abete P, Ferrara N, et al. The role of blood pressure in cognitive impairment in an elderly population. Osservatorio Geriatrico Campano Group. *J Hypertens*. 1997; 15(2):135–142. [PubMed: 9469788]
16. Glynn RJ, Beckett LA, Hebert LE, et al. Current and remote blood pressure and cognitive decline. *Jama-J Am Med Assoc*. 1999; 281(5):438–445.
17. Madden D, Langley L, Thurston R, et al. Interaction of blood pressure and adult age in memory search and visual search performance. *Aging, Neuropsychol Cogn*. 2003; 10(4):241–254.
18. Li G, Rhew IC, Shofer JB, et al. Age-varying association between blood pressure and risk of dementia in those aged 65 and older: a community-based prospective cohort study. *J Am Geriatr Soc*. 2007; 55(8):1161–1167. [PubMed: 17661953]
19. Qiu CX, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurol*. 2005; 4(8):487–499. [PubMed: 16033691]

20. Guo Z, Qiu C, Viitanen M, et al. Blood pressure and dementia in persons 75+ years old: 3-year follow-up results from the Kungsholmen Project. *J Alzheimers Dis.* 2001; 3(6):585–591. [PubMed: 12214025]
21. Bellew KM, Pigeon JG, Stang PE, et al. Hypertension and the rate of cognitive decline in patients with dementia of the Alzheimer type. *Alzheimer Dis Assoc Disord.* 2004; 18(4):208–213.
22. He, W.; Sengupta, M.; Velkoff, VA., et al. 65+ in the United States: current population reports, special studies. Department of Health Services and Department of Commerce; 2005. p. 23–209.
23. Folstein M, Folstein S, McHugh P. “Mini-Mental State”: a practical method for grading the cognitive state of patients for the clinician. *J Psychiat Res.* 1975; 12(3):189–198. [PubMed: 1202204]
24. Morris JC. The clinical dementia rating (CDR): current version and scoring rules. *Neurology.* 1993; 43:2412–2414. [PubMed: 8232972]
25. Appel LJ, Brands MW, Daniels SR, et al. Dietary approaches to prevent and treat hypertension: a scientific statement from the American Heart Association. *Hypertension.* 2006; 47(2):296–308. [PubMed: 16434724]
26. Jones RN, Gallo JJ. Education bias in the mini-mental state examination. *Int Psychogeriatr.* 2001; 13(3):299–310. [PubMed: 11768377]
27. Dufouil C, Alperovitch A, Tzourio C. Influence of education on the relationship between white matter lesions and cognition. *Neurology.* 2003; 60(5):831–836. [PubMed: 12629242]
28. McDougall GJ Jr, Vaughan PW, Acee TW, et al. Memory performance and mild cognitive impairment in Black and White community elders. *Ethn Dis.* 2007; 17(2):381–388. [PubMed: 17682374]
29. Fleiss, JL. Statistical methods for rates and proportions. 3. Wiley-Interscience; 2003.
30. Stern Y. Cognitive reserve and Alzheimer disease. *Alzheimer Dis Assoc Disord.* 2006; 20(3 suppl 2):S69–S74. [PubMed: 16917199]
31. Morris JC, Storandt M, Miller JP, et al. Mild cognitive impairment represents early-stage Alzheimer disease. *Arch Neurol.* 2001; 58(3):397–405. [PubMed: 11255443]
32. Petrovitch H, White LR, Izmirlian G, et al. Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: the HAAS. *Neurobiology of Aging.* 2000; 21:57–62. [PubMed: 10794849]
33. Hoffman LB, Schmeidler J, Lesser G, et al. Less Alzheimer disease neuropathology in medicated hypertensive than nonhypertensive persons. *Neurology.* 2009; 72 (20):1720–1726. [PubMed: 19228583]
34. Ruitenberg A, den Heijer T, Bakker SL, et al. Cerebral hypoperfusion and clinical onset of dementia: the Rotterdam Study. *Ann Neurol.* 2005; 57(6):789–794. [PubMed: 15929050]
35. Beason-Held LL, Moghekar A, Zonderman AB, et al. Longitudinal changes in cerebral blood flow in the older hypertensive brain. *Stroke.* 2007; 38(6):1766–1773. [PubMed: 17510458]
36. de la Torre JC. Critically attained threshold of cerebral hypoperfusion: the CATCH hypothesis of Alzheimer’s pathogenesis. *Neurobiol Aging.* 2000; 21(2):331–342. [PubMed: 10867218]
37. Beeri MS, Rapp M, Silverman JM, et al. Coronary artery disease is associated with Alzheimer’s disease neuropathology in APOE 4 carriers. *Neurology.* 2006; 66(9):1399–1404. [PubMed: 16682673]
38. Gentile MT, Poulet R, Di Pardo A, et al. Beta-amyloid deposition in brain is enhanced in mouse models of arterial hypertension. *Neurobiol Aging.* 2009; 30(2):222–228. [PubMed: 17673335]
39. Dede DS, Yavuz B, Yavuz BB, et al. Assessment of endothelial function in Alzheimer’s disease: is Alzheimer’s disease a vascular disease? *J Am Geriatr Soc.* 2007; 55(10):1613–1617. [PubMed: 17711428]
40. Sachdev P, Chen X, Wen W. White matter hyperintensities in mid-adult life. *Curr Opin Psychiatry.* 2008; 21:268–274. [PubMed: 18382226]

