HHS Public Access

Author manuscript

Alzheimer Dis Assoc Disord. Author manuscript; available in PMC 2016 April 01.

Published in final edited form as:

Alzheimer Dis Assoc Disord. 2015 ; 29(2): 117–123. doi:10.1097/WAD.0000000000000059.

Midlife Cardiovascular Risk Impacts Memory Function: The Framingham Offspring Study

Apar Gupta, BA.,
Framingham Heart Study, Department of Neurology, Boston University School of Medicine

Sarah R. Preis, ScD, MPH.,
Framingham Heart Study, Department of Biostatistics, Boston University School of Public Health

Alexa Beiser, PhD.,
Framingham Heart Study, Department of Neurology, Boston University School of Medicine, Department of Biostatistics, Boston University School of Public Health

Sherral Devine, PhD.,
Framingham Heart Study, Department of Neurology, Boston University School of Medicine

Lisa Hankee, PsyD.,
Framingham Heart Study, Department of Neurology, Boston University School of Medicine

Sudha Seshadri, MD.,
Framingham Heart Study, Department of Neurology, Boston University School of Medicine

Philip A. Wolf, MD., and
Framingham Heart Study, Department of Neurology, Boston University School of Medicine

Rhoda Au, PhD.
Framingham Heart Study, Department of Neurology, Boston University School of Medicine

Abstract

Introduction—This study incorporates unique error response analyses with traditional measures of memory to examine the association between mid-life cardiovascular risk factors (CVRF) and later-life memory function.

Methods—The Framingham Stroke Risk Profile (FSRP), a composite score of cardiovascular risk, was assessed in 1755 Framingham Offspring participants (54% women, mean age=54±9 years) from 1991-1995. Memory tests including Logical Memory (LM) and Visual Reproductions (VR) were administered from 2005-2008. Linear and logistic regression examined the association between FSRP and memory measures. Interaction between presence of the ApoE4 allele and each FSRP component on the memory measures was also assessed.

Results—FSRP and the individual components of age, sex, and smoking were related to lower standard scores of memory. The new error response analyses reinforced the standard analyses and

Corresponding Author: Rhoda Au, PhD. Fax: 617-638-8086 Telephone: 617-638-5450 rhodaau@bu.edu Mailing address: 72 East Concord St. Boston University School of Medicine Boston, MA 02118.

Disclosure: The authors report no conflicts of interest.

also identified new relationships. Participants with diabetes were found to make more errors on LM, and those with a history of smoking were found to make more errors on VR. Lastly, ApoE4+ smokers experienced significant verbal memory loss whereas ApoE4- smokers did not.

Conclusion—Middle-aged healthy adults with CVRF including diabetes, history of smoking, and ApoE4 positivity were found to have greater later-life memory impairments.

Keywords

Neuropsychological assessment; Memory; Mild cognitive impairment; ApolipoproteinE allele 4

Introduction

Epidemiologic studies have linked cardiovascular risk factors (CVRF) at mid-life to dementia and Alzheimer's disease (AD) in later life.[1] With an increasing focus on identifying preclinical markers of dementia/AD, studies have targeted specific cognitive endophenotypes of dementia/AD. However, most of these studies find CVRF related to executive function,[2-4] and few have found relationships between CVRF and memory, the loss of which is a hallmark sign of dementia/AD.

There are conflicting results assessing whether CVRF relate to memory. While one study reported finding no longitudinal relationship between a composite CVRF measure and memory,[3] other studies have found a significant inverse association cross-sectionally[5] or when focused on an elderly cohort.[6] For individual CVRF, there is similarly no clear evidence supporting mid- to late-life correlations. Studies reporting an association between diabetes and memory impairment were again cross-sectional or restricted to the elderly,[7,8] and two recent longitudinal studies with middle-aged baseline cohorts found no relationship.[9,10] Furthermore, a meta-analysis of studies focused on younger individuals found that diabetes had an effect on multiple cognitive domains but spared memory function.[11] Similarly for other CVRF, studies with elderly cohorts found an association between memory impairment and hypertension[6,12] and smoking,[6,13] while a study with a middle-aged baseline cohort failed to identfy any such relationships.[9] For CVD, studies have again been cross-sectional or focused on an elderly cohort, and have reported varying results dependent upon the memory test used.[14,15]

The apolipoprotein ε4 (ApoE4) allele is a well-documented risk factor of AD[16,17] as well as memory impairment in the elderly.[18] However, it is less clear what effect ApoE4 positivity has on those who are still cognitively healthy. While some studies did not find that ApoE4 positivity correlates with memory decline,[19,20] other studies have found that ApoE4 carriers perform worse on measures of memory than non-carriers while remaining clinically asymptomatic.[21,22] Though the ApoE4 allele has been linked to increased cardiovascular risk,[23,24] there is also evidence that ApoE4 is associated with dementia/AD independent of CVRF.[25] Finally, recent findings indicate that ApoE4 can modify the effect of CVRF on brain aging,[26] though further confirmatory research is needed.

