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Midlife Hypertension Risk and Cognition in the Non-Demented Oldest Old: Framingham Heart Study

Arvind Nishtala[a], **Jayandra J. Himali**[a], **Alexa Beiser**[a,b], **Joanne M. Murabito**[c], **Sudha Seshadri**[a], **Philip A. Wolf**[a], and **Rhoda Au**[a,*]

[a]Framingham Heart Study, Department of Neurology, Boston University School of Medicine, Boston, MA, USA

[b]Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA

[c]Framingham Heart Study, Department of Medicine, Section of General Internal Medicine, Boston University School of Medicine, Boston, MA, USA

Abstract

Midlife cardiovascular risk, hypertension (HTN) in particular, has been related cross-sectionally to poorer neuropsychological (NP) performance in middle age and older adults. This study investigated whether a similar relationship persists between midlife HTN or systolic blood pressure (SBP) and NP performance approximately 30 years later. 378 Framingham stroke and dementia-free Original cohort participants, with HTN and SBP ascertained between 50–60 years of age (mean age 55 ± 1, 65% women), were administered a NP assessment at age ≥80 years. Tests included Logical Memory, Visual Reproduction, Paired Associate, Hooper Visual Organization Test, Trail Making A & B, Digit Span Forward and Backward, Controlled Word Association Test (COWAT), and Similarities. Multivariable linear regression, adjusted for age, time interval between risk factor and NP testing, gender, and premorbid intelligence, assessed association between midlife HTN/SBP and NP outcomes. Midlife HTN was not significantly associated with NP outcome measures. Midlife SBP was associated with poorer Digit Span Forward and COWAT performance ($p < 0.05$). No significant interaction of age on HTN/SBP to NP associations was found. There was a significant interaction between ApoE4 status and SBP in their effects on COWAT ($p_{interaction} = 0.074$); SBP was negatively associated with COWAT only in those with the ApoE4 allele ($p = 0.025$). While midlife HTN is not associated with late life cognitive impairment, midlife SBP is related to late life attention and verbal fluency impairments, particularly among ApoE4+ individuals. These results offer insight into processes that are operative in the absence of overt cognitive impairment and dementia.

Keywords

Apolipoprotein E4; blood pressure; cognition; executive function; hypertension; memory; neuropsychological assessment

*Correspondence to: Rhoda Au, PhD, Department of Neurology, 72 East Concord Street, Boston University School of Medicine, Boston, MA 02118, USA. Tel.: +1 617 638 5450; Fax: +1 617 638 8086; rhodaau@bu.edu.

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INTRODUCTION

Life expectancy is on the rise and the oldest old (≥80 years old) [1, 2] is the fastest growing demographic in the world [3]. Several studies have demonstrated that high cardiovascular risk at midlife, particularly hypertension (HTN), is linked to subsequent increased risk of dementia [4–8]. However, there is a dearth of studies examining the impact of accumulated midlife cardiovascular risk on early cognitive impairment in non-demented individuals in the later decades.

The relation of blood pressure with cognitive function and dementia has, in recent years, received much attention from epidemiological research. Nine studies, five of which only studied men, found a significant association between midlife HTN, specifically high systolic blood pressure (SBP), and cognitive impairment 20–30 years later [9–15], with two of these studies reporting that this association exists with high diastolic blood pressure [16, 17]. The Framingham Heart Study extended these results to include longitudinal change in cognition, reporting that midlife HTN was related to worsening executive function nearly a decade later [18]. Across all these studies' of midlife risk, however, definition of later-life was limited to young-old subjects with the oldest participants being in their late 70s.

For studies focused on the very elderly, most studies rely on cross-sectional data [19–21] and less sensitive measures of global cognition [20–22]. Studies that looked at the relationship between blood pressure and cognitive performance in the very elderly found that a lower SBP was associated with greater cognitive dysfunction both cross-sectionally and longitudinally, while higher blood pressure was associated with better cognitive performance [20–22], however, these studies relied on HTN measures acquired at old age and a single composite cognitive score. There was also evidence of associations between HTN, stroke, and cognitive impairment in those 90 years and older [19].

