HHS Public Access

Author manuscript

Alzheimer Dis Assoc Disord. Author manuscript; available in PMC 2018 April 01.

Published in final edited form as:

Alzheimer Dis Assoc Disord. 2017 ; 31(2): 94–100. doi:10.1097/WAD.0000000000000203.

Total Brain and Hippocampal Volumes and Cognition in Older American Indians: The Strong Heart Study

Brenna Cholerton, PhD[a], **Adam Omidpanah**[b], **Tara M. Madhyastha, PhD**[c], **Thomas J. Grabowski, MD**[c,d], **Astrid M. Suchy-Dicey, PhD**[e], **Dean K. Shibata, MD**[c], **Lonnie A. Nelson, PhD**[e], **Steven P. Verney, PhD**[f], **Barbara V. Howard, PhD**[g], **William T. Longstreth Jr, MD**[d,h], **Thomas J. Montine, MD, PhD**[a], and **Dedra Buchwald, MD**[i]

[a]Department of Pathology, Stanford University, Palo Alto, California, USA

[b]Institute for Research and Education to Advance Community Health, Washington State University, Seattle, Washington, USA

[c]Department of Radiology, School of Medicine, University of Washington, Seattle, Washington, USA

[d]Department of Neurology, School of Medicine, University of Washington, Seattle, Washington, USA

[e]College of Nursing, Washington State University, Seattle, Washington, USA

[f]Department of Psychology, University of New Mexico, Albuquerque, New Mexico, USA

[g]MedStar Health Research Institute, Hyattsville, MD, USA

[h]Department of Epidemiology, School of Public Health, University of Washington, Seattle, Washington, USA

[i]College of Medicine, Washington State University, Seattle, Washington, USA

Abstract

Background—Estimates of hippocampal volume by magnetic resonance imaging (MRI) have clinical and cognitive correlations and can assist in early Alzheimer's disease (AD) diagnosis. However, little is known about the relationship between global or regional brain volumes and cognitive test performance in American Indians.

Methods—American Indian participants (n=698; median age 72 years) recruited for the Cerebrovascular Disease and its Consequences in American Indians study, an ancillary study of the Strong Heart Study cohort, were enrolled. Linear regression models assessed the relationship between MRI brain volumes (total brain and hippocampi) and cognitive measures of verbal learning and recall, processing speed, verbal fluency, and global cognition.

Results—After controlling for demographic and clinical factors, all volumetric measurements were positively associated with processing speed. Total brain volume was also positively

Corresponding author: Brenna Cholerton, PhD, Department of Pathology, Stanford University, 1043 Paiute Trail FI, Fox Island, WA 98333, 253-226-4842, bchol@stanford.edu.

The authors report no conflicts of interest.

associated with verbal learning, but not with verbal recall. Conversely, left hippocampal volume was associated with both verbal learning and recall. The relationship between hippocampal volume and recall performance was more pronounced among