The potential insensitivity of current measurement tools in detecting cognitive deficits in those who are largely asymptomatic for clinical disease compounds the issue of determining

whether CVRF are linked to impaired memory. The Framingham Heart Study (FHS) developed a set of new error measures that aims to quantify more subtle differences in cognitive performance as well as more accurately define the role non-memory processes, such as executive function, play in traditional memory tests.

The primary objective of this study is to determine whether CVRF measured at midlife are related to performance indices on memory tests 12-16 years later in the community-based FHS Offspring cohort. The inclusion of unique error response analyses allows for the examination of relationships not assessed by traditional measures. The study additionally examines how the ApoE4 allele modifies these relationships.

Methods

Study Participants

The Framingham Offspring Cohort was initially recruited in 1971 (n=5124).[27] Inclusion criteria included having at least one biological parent in the Original Framingham Cohort or being the spouse of a biological Offspring. Participants have been examined for cardiovascular and cerebrovascular disease approximately every four years, with 3799 attending Exam 5 (1991-1995). In order to assess the relationship between mid-life cardiovascular risk and late-life cognition, the study sample was restricted to 2037 participants who both attended Exam 5 and agreed to neuropsychological (NP) testing at Exam 8 (2005-2008). Additionally, subjects with prevalent clinical stroke, dementia, or other neurologic illnesses (eg., multiple sclerosis, severe head trauma, etc.) at the time of the NP assessment (n=128) and subjects with missing data (n=154) were excluded from the analysis, resulting in a study sample size of 1,755 (53.6% women) subjects. The study was approved by the Boston University Institutional Review Board and all participants provided signed consent at the time of the health and NP examinations.

Stroke Risk Profile

A composite score of cardiovascular risk, the Framingham Stroke Risk Profile (FSRP) represents the 10-year probability of a stroke.[28] This well-validated risk score is calculated based on the subject's age, gender, and specific cardiovascular risk factors including current smoking, diabetes, hypertension, cardiovascular disease, atrial fibrillation, and left ventricular hypertrophy as measured by EKG. The FSRP, measured at an average age of 53.6 years (SD=9.1 y), was used as a measure of cardiovascular risk at mid-life, and the individual risk factors of current smoking, diabetes, hypertension, and prevalent CVD were also considered separately.

Neuropsychological Test Battery

Participants were administered a neuropsychological test battery that included the immediate and delayed recall conditions of the Logical Memory (LM-I and LM-D, respectively) and Visual Reproductions (VR-I and VR-D, respectively) subtests of the Wechsler Memory Scale. Standard test administration and scoring procedures, as described in previous FHS publications,[29] were used. All testing was also tape recorded to ensure precision and

completeness in documenting participants' responses. This procedure was essential to allow the unique identification and characterization of error responses described below.

Logical Memory (LM)—In addition to the traditional measure of total number of correctly immediately recalled items (LM-IR), the examiner also tallied the total number of errors that were made, including 1) confabulations (extraneous details that were never presented) and 2) intrusions (details recalled from different tests). For the delayed condition, the same standard measure (LM-DR) was obtained, and errors were again counted, differentiating between new errors and those repeated from the immediate condition. A percent retention score LM-PR was also computed to capture the percentage of total correct responses retained from the immediate condition, as follows: (LM-DR/LM-IR) x 100.

Visual Reproductions (VR)—Similar to LM, standard total correct responses were scored at immediate and delayed recall (VR-IR and VR-DR). The following types of errors were additionally recorded: 1) drew right to left; 2) contaminated the drawing with a motif from another design; 3) drew extremely small; 4) had tremors; 5) started to draw before told to do so; 6) did not attempt to make any drawing; and 7) reported the location of a design while not being able to recall it specifically. A percent retention score VR-PR ((VR-DR/VR-IR) x 100) was also computed.

Statistical Analysis

Linear regression was used to examine the associations between the FSRP score and its components and continuous memory variables. Due to the small number of errors made by the participants and the skewed nature of the error variables, all error measurements, except for percent retention scores, were dichotomized into $\geq 75^{th}$ versus $<75^{th}$ percentile (quartile 4 versus quartiles 1-3). LM-PR and VR-PR were dichotomized into $<25^{th}$ versus $\geq 25^{th}$ percentile (quartile 1 versus quartiles 2-4) since lower scores correspond to poorer performance. Logistic regression was used to examine the associations between the FSRP score and its components and the dichotomous error variables. All analyses were adjusted for age at neuropsychological testing, sex, education group (<High school degree, High school degree, College degree, >College degree), and time between FSRP measurement (Exam 5) and neuropsychological testing (Exam 8). The interaction between the FSRP score and its components and ApoE4 was assessed using a Wald test. A p-value of <0.05 was considered statistically significant. All statistical analyses were done using SAS version 9.2 (Cary, NC).