The apolipoprotein ε4 (ApoE4) allele is a known genetic risk factor for cognitive impairment and Alzheimer's disease, and a synergism between the ApoE4 allele and cerebrovascular risk factors has been reported [23–26], although this finding has been disputed in the elderly [27]. An ApoE4 interaction has most consistently been found with SBP with results suggesting that high midlife SBP has a stronger adverse effect on cognitive function in genetically susceptible individuals [23, 24]. Once again, this relationship has not been explored in the oldest old.

To our knowledge, there is no documentation of the impact of midlife blood pressure on cognitive function in the non-demented oldest old, nor whether any potentially significant relationship is consistent across oldest old age stratified groups. This study, therefore, proposes to explore the relationship between midlife cardiovascular risk and cognition 25+ years later in a community-based cohort of the non-demented oldest old from the Framingham Heart Study and investigate how ApoE4 modifies this relationship.

METHODS

Study sample

The Framingham Heart Study began prospective examination of the community-based Original cohort in 1948. The Original study cohort consisted of 5,209 participants aged 28 through 62 years residing in Framingham, Massachusetts, USA, between 1948 and 1953, who were examined biennially for cardiovascular risk factors and cardiovascular endpoints. Since 1999, all surviving members of the Original cohort have been invited to participate in a larger study of brain imaging and cognition. The present study sample was derived from participants who underwent a neuropsychological (NP) assessment between 1999 and 2009 and were of a minimum age of 80 years old. Participants with documented clinical stroke, clinical dementia, or other neurological disorders (n = 159) were excluded resulting in a final sample size of 378. The study was in accordance with the Helsinki Declaration of 1975. The Boston University Institutional Review Board approved the study protocol and all participants provided written informed consent.

Cardiovascular risk and covariate assessment

Midlife SBP and HTN status were measured when each participant was 55 ± 5 years of age. SBP was recorded as an average of two physician recorded measurements using a mercury column sphygmomanometer with a cuff of appropriate width. HTN was defined as a SBP greater than or equal to 140 mm Hg or a diastolic blood pressure greater than or equal to 90 mmHg or being under treatment for HTN.

Neuropsychological measures

A NP test battery has been administered since 1999 for participants 80 years and older, and the first administration of these exams for each participant was selected as the NP test of interest so as to eliminate practice effects. The test battery is administered using standardized testing protocols and scoring procedures, details of which have been described previously [28]. It is comprised of tests measuring performance across major cognitive domains, including verbal and visual memory, learning, attention and executive function (EF), visuospatial perception and organization, confrontation naming, and abstract reasoning [28]. The Wide Range Achievement Test (WRAT)-III Reading score was used as a measure of baseline intelligence and education attainment since it has been demonstrated to offset socioeconomic status and gender factors that impact years of education [29].

One measure of EF was obtained by subtracting the Trail-making Test A (TMA) completion time from the Trail-making Test B (TMB) completion time (TMB-TMA) to control for the potential confound of attention and psychomotor speed. Higher scores represent better performance on all tests with the exception of the TMA and TMB-TMA tests, where a lower score is deemed to be better.

Statistical analysis

The TMA, TMB-TMA, Hooper Visual Organization Test (HVOT) test scores and the WRAT-III reading score were natural log-transformed to normalize their skewed

distributions. We standardized the NP outcome measures to a mean of 0 and standard deviation of 1 to facilitate comparisons across these measures.

Our primary analysis consisted of assessing the association of cardiovascular risk factors (midlife SBP and Stage I HTN status) with NP measures: Logical Memory Delayed Recall, Visual Reproductions Delayed Recall, Paired Associates Learning – Delayed Recall, Digit Span Forward (DSF), Digit Span Backward, TMA, TMB-TMA, HVOT, Controlled Word Association Test (COWAT), and Similarities. We used multivariable linear regression to separately relate midlife SBP and HTN to continuous measures of NP assessment. All analyses related to midlife HTN were adjusted for age, time from cardiovascular risk assessment to first NP exam, gender, natural logarithm of WRAT, and HTN status at NP exam. Analyses with midlife SBP were adjusted for age, time from cardiovascular risk assessment to first NP exam, gender, natural log of WRAT, and SBP at NP exam. The rationale for adjusting for HTN and SBP measures at the NP assessment is to effectively observe the effect of HTN and SBP at midlife above and beyond that of recent HTN and SBP status.