FIGURE 1.
Estimated MMSE score over time in nondemented group (CDR 0)

FIGURE 2.
Estimated MMSE score over time in questionably demented group (CDR = 0.5)

FIGURE 3.
Estimated MMSE score over time in demented group (CDR ≥ 1.0)

Table 1

Demographic characteristics of participants stratified by baseline CDR score and

	CDR Score at Baseline									
	0		.5		≥1		Total by HTN Status		Total	
HTN Status	+	−	+	−	+	−	+	−		
N	33	22	33	30	68	38	134	90	224	
Mean Age	80.3 (±9.4)	82.2 (±8.1)	84.4 (±7.0)	87.3 (±6.2)	86.3 (±6.6)	86.5 (±7.1)	84.3 (±7.8)	85.7 (±7.26)	84.9 (±7.6)	
% Female	75.8	54.5	75.8	76.7	88.2	76.3	82.1	71.1	77.7	
Mean Education	12.2 (±2.8)	12.6 (±4.02)	10.5 (±3.7)	11.6 (±3.5)	11.4 (±3.5)	11.9 (3.7)	11.3 (3.4)	12.0 (±3.7)	11.6 (±3.5)	
% Caucasian	84.8	81.8	75.8	83.3	63.2	78.9	71.6	81.1	75.4	
Mean MMSE Score	27.4 (±2.3)	26.9 (±2.4)	24.2 (±2.9)	23.1 (±2.9)	17.9 (±3.6)	17.7 (3.5)	21.8 (±5.2)	21.7 (±4.8)	21.8 (5.0)	

Table 2

Parameter Estimates of Linear Mixed Models by CDR groups*

	CDR = 0 (DF = 99)			CDR = 0.5 (DF = 38)			CDR ≥ 1 (DF = 183)		
	p	Co-efficient	SE	p	Co-efficient	SE	p	Co-efficient	SE
Age	.7091	-.01	.025	.2294	.07	.057	.7381	-.028	.083
Sex**	.2847	-.52	.487	.8229	.18	.816	.9869	-.024	1.446
Educ: < 8 yrs**	.3251	-.75	.787	.0056	-2.89	.985	.3045	1.67	1.620
Educ: 8-12 yrs	.1238	.76	.492	.0210	-2.10	.871	.0504	2.43	1.236
Race**	.4055	.49	.585	.3761	-0.89	-0.890	.1693	1.807	1.309
HTN Status**	.7590	-.154	.498	.0010	3.90	1.090	.3826	-1.085	1.239
Time	.3155	-.11	.109	.0069	.76	.264	<.0001	-2.040	.240
HTN/Time Interaction	.0985	.24	.142	.0058	-1.54	.526	.8343	-.068	.323

* p based on Z test of coefficient/standard error

** Reference groups are as follows: Sex: Male, Education greater than 12 years, Race: White, HTN Status: No HTN