Results

Study Sample Characteristics

Table 1 presents the characteristics of the 1755 participants included in the analysis. The participants' mean age at the time of the cardiovascular assessment was 53.6 years (SD=9.1 y), and at an average of 14.1 years (SD=1.2 y) later, they underwent neuropsychological testing at a mean age of 67.2 years (SD=9.1 y). The mean MMSE score at Exam 5 was 29.1 (SD=1.2) out of a maximum score of 30.

Table 1 also presents mean values for each neuropsychological test result assessed in the study.

Relationship between Cardiovascular Risk Factors and Traditional NP Measures

Table 2 presents the association between the FSRP score and its components and the established outcome measures of the neuropsychological tests described above.

There was a statistically significant inverse association between FSRP score and VR-DR traditional score. For each one percentage point increase in FSRP score, VR-DR decreased by 0.072 units (Beta=−0.072, p=0.007).

When looking at the association between individual FSRP components and traditional measures, age and sex were the most predictive but smoking status also displayed a significant relationship. Increasing age was related to lower immediate and delayed scores from each test: LM-IR (Beta=−0.087, p<0.0001), LM-DR (Beta=-0.10, p<0.0001), VR-IR (Beta=−0.15, p<0.0001), and VR-DR (Beta=−0.16, p<0.0001). Women displayed significantly higher scores on LM-IR (Beta=0.92, p<0.0001) and LM-DR (Beta=1.06, p<0.0001) than men, but no such association was found with VR scores. Conversely, participants who smoked at the time of the cardiovascular risk assessment had significantly lower scores on VR-IR (Beta=-0.43, p=0.02) and VR-DR (Beta=−0.40, p=0.04) than those who did not. There were no other statistically significant associations between FSRP components and traditional NP scores.

Relationship between Cardiovascular Risk Factors and Error Response NP Measures

Table 3 presents the association between the FSRP score and its components and the newly-established error response measures of the same neuropsychological tests.

The composite FSRP score was related to lower VR-PR only (OR=1.05, p=0.02), where higher FSRP scores were associated with a greater likelihood of being in the lowest quartile of percent retention.

Among the individual FSRP components, increasing age was related to more total errors on LMI (OR=1.02, p=0.0009), VR-I (OR=1.08, p<0.0001), and VR-D (OR=1.08, p<0.0001), as well as being in the lowest quartile of LM (OR=1.03, p<0.0001) and VR (OR=1.04, p<0.0001) percent retention. Women were 34% and 28% more likely than men to have repeated errors (OR=1.34, p=0.04) and total errors (OR=1.28, p=0.03) in the highest quartile on LM-D, respectively, but they were also less likely to have a lower percent retention score on LM (OR=0.73, p=0.008).

The individual factors of smoking and diabetes were associated with several of the new outcome measures. Participants who smoked at the time of cardiovascular risk assessment were 60% more likely to have VR-D total errors ≥75th percentile than those who did not (OR=1.60, p=0.004). Participants with diabetes were 56% more likely to have LM-I total errors ≥75^{th} percentile (OR=1.56, p=0.04) than those without diabetes. There was no association between hypertension or prevalent CVD and any of the error response outcomes.

Interaction between ApoE4 Status and Cardiovascular Risk Factors on NP Measures

Table 4 presents the statistically significant interactions between ApoE4 and the FSRP score and its components on the NP outcome measures.

When examining the traditional outcome measures, there was an interaction between ApoE4 and smoking on LM-IR score (p-value for interaction=0.01). Among ApoE4- participants, there was no association between smoking and LM-IR score (Beta=0.37, p=0.15), while among ApoE4+ participants, those who smoked were more likely to have a lower LM-IR score (Beta=−1.10, p=0.049).

For the error response NP measures, there was an interaction between ApoE4 and age for LM-I total errors (p-value for interaction=0.048). Older participants were more likely to have LM-I errors ≥75th percentile, but only among those without ApoE4 (OR=1.03, p=0.0002). There was also an interaction between ApoE4 and sex for LM-D new errors (p-value for interaction=0.03). Among ApoE4- participants, there was no association between sex and LM-D new errors (OR=0.96, p=0.71), while among ApoE4+ participants, women were more likely to have LM-D new errors ≥75th percentile than men were (OR=1.74, p=0.02).