Secondary analyses were performed using interaction terms to assess effect modification of relations by ApoE4 status and age.

Significance was set at $p < 0.05$ for all models and $p < 0.10$ for analyses assessing effect modification. All data were analyzed using SAS version 9.3 (SAS Institute Inc., Cary, NC).

RESULTS

Study sample characteristics

Table 1 shows the descriptive characteristics of the 378 participants included in the analysis from the Framingham original cohort, classified by HTN status. The mean age at midlife was 55 ± 1 years while the mean age at the time of NP assessment is 86 ± 4 years, a mean time of 31 ± 4 years between midlife cardiovascular risk assessment and NP testing. The median WRAT score of 48 is reported because the distribution of the WRAT score is skewed in this sample.

The Original cohort is 65% female, with 42% of the cohort carrying a high school degree but only 15% having completed a college-level education. Nearly 30% of the sample endorsed a diagnosis of HTN at midlife cardiovascular risk assessment. There was no significant difference between participants with HTN and those without HTN in the descriptive characteristics mentioned above.

Additionally, Table 1 displays the prevalence of cardiovascular risk factors, classified by HTN status, at midlife, and their prevalence in late life at the time of NP assessment. The prevalence of atrial fibrillation, diabetes mellitus, and prevalent CVD was too low at midlife (0–4%) for these risk factors to be considered in the analysis. 75 participants, or 20% of the sample, were carriers of the ApoE4 allele. The prevalence of HTN rose from 28% in midlife to 70% in late life.

Table 2 lists the tests administered, the cognitive domains measured, and the summary statistics for the whole sample, in addition to the subgroups classified by HTN status. There was no significant difference in the performance of participants with and without HTN.

Table 3 shows the distribution of SBP categorically at midlife and in late life at the exam closes to NP assessment. Of the 126 participants who were not hypertensive at midlife, only 32 remained so in late life. 3 of 16 participants with SBP greater than 160 mmHg at midlife continued to have a severely elevated SBP in late life. Most participants who were hypertensive at midlife remained hypertensive 25 to 30 years later.

Association between midlife risk factor exposure and NP outcome measures

Table 4 shows the association between midlife HTN and SBP and the outcome measures from the NP tests.

There was a statistically significant inverse association between midlife SBP and DSF score. For each one unit increase in midlife SBP, the score on the DSF test decreased by −0.008 standard deviations (SDs) ($p < 0.05$). SBP at midlife was also inversely associated with COWAT ($\beta \pm SE = -0.008 \pm 0.004$, $p < 0.05$) test. There were no significant relationships found between midlife SBP and memory measures. Midlife HTN did not significantly correlate with any NP measures in late life.

Interactions between ApoE4 status or age and midlife risk factor exposure on NP outcome measures

Table 5 shows the interactions between ApoE4 status or age and midlife risk factor exposure on NP outcome measures. There was a significant interaction between midlife HTN and ApoE4 status in their effect on the TMA scores ($p = 0.052$). Stratified analysis by ApoE4 status revealed that increased midlife HTN was associated with worst performance in TMA in those with ApoE4 allele than without, but neither of these reached significance.

We found a significant interaction between midlife SBP and ApoE4 status in their effect on the COWAT ($p = 0.074$), an association of poorer performance on the COWAT was observed among those with presence of ApoE4 allele ($\beta \pm SE$: -0.23 ± 0.01, $p = 0.025$).

No significant effect modification by age on each of the midlife cardiovascular risk factors was observed for associations with any of the NP measures.

DISCUSSION

Our primary analyses revealed that midlife HTN was not significantly associated with impairment in either memory or EF in late life. These results are inconsistent with those studies that looked at HTN longitudinally at midlife [13, 15, 18] and late life [30–32], although a number of these studies used a single composite measure for cognition. A previous Framingham study by Debette et al. [18] found that midlife HTN was associated with a more marked decline in performance on the TMA test, however, the cohort in this study was wholly different, younger, and followed only at midlife. To our knowledge, there is no study that has considered the remote effect of HTN at midlife on cognition in the oldest

old; it does appear that the documented adverse effects of HTN on cognition, particularly EF, do not apply to this older population.