Discussion

Analyses of cardiovascular risk on traditional measures of memory yielded similar results to previous studies and the new error response analyses revealed additional significant associations. In determining the impact of overall cardiovascular risk on memory, higher midlife FSRP score was associated with reduced visual memory function. The finding from the error analyses that FSRP score was inversely associated with visual memory retention further reinforced this result. The absence of significant findings related to verbal memory suggests that the visuospatial aspects of the test may account for this relationship, corroborating previous studies suggesting that cardiovascular risk is linked to frontal systems.[2,9,13,30]

For individual FSRP components, a novel relationship between diabetes and more errors on immediate verbal recall was found, which was not detected for traditional delayed recall measures – further illustrating why the impact of diabetes on memory remains an on-going debate.[7-11] The finding that those with diabetes are more likely to generate erroneous content at immediate verbal recall suggests that the impact of diabetes on memory may be at the acquisition stage. Additionally, smoking earlier in life was related to lower traditional recall and error measures of visual memory function, but not visual memory retention, reflecting the lack of clearly established findings in the literature.[6,9,13]

Demographic factors of the FSRP, as expected, were inversely associated with both verbal and visual memory. Age was positively associated with total errors for both verbal and visual memory, and negatively with verbal and visual retention. The low number of total errors at delay did not allow determination of whether the persistence of these errors for visual memory was related to the production of new errors or the retention of previously created errors. Women remembered more verbal information than men, a pattern reported

previously in the neuropsychological literature.[31] However, it is interesting that while women did better than men on verbal memory using traditional measures and were less likely to be in the lowest quartile of verbal retention, they were also more likely to include recall of previous errors in the verbal memory error analyses. This suggests that they did not in fact retain more correct information over time but were actually more fully integrating embellished information into their long-term memory.

Stratified analyses confirmed ApoE4 status has a modifying effect on previously-examined traditional memory scores and identified additional relationships involving new memory measures. Smoking was related to poorer performance only in visual memory in the primary analyses, but in those who are ApoE4+, it was also related to poorer performance on verbal memory. This finding is consistent with previous research that has suggested a link between ApoE4 and cardiovascular risk.[23,24]

While previous studies have also shown that ApoE4 confers additional risk for poorer cognition,[21,22,32] the finding that those who were ApoE4- were more likely to produce erroneous content at verbal recall raises the question of a greater awareness of missing information, and the possible use of compensatory strategies that lead to more errors but better mask the lack of recalled information. Another interesting finding was that women who were ApoE4+ were significantly more likely to have more new verbal memory errors than ApoE4+ men, again suggesting a compensatory strategy for lower recall of presented information.

Recent research suggests regional associations between sub-regions of the hippocampus and stages of memory processing. The additional relationships involving greater error production at immediate recall implicate the hippocampus' CA3 sub-region and dentate gyrus, both of which have been linked to acquisition of new information.[33-35] The novel finding of new error production at delayed recall is consistent with functional MRI studies also reporting that CA1 and subicular cortices[36,37] and projections to the medial prefrontal cortex are linked to retrieval[38] and differentiation of new from old information.[39] The posterior parahippocampal cortex has also been postulated to be involved in retrieval of contextual information.[40] Our results further suggest that genetic risk may mediate these potential pathways.

The strengths of this study include the established community-based FHS cohort and the prospective design in which assessment of cardiovascular risk factors can be compared to cognitive function 10-15 years later, as well as the measurement of error performance on standard memory tests. The limitations of this study include the low variability of FSRP and its components as well as total errors in the study population, which is predominantly Caucasian, highly educated, and relatively healthy. Low overall cardiovascular risk reduces the generalizability of our study to a more ethnically-diverse population in which cardiovascular risk is generally higher. Another limitation is that adjustment could not be made for the chronicity of exposure, and thus results that are attributed to mid-life exposure may in fact be contaminated by ongoing, long-term exposure occurring between the vascular risk and cognitive assessments. Of interest was also the absence of a significant relationship between hypertension and any of the memory measures. It is unclear whether this resulted

from the relatively high proportion of those who are hypertensive who are on anti-hypertensive medications or from the overall level of hypertension being lower than it may be in other studies. Lastly, further research comparing the relationship between traditional scoring and error response analyses, as well as longitudinal follow-up of cognitive status, is needed to assess the potential clinical importance of error-based rates.

In conclusion, the new error response analyses expanded upon relationships seen with traditional scoring methods on standardized memory tests. These results suggest the added value that error analyses may provide in detecting cognitive change and identifying potential underlying substrates. Further research is needed to verify these findings and longitudinal study will be necessary to determine whether there is long-term clinical relevance.

Acknowledgments

Study funding: This work (design and conduct of the study, collection and management of the data) was supported by the Framingham Heart Study's National Heart, Lung, and Blood Institute contract (N01-HC-25195) and by grants from the National Institute of Neurological Disorders and Stroke (R01 NS17950) and from the National Institute on Aging (R01 AG16495; AG08122).

References

1. Luchsinger JA, Reitz C, Honig LS, et al. Aggregation of vascular risk factors and risk of incident Alzheimer disease. Neurology. 2005; 65(4):545–551. [PubMed: 16116114]
2. Debette S, Seshadri S, Beiser A, et al. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. Neurology. 2011; 77(5):461–468. [PubMed: 21810696]
3. Kaffashian S, Dugravot A, Brunner EJ, et al. Midlife stroke risk and cognitive decline: a 10-year follow-up of the Whitehall II cohort study. Alzheimers Dement. 2013; 9(5):572–579. [PubMed: 23199495]
4. Nishtala A, Preis SR, Beiser A, et al. Midlife cardiovascular risk impacts executive function: Framingham Offspring Study. Alzheimer Dis Assoc Disord. 2013 [published online ahead of print August 29 2013] doi: 10.1097/WAD.0b013e3182a715bc.
5. Llewellyn DJ, Lang IA, Xie J, et al. Framingham stroke risk profile and poor cognitive function: a population-based study. BMC Neurol. 2008; 8:12. [PubMed: 18430227]
6. Dregan A, Stewart R, Gulliford MC. Cardiovascular risk factors and cognitive decline in adults aged 50 and over: a population-based cohort study. Age Ageing. 2013; 42(3):338–345. [PubMed: 23179255]
7. Arvanitakis Z, Wilson RS, Li Y, et al. Diabetes and function in different cognitive systems in older individuals without dementia. Diabetes Care. 2006; 29(3):560–565. [PubMed: 16505506]
8. Luchsinger JA, Reitz C, Patel B, et al. Relation of diabetes to mild cognitive impairment. Arch Neurol. 2007; 64(4):570–575. [PubMed: 17420320]
9. Knopman DS, Mosley TH, Catellier DJ, et al. Fourteen-year longitudinal study of vascular risk factors, APOE genotype, and cognition: the ARIC MRI Study. Alzheimers Dement. 2009; 5(3): 207–214. [PubMed: 19362884]
10. Spauwen PJ, Köhler S, Verhey FR, et al. Effects of type 2 diabetes on 12-year cognitive change: results from the Maastricht Aging Study. Diabetes Care. 2013; 36(6):1554–1561. [PubMed: 23275366]
11. Brands AM, Biessels GJ, de Haan EH, et al. The effects of type 1 diabetes on cognitive performance: a meta-analysis. Diabetes Care. 2005; 28(3):726–735. [PubMed: 15735218]
12. Paran E, Anson O. The dynamics of blood pressure and cognitive functioning: results from 6-year follow-up of an elderly cohort. J Clin Hypertens (Greenwich). 2011; 13(11):813–817. [PubMed: 22051425]