In comparison, midlife SBP is associated with poorer performance on measures of attention and verbal fluency, but does not demonstrate any significant associations with memory. Previous research relating SBP to cognition report mixed findings. Midlife SBP was noted to have a significant inverse association with cognition, but these results were identified in young old subjects [9, 11, 12, 14, 18]. Cross-sectional studies focused on the upper age ranges suggest that high SBP later in life is protective for cognition [9, 33, 34]. The results from this study seem to imply that the adverse effects from the cumulative exposure to an elevated SBP in the middle ages persists into the later years.

Alzheimer's disease genetic risk persists in its mediation of cardiovascular impact on cognition into the oldest decades, which had not been previously found [26]. While significant interactions between ApoE4 status were found between HTN and TMA, a test of attention, the stratified analyses are non-significant making this result unfit for interpretation. However, a significant interaction between ApoE4 was found for the relationship between SBP and COWAT, a test of verbal fluency. Stratified analyses suggest that the relationship was evident or exacerbated for those who were ApoE4+ with consistently poorer performance on these tests. These results point to a possible amplification of susceptibility to cognitive dysfunction in genetically predisposed participants with an elevated SBP at midlife. Similarly, Zade et al. [23] and Peila et al.[24] found that the ApoE4 carriers with high SBP were likely to demonstrate greater cognitive impairment although this was observed in middle age to young-old populations, thereby suggesting that the synergistic effects of ApoE4 and SBP may endure in the old-old.

The relationships between vascular risk factors and cognition are subtle and intricate. ApoE4 has been associated with multiple neuropathologic processes including neuronal dysfunction and degeneration secondary to toxic effects, increased amyloid-β deposition and reduced clearance, activation of proinflammatory pathways compromising cerebrovascular integrity, and inefficient responses to central nervous system stressors such as ischemia or inflammation [35–37]. It could be postulated that the adverse vascular effects of an elevated SBP at midlife lower the threshold for these neuropathologic mechanisms to accelerate ongoing cognitive decline as much as three to four decades later.

The strengths of this study include the community-based setting and the prospective design of cardiovascular risk measures at midlife and cognitive abilities 28 to 35 years later. The midlife exposure may reflect chronicity of high blood pressure and the cumulative impact of years of risk on cognition. These results support the potential clinical postulation that management of cardiovascular risk early on can reduce risk of poorer cognitive outcomes later in life. The study, however, has a number of limitations that require restrained interpretation of findings. The study participants are predominantly white, highly educated, and comparatively healthy with a low prevalence of cardiovascular risk at midlife. In addition, the cognitive measures are cross-sectional, which could lead to over-estimation of the effects. Finally, there is a significant survival bias that needs to be considered as the study includes only those participants of the Framingham Heart Study who have survived to

at least 80 years of age without dementia or other neurologic disorders. Therefore, the association of midlife vascular risk on cognition in this study is that in survivors to the oldest old only, which may not be truly representative. Given the study's limitations and findings that conflict with previous reports, it is important for other studies to confirm that the absence of this relationship is not due to cohort effects specific to the Framingham Heart Study.

Despite these limitations, it is of interest that there were novel relationships between SBP at midlife and measures of attention and verbal fluency, primarily among those who are ApoE4+. These results offer insight into processes that are operative in the absence of mild cognitive impairment and dementia and the impact of years of cumulative risk on cognition. Although more research is needed in the non-demented oldest old, these findings have important implications for managing modifiable risk factors at midlife, altering treatments, focusing health care resources, and advocating for health care policy.

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REFERENCES

1. Katsumata Y, Todoriki H, Higashiuesato Y, Yasura S, Willcox D, Ohya Y, Willcox BJ, Dodge HH. Metabolic syndrome and cognitive decline among the oldest old in Okinawa: In search of a mechanism. The KOCOA Project. J Gerontol A Biol Sci Med Sci. 2012; 67:126–134. [PubMed: 22016359]
2. Lucca U, Garrì M, Recchia A, Logroscino G, Tiraboschi P, Franceschi M, Bertinotti C, Biotti A, Gargantini E, Maragna M, Nobili A, Pasina L, Franchi C, Riva E, Tettamanti M. A Population-based study of dementia in the oldest old: The Monzino 80-plus study. BMC Neurol. 2011; 11:54. [PubMed: 21612585]
3. Kinsella, K.; Wan, H. [Accessed May 24, 2013] An Aging World: 2008. 2009. https://www.census.gov/prod/2009pubs/p95-09-1.pdf. Posted June 2009
4. Launer LJ, Ross GW, Petrovitch H, Masaki K, Foley D, Wright LR, Havlik RJ. Midlife blood pressure and dementia: The Honolulu-Asia aging study. Neurobiol Aging. 2000; 21:49–55. [PubMed: 10794848]
5. Kivipelto M, Helkala EL, Laakso MP, Hallikainen M, Alhainen K, Soininen H, Tuomilehto J, Nissinen A. Midlife vascular risk factors and Alzheimer's disease in later life: Longitudinal, population based study. BMJ. 2001; 322:1447–1451. [PubMed: 11408299]
6. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology. 2005; 64:277–281. [PubMed: 15668425]
7. Wu C, Zhou D, Wen C, Zhang L, Como P, Qiao Y. Relationship between blood pressure and Alzheimer's disease in Linxian County, China. Life Sci. 2003; 72:1125–1133. [PubMed: 12505543]
8. Yamada M, Kasagi F, Sasaki H, Masunari N, Mimori Y, Suzuki G. Association between dementia and midlife risk factors: The Radiation Effects Research Foundation Adult Health Study. J Am Geriatr Soc. 2003; 51:410–414. [PubMed: 12588587]
9. Launer LJ, Masaki K, Petrovitch H, FoleyD,Havlik RJ. The association between midlife blood pressure levels and late-life cognitive function. The Honolulu-Asia Aging Study. JAMA. 1995; 274:1846–1851. [PubMed: 7500533]

10. Kivipelto M, Helkala EL, Laakso MP, Hallikainen M, Alhainen K, Soininen H, Tuomilehto J, Nissinen A. Midlife vascular risk factors and late-life mild cognitive impairment: A population-based study. Neurology. 2001; 56:1683–1689. [PubMed: 11425934]
11. Swan GE, DeCarli C, Miller BL, Reed T, Wolf PA, Jack LM, Carmelli D. Association of midlife blood pressure to late-life cognitive decline and brain morphology. Neurology. 1998; 51:986–993. [PubMed: 9781518]
12. Swan GE, Carmelli D, Larue A. Systolic blood pressure tracking over 25 to 30 years and cognitive performance in older adults. Stroke. 1998; 29:2334–2340. [PubMed: 9804644]
13. Elias MF, Wolf PA, D'Agostino RB, Cobb J, White LR. Untreated blood pressure level is inversely related to cognitive functioning: The Framingham Study. Am J Epidemiol. 1993; 138:353–364. [PubMed: 8213741]
14. Elias PK, Elias MF, Robbins MA, Budge MM. Blood pressure-related cognitive decline: Does age make a difference? Hypertension. 2004; 44:631–636. [PubMed: 15466661]
15. Unverzagt FW, McClure LA, Wadley VG, Jenny NS, Go RC, Cushman M, Kissela BM, Kelley BJ, Kennedy R, Moy CS, Howard V, Howard G. Vascular risk factors and cognitive impairment in a stroke-free cohort. Neurology. 2011; 77:1729–1736. [PubMed: 22067959]
16. Kilander L, Nyman H, Boberg M, Hansson L, Lithell H. Hypertension is related to cognitive impairment: A 20-year follow-up of 999 men. Hypertension. 1998; 31:780–786. [PubMed: 9495261]
17. Kilander L, Nyman H, Boberg M, Lithell H. The association between low diastolic blood pressure in middle age and cognitive function in old age. A population-based study. Age Ageing. 2000; 29:243–248. [PubMed: 10855907]
18. Debette S, Seshadri S, Beiser A, Au R, Himali JJ, Palumbo C, Wolf PA, DeCarli C. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. Neurology. 2011; 77:461–468. [PubMed: 21810696]
19. Peltz CB, Corrada MM, Berlau DJ, Kawas CH. Cognitive impairment in nondemented oldest-old: Prevalence and relationship to cardiovascular risk factors. Alzheimers Dement. 2012; 8:87–94. [PubMed: 22055654]
20. Richmond R, Law J, Kay-Lambkin F. Higher blood pressure associated with higher cognition and functionality among centenarians in Australia. Am J Hypertens. 2011; 24:299–303. [PubMed: 21164496]
21. Szewieczek J, Dulawa J, Gminski J, Kurek A, Legierska K, Francuz T, Wlodarczyk-Sporek I, Janusz-Jenczen M, Hornik B. Better cognitive and physical performance is associated with higher blood pressure in centenarians. J Nutr Health Aging. 2011; 15:618–622. [PubMed: 21968855]
22. Nilsson SE, Read S, Berg S, Johansson B, Melander A, Lindblad U. Low systolic blood pressure is associated with impaired cognitive function in the oldest old: Longitudinal observations in a population-based sample 80 years and older. Aging Clin Exp Res. 2007; 19:41–47. [PubMed: 17332720]
23. Zade D, Beiser A, McGlinchey R, Au R, Seshadri S, Palumbo C, Wolf PA, DeCarli C, Milberg W. Interactive effects of apolipoprotein E type 4 genotype and cerebrovascular risk on neuropsychological performance and structural brain changes. J Stroke Cerebrovasc Dis. 2010; 19:261–268. [PubMed: 20471857]
24. Peila R, White LR, Petrovich H, Masaki K, Ross GW, Havlik RJ, Launer LJ. Joint effect of the APOE gene and midlife systolic blood pressure on late-life cognitive impairment: The Honolulu-Asia aging study. Stroke. 2001; 32:2882–2889. [PubMed: 11739991]
25. Haan MN, Shemanski L, Jagust WJ, Manolio TA, Kuller L. The role of APOE epsilon4 in modulating effects of other risk factors for cognitive decline in elderly persons. JAMA. 1999; 282:40–46. [PubMed: 10404910]
26. Carmelli D, Swan GE, Reed T, Miller B,Wolf PA, Jarvik GP, Schellenberg GD. Midlife cardiovascular risk factors, ApoE, and cognitive decline in elderly male twins. Neurology. 1998; 50:1580–1585. [PubMed: 9633697]
27. Qiu C, Winblad B, Fratiglioni L. Cerebrovascular disease, APOE epsilon4 allele and cognitive decline in a cognitively normal population. Neurol Res. 2006; 28:650–656. [PubMed: 16945218]