13. Arntzen KA, Schirmer H, Wilsgaard T, et al. Impact of cardiovascular risk factors on cognitive function: the Tromsø study. Eur J Neurol. 2011; 18(5):737–743. [PubMed: 21143340]
14. Okonkwo OC, Cohen RA, Gunstad J, et al. Longitudinal trajectories of cognitive decline among older adults with cardiovascular disease. Cerebrovasc Dis. 2010; 30(4):362–373. [PubMed: 20693791]
15. Muller M, Grobbee DE, Aleman A, et al. Cardiovascular disease and cognitive performance in middle-aged and elderly men. Atherosclerosis. 2007; 190(1):143–149. [PubMed: 16488420]
16. Crean S, Ward A, Mercaldi CJ, et al. Apolipoprotein E ε4 prevalence in Alzheimer's disease patients varies across global populations: a systematic literature review and meta-analysis. Dement Geriatr Cogn Disord. 2011; 31(1):20–30. [PubMed: 21124030]
17. Spampinato MV, Rumboldt Z, Hosker RJ, et al. Apolipoprotein E and gray matter volume loss in patients with mild cognitive impairment and Alzheimer disease. Radiology. 2011; 258(3):843–852. [PubMed: 21163916]
18. Liu F, Pardo LM, Schuur M, et al. The apolipoprotein E gene and its age-specific effects on cognitive function. Neurobiol Aging. 2010; 31(10):1831–1833. [PubMed: 19004527]
19. Bunce D, Fratiglioni L, Small BJ, et al. APOE and cognitive decline in preclinical Alzheimer disease and non-demented aging. Neurology. 2004; 63(5):816–821. [PubMed: 15365129]
20. Kim KW, Youn JC, Jhoo JH, et al. Apolipoprotein E ε4 allele is not associated with the cognitive impairment in community-dwelling normal elderly individuals. Int J Geriatr Psychiatry. 2002; 17(7):635–640. [PubMed: 12112161]
21. Caselli RJ, Dueck AC, Locke DE, et al. Cerebrovascular risk factors and preclinical memory decline in healthy APOE ε4 homozygotes. Neurology. 2011; 76(12):1078–1084. [PubMed: 21325652]
22. Wisdom NM, Callahan JL, Hawkins KA. The effects of apolipoprotein E on non-impaired cognitive functioning: a meta-analysis. Neurobiol Aging. 2011; 32(1):63–74. [PubMed: 19285755]
23. Bennet AM, Di Angelantonio E, Ye Z, et al. Association of apolipoprotein E genotypes with lipid levels and coronary risk. JAMA. 2007; 298(11):1300–1311. [PubMed: 17878422]
24. Niu W, Qi Y, Qian Y, et al. The relationship between apolipoprotein E epsilon2/epsilon3/epsilon4 polymorphisms and hypertension: a meta-analysis of six studies comprising 1812 cases and 1762 controls. Hypertens Res. 2009; 32(12):1060–1066. [PubMed: 19816504]
25. Eriksson UK, Bennet AM, Gatz M, et al. Nonstroke cardiovascular disease and risk of Alzheimer disease and dementia. Alzheimer Dis Assoc Disord. 2010; 24(3):213–219. [PubMed: 20473139]
26. Zade D, Beiser A, McGlinchey R, et al. Apolipoprotein epsilon 4 allele modifies waist-to-hip ratio effects on cognition and brain structure. J Stroke Cerebrovasc Dis. 2013; 22(2):119–125. [PubMed: 21835633]
27. Feinleib M, Kannel WB, Garrison RJ, et al. The Framingham Offspring Study. Design and preliminary data. Prev Med. 1975; 4(4):518–525. [PubMed: 1208363]
28. Wolf PA, D'Agostino RB, Belanger AJ, et al. Probability of stroke: a risk profile from the Framingham Study. Stroke. 1991; 22(3):312–318. [PubMed: 2003301]
29. Au R, Seshadri S, Wolf PA, et al. New norms for a new generation: cognitive performance in the Framingham Offspring Cohort. Exp Aging Res. 2004; 30(4):333–358. [PubMed: 15371099]
30. Unverzagt FW, McClure LA, Wadley VG, et al. Vascular risk factors and cognitive impairment in a stroke-free cohort. Neurology. 2011; 77(19):1729–1736. [PubMed: 22067959]
31. Kramer JH, Yaffe K, Lengenfelder J, et al. Age and gender interactions on verbal memory performance. J Int Neuropsychol Soc. 2003; 9(1):97–102. [PubMed: 12570363]
32. Bender AR, Raz N. Age-related differences in memory and executive functions in healthy APOE ε4 carriers: the contribution of individual differences in prefrontal volumes and systolic blood pressure. Neuropsychologia. 2012; 50(5):704–714. [PubMed: 22245009]
33. Barbosa FF, Pontes IM, Ribeiro S, et al. Differential roles of the dorsal hippocampal regions in the acquisition of spatial and temporal aspects of episodic-like memory. Behav Brain Res. 2012; 232(1):269–277. [PubMed: 22546523]
34. Newmark RE, Schon K, Ross RS, et al. Contributions of the hippocampal subfields and entorhinal cortex to disambiguation during working memory. Hippocampus. 2013; 23(6):467–475. [PubMed: 23504938]

35. Saab BJ, Georgiou J, Nath A, et al. NCS-1 in the dentate gyrus promotes exploration, synaptic plasticity, and rapid acquisition of spatial memory. Neuron. 2009; 63(5):643–656. [PubMed: 19755107]

36. Chen J, Olsen RK, Preston AR, et al. Associative retrieval processes in the human medial temporal lobe: hippocampal retrieval success and CA1 mismatch detection. Learn Mem. 2011; 18(8):523–528. [PubMed: 21775513]

37. Suthana N, Ekstrom A, Moshirvaziri S, et al. Dissociations within human hippocampal subregions during encoding and retrieval of spatial information. Hippocampus. 2011; 21(7):694–701. [PubMed: 20882543]

38. Churchwell JC, Morris AM, Musso ND, et al. Prefrontal and hippocampal contributions to encoding and retrieval of spatial memory. Neurobiol Learn Mem. 2010; 93(3):415–421. [PubMed: 20074655]

39. Euston DR, Gruber AJ, McNaughton BL. The role of medial prefrontal cortex in memory and decision making. Neuron. 2012; 76(6):1057–1070. [PubMed: 23259943]