28. Au R, Seshadri S, Wolf PA, Elias M, Elias P, Sullivan L, Beiser A, D'Agostino RB. New norms for a new generation: Cognitive performance in the Framingham offspring cohort. Exp Aging Res. 2004; 30:333–358. [PubMed: 15371099]

29. Manly JJ, Jacobs DM, Touradji P, Small SA, Stern Y. Reading level attenuates differences in neuropsychological test performance between African American and White elders. J Int Neuropsychol Soc. 2002; 8:341–348. [PubMed: 11939693]

30. Knopman D, Boland LL, Mosley T, Howard G, Liao D, Szklo M, McGovern P, Folsom AR. Cardiovascular risk factors and cognitive decline in middle-aged adults. Neurology. 2001; 56:42–48. [PubMed: 11148234]

31. Elias MF, Elias PK, Sullivan LM, Wolf PA, D'Agostino RB. Lower cognitive function in the presence of obesity and hypertension: The Framingham heart study. Int J Obes Relat Metab Disord. 2003; 27:260–268. [PubMed: 12587008]

32. Piguet O, Grayson DA, Creasey H, Bennett HP, Brooks WS, Waite LM, Broe GA. Vascular risk factors, cognition and dementia incidence over 6 years in the Sydney Older Persons Study. Neuroepidemiology. 2003; 22:165–171. [PubMed: 12711848]

33. Guo Z, Fratiglioni L, Winblad B, Viitanen M. Blood pressure and performance on the Mini-Mental State Examination in the very old. Cross-sectional and longitudinal data from the Kungsholmen Project. Am J Epidemiol. 1997; 145:1106–1113. [PubMed: 9199540]

34. Kahonen-Vare MB-H. Left ventricular hypertrophy and blood pressure as predictors of cognitive decline in old age. Aging Clin Exp Res. 2004; 16:147–152. [PubMed: 15195990]