40. Tendolkar I, Arnold J, Petersson KM, et al. Contributions of the medial temporal lobe to declarative memory retrieval: manipulating the amount of contextual retrieval. Learn Mem. 2008; 15(9):611–617. [PubMed: 18723430]

Table 1

Baseline Characteristics of Offspring Cohort Participants with FSRP and NP measures

	N=1755
Categorical characteristics, n (%)	
Female sex	941 (53.6)
Education group	
<High school	60 (3.4)
High school graduate	996 (56.8)
College graduate	369 (21.0)
>College graduate	330 (18.8)
Current smoking	287 (16.4)
Diabetes	94 (5.4)
Hypertension	476 (27.1)
Hypertension treatment	239 (13.6)
History of CVD	83 (4.7)
ApoE4 carriers	364 (21.1)
Continuous characteristics, mean (SD)	
Age at exam 5 (years)	53.6 (9.1)
Age at NP exam (years)	67.2 (9.1)
Time between exam 5 and NP exam (years)	14.1 (1.2)
FSRP score at exam 5	3.6 (3.7)
MMSE score at exam 5	29.1 (1.2)
Logical Memory-Immediate recall score (LM-IR)	12.1 (3.8)
Logical Memory-Delayed recall score (LM-DR)	11.1 (4.0)
Visual Reproductions-Immediate recall score (VR-IR)	8.8 (3.1)
Visual Reproductions-Delayed recall score (VR-DR)	7.9 (3.4)
Categorical characteristics, median (25^{th}, 75^{th} percentile)	
Logical Memory-Immediate total errors	1 (0, 2)
Logical Memory-Delayed new errors	1 (0, 2)
Logical Memory-Delayed repeated errors	0 (0, 1)
Logical Memory-Delayed total errors	2 (1, 2)
Logical Memory percent retention score (LM-PR)	92.3 (81.8, 100)
Visual Reproductions-Immediate total errors	0 (0, 1)
Visual Reproduction-Delayed total errors	1 (0, 1)
Visual Reproductions percent retention score (VR-PR)	92.3 (77.8, 100)

Abbreviations: FSRP = Framingham Stroke Risk Profile; NP = neuropsychological; CVD = cardiovascular disease; ApoE4 = apolipoprotein ε4; SD = standard deviation; MMSE = Mini-Mental State Examination

Table 2

Association between Midlife Cardiovascular Risk Factors and Traditional NP Outcome Measures

	FSRP Score		Age		Sex		Current Smoking		Diabetes		Hypertension		Prevalent CVD	
Continuous Outcomes	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**
Logical Memory-Immediate recall score (LM-IR)	−0.011 (0.031)	0.72	−0.087 (0.0096)	<0.0001	0.92 (0.17)	<0.0001	0.12 (0.23)*	0.62	−0.13 (0.38)	0.73	0.011 (0.20)	0.96	0.023 (0.41)	0.95
Logical Memory-Delayed recall score (LM-DR)	−0.047 (0.033)	0.15	−0.10 (0.0099)	<0.0001	1.06 (0.18)	<0.0001	−0.10 (0.24)	0.67	−0.43 (0.39)	0.28	0.038 (0.21)	0.86	0.14 (0.42)	0.74
Visual Reproductions-Immediate recall score (VR-IR)	−0.047 (0.024)	0.05	−0.15 (0.0073)	<0.0001	−0.025 (0.13)	0.85	−0.43 (0.18)	0.02	0.064 (0.29)	0.82	−0.11 (0.15)	0.48	−0.25 (0.31)	0.43
Visual Reproductions-Delayed recall score (VR-DR)	−0.072 (0.027)	0.007	−0.16 (0.0081)	<0.0001	−0.14 (0.14)	0.35	−0.40 (0.20)	0.04	−0.28 (0.32)	0.38	−0.079 (0.17)	0.64	−0.045 (0.34)	0.90

Abbreviations: NP = neuropsychological; FSRP = Framingham Stroke Risk Profile; CVD = cardiovascular disease; SE = standard error

Note: All models are adjusted for age, sex, education group (<high school degree, high school degree, college degree, >college degree), and time between risk factor measurement and neuropsychological testing. Sample size for each test is as follows: LM-I (n=1749), LM-D (n=1743), VR-I (n=1740), VR-D (n=1733).

*Indicates interaction with APOE genotype p<0.05.