35. Zlokovic BV. Cerebrovascular effects of apolipoprotein E: Implications for Alzheimer disease. JAMA Neurol. 2013; 70:440–444. [PubMed: 23400708]

36. Mahley RW, Weisgraber KH, Huang Y. Apolipoprotein E: Structure determines function, from atherosclerosis to Alzheimer's disease to AIDS. J Lipid Res. 2009; 50:S183–S188. [PubMed: 19106071]

37. Kim J, Basak JM, Holtzman DM. The role of apolipoprotein E in Alzheimer's disease. Neuron. 2009; 63:287–303. [PubMed: 19679070]

Table 1

Demographics and risk factor characteristics of sample, classified by HTN status at midlife

	Total Sample (*n* = 378)	Presence of Stage I HTN (*n* = 97)	Absence of Stage I HTN (*n* = 251)
Age at NP Battery, years (Mean ± SD)	86 ± 4	86 ± 4	86 ± 4
Age at CV Risk Assessment, years (Mean ± SD)	55 ± 1	55 ± 0.7	55 ± 0.8
Time between CV Risk Assessment and NP Battery, years (Mean ± SD)	31 ± 4	30.6 ± 4.3	30.5 ± 4.2
Female, *n* (%)	246 (65)	63 (65)	162 (65)
WRAT, Median [Q1, Q3]	48 [43, 51]	46 [42, 50]	48 [43, 51]
Education group, n (%)			
<HS Degree	92 (24)	23 (24)	59 (24)
HS Degree	157 (42)	47 (48)	94 (38)
Some College	71 (19)	17 (18)	53 (21)
College Graduate	57 (15)	10 (10)	44 (17)
Measures at Midlife			
Systolic Blood Pressure, mmHg (Mean ± SD)	127 ± 16	148 ± 12	120 ± 10
ApoE4 Carriers, *n* (%)	75 (20)	14 (15)	55 (22)
Current Smoking, *n* (%)	98 (29)	25 (28)	78 (30)
Diabetes Mellitus, *n* (%)	0	0	0
Atrial Fibrillation, *n* (%)	0	0	0
Hypertension, *n* (%)	97 (28)	97 (100)	251 (0)
Prevalent CVD, *n* (%)	16 (4)	3 (3)	11 (4)
Measures at NP Assessment			
Systolic Blood Pressure, mmHg (Mean ± SD)	136 ± 21		
ApoE4 Carriers, *n* (%)	75 (20)		
Current Smoking, *n* (%)	13 (3)		
Diabetes Mellitus, *n* (%)	50 (13)		
Atrial Fibrillation, *n* (%)	94 (25)		
Hypertension, *n* (%)	265 (70)		
Prevalent CVD, *n* (%)	190 (50)		

HTN, hypertension; NP, neuropsychological; SD, standard deviation; CV, cardiovascular; WRAT-III, Wide Range Achievement Test; HS, high school; ApoE4, apolipoprotein ε4; CVD, cardiovascular disease.

Table 2

Description of the neuropsychological test battery administered to oldest-old participants, classified by HTN status at midlife

Neuropsychological Test	Cognitive Domain	Total Sample (*n* = 378) Raw Scores	Presence of Stage I HTN (*n* = 97) Raw Scores	Absence of Stage I HTN (*n* = 251) Raw Scores
LM-DR, Mean ± SD	Verbal Memory	7.5 ± 3.9	7.8 ± 3.6	7.6 ± 4.0
VR-DR, Mean ± SD	Visual Memory	4.0 ± 3.0	3.8 ± 2.7	4.1 ± 3.1
PA-DR, Mean ± SD	Verbal learning, Immediate & Delayed recall	7.2 ± 1.5	7.2 ± 1.6	7.2 ± 1.5
DSF, Mean ± SD	Attention	6.1 ± 1.2	5.8 ± 1.1	6.2 ± 1.2
DSB, Mean ± SD	EF	4.3 ± 1.1	4.0 ± 1.0	4.3 ± 1.2
TMA, Median [Q1,Q3]	Attention	0.85[0.67, 1.12]	0.85[0.72, 1.18]	0.85[0.63, 1.10]
TMB-TMA, Median [Q1,Q3]	EF	1.67[1.10, 3.21]	1.95[1.15, 3.78]	1.58[1.08, 3.00]
HVOT, Median [Q1,Q3]	Visuospatial organization and EF	19.50[16.0, 22.5]	19.0[15.5, 21.0]	20.0[16.0, 22.5]
COWAT, Mean ± SD	Verbal fluency	31.2 ± 13.5	28.6 ± 12.2	32.6 ± 13.8
SIM, Mean ± SD	Abstract reasoning	13.1 ± 5.0	13.2 ± 4.8	13.1 ± 5.0