Table 3

Association between Midlife Cardiovascular Risk Factors and Error Response NP Outcome Measures

	FSRP Score		Age		Sex		Current Smoking		Diabetes		Hypertension		Prevalent CVD	
Categorical Outcome (≥75th vs. <75th percentile)	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Logical Memory-Immediate total errors	0.98 (0.94-1.02)	0.26	1.02 (1.01-1.03)*	0.0009	1.16 (0.95-1.43)	0.15	1.02 (0.77-1.35)	0.90	1.56 (1.01-2.40)	0.04	0.85 (0.67-1.09)	0.20	1.07 (0.66-1.73)	0.77
Logical Memory-Delayed new errors	0.98 (0.94-1.02)	0.40	1.01 (1.00-1.02)	0.16	1.07 (0.87-1.32)*	0.54	1.14 (0.86-1.51)	0.38	0.84 (0.52-1.36)	0.48	0.88 (0.69-1.13)	0.32	0.61 (0.35-1.06)	0.08
Logical Memory-Delayed repeated errors	0.95 (0.89-1.01)	0.10	1.01 (1.00-1.03)	0.10	1.34 (1.01-1.76)	0.04	1.06 (0.73-1.54)	0.77	1.51 (0.86-2.62)	0.15	0.82 (0.59-1.15)	0.25	0.68 (0.32-1.45)	0.32
Logical Memory-Delayed total (new + repeated) errors	1.00 (0.96-1.04)	0.95	1.01 (1.00-1.03)	0.05	1.28 (1.02-1.60)	0.03	1.31 (0.98-1.76)	0.07	1.09 (0.67-1.78)	0.72	1.07 (0.83-1.39)	0.59	0.55 (0.30-1.02)	0.06
Visual Reproductions-Immediate total errors	0.99 (0.94-1.03)	0.51	1.08 (1.06-1.10)	<0.0001	1.27 (0.95-1.71)	0.11	1.47 (1.00-2.16)	0.05	0.62 (0.33-1.19)	0.15	0.82 (0.59-1.13)	0.22	0.93 (0.51-1.70)	0.81
Visual Reproductions-Delayed total errors	0.99 (0.96-1.03)	0.72	1.08 (1.06-1.09)	<0.0001	1.22 (0.95-1.56)	0.11	1.60 (1.16-2.21)	0.004	0.86 (0.52-1.44)	0.57	0.81 (0.62-1.07)	0.15	1.21 (0.74-2.00)	0.45
Categorical Outcome (<25th vs. ≥25th percentile)														
Logical Memory percent retention score (LM-PR)	1.02 (0.98-1.06)	0.33	1.03 (1.02-1.05)	<0.0001	0.73 (0.58-0.92)	0.008	1.04 (0.76-1.41)	0.82	0.99 (0.62-1.60)	0.97	0.98 (0.76-1.27)	0.87	0.84 (0.50-1.40)	0.51
Visual Reproductions percent retention score (VR-PR)	1.05 (1.01-1.09)	0.02	1.04 (1.03-1.06)	<0.0001	1.18 (0.94-1.48)	0.17	1.09 (0.80-1.49)	0.58	1.36 (0.86-2.15)	0.19	1.12 (0.86-1.44)	0.40	0.96 (0.58-1.58)	0.86

Abbreviations: NP = neuropsychological; FSRP = Framingham Stroke Risk Profile; CVD = cardiovascular disease; OR = odds ratio; CI = confidence interval; SE = standard error

Note: All models are adjusted for age, sex, education group (<high school degree, high school degree, college degree, >college degree), and time between risk factor measurement and neuropsychological testing.

*Indicates interaction with APOE genotype p<0.05.

Table 4

Statistically Significant Interactions (P-value<0.05) between ApoE4 and Midlife Cardiovascular Risk Factor Exposures on NP Outcome Measures

	Exposure	ApoE4− (N=1359)		ApoE4+ (N=364)		P-value for Interaction
Continuous Outcomes		**Beta (SE)**	**P-value**	**Beta (SE)**	**P-value**	
Logical Memory-Immediate recall score (LM-IR)	Current smoking	0.37 (0.26)	0.15	−1.10 (0.56)	0.049	0.01

Categorical Outcomes (≥75th vs. <75th percentile)		**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**	
Logical Memory-Immediate total errors	Age	1.03 (1.01-1.04)	0.0002	1.00 (0.97-1.02)	0.76	0.048
Logical Memory-Delayed new errors	Sex	0.96 (0.75-1.22)	0.71	1.74 (1.08-2.78)	0.02	0.03

Abbreviations: ApoE4 = apolipoprotein ε4; NP = neuropsychological; ApoE4− = apolipoprotein ε4 negative group; ApoE4+ = apolipoprotein ε4 positive group; SE=standard error; OR = odds ratio; CI=confidence interval

Note: All models are adjusted for age, sex, education group (<high school degree, high school degree, college degree, >college degree), and time between risk factor measurement and neuropsychological testing.