HTN, hypertension; LM-DR, Logical Memory Delayed Recall; VR-DR, Visual Reproductions Delayed Recall; PA-DR, Paired Associate Learning – Delayed Recall; DSF, Digit Span Forward Span; DSB, Digit Span Backward Span; EF, Executive Function; TMA, Trail-making Test A completion time; TMB-TMA, Trail-making Test B completion time – Trail-making Test A completion time; HVOT, Hooper Visual Organization Test; COWAT, Controlled Word Association Test; SIM, Similarities.

Table 3

Distribution by systolic blood pressure subgroup at midlife and at exam closest to NP assessment

SBP at Midlife		SBP at NP Assessment			
		<120 mmHg	**120–139 mmHg**	**140–159 mmHg**	**≥160 mmHg**
<120 mmHg	126	32	57	28	9
120–139 mmHg	169	36	62	44	27
140–159 mmHg	67	14	14	27	12
≥160 mmHg	16	4	7	2	3

SBP, systolic blood pressure; NP, neuropsychological.

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Table 4

Association of Midlife SBP and HTN on cognitive performance in the oldest old

	β±SE	
	HTN‡	**SBP‡‡**
LM-DR	0.22 ± 0.13	−0.001 ± 0.004
VR-DR	0.02 ± 0.14	−0.003 ± 0.004
PA-DR	0.14 ± 0.14	−0.003 ± 0.004
DSF	−0.23 ± 0.14	**−0.008 ± 0.004** *
DSB	−0.17 ± 0.14	−0.006 ± 0.004
TMA	−0.13 ± 0.14	−0.005 ± 0.004
TMB-TMA	−0.09 ± 0.13	−0.002 ± 0.004
HVOT	−0.17 ± 0.13	−0.006 ± 0.004
COWAT	−0.23 ± 0.13	**−0.008 ± 0.004** *
SIM	0.18 ± 0.12	−0.002 ± 0.003

* $p < 0.05$.

‡Adjusted for age, time from cardiovascular risk assessment to first NP exam, gender, natural log of WRAT and HTN status at NP exam.

‡‡Adjusted for age, time from cardiovascular risk assessment to first NP exam, gender, natural log of WRAT and SBP at NP exam.

HTN, Stage I hypertension; SBP, systolic blood pressure; β, estimate; SE, standard error; LM-DR, Logical Memory Delayed Recall; VR-DR, Visual Reproductions Delayed Recall; PA-DR, Paired Associate Learning – Delayed Recall; DSF, Digit Span Forward span; DSB, Digit Span Backward span; TMA, Trail-making Test A completion time; TMB-TMA, Trail-making Test B completion time – Trail-making Test A completion time; HVOT, Hooper Visual Organization Test; COWAT, Controlled Word Association Test; SIM, Similarities.

Table 5

Significant interactions between ApoE4 and midlife cardiovascular risk factor exposure on NP outcome measures

	ApoE4−		ApoE4+		
	TMA				
	Beta (SE)	*p*-value	Beta (SE)	*p*-value	*p*-value for Interaction
HTN	−0.002 ± 0.15	0.990	−0.67 ± 0.36	0.065	**0.052**
	COWAT				
	Beta (SE)	*p*-value	Beta (SE)	*p*-value	*p*-value for Interaction
SBP	−0.004 ± 0.004	0.288	**−0.023 ± 0.010**	**0.025**	**0.074**

ApoE4−, participants without the apolipoprotein ε4 allele; ApoE4+, participants with the apolipoprotein ε4 allele; HTN, hypertension; SBP, systolic blood pressure; Beta, estimate; SE, standard error; TMA, Trail-making Test A completion time; COWAT, Controlled Word Association Test; Bold values are statistically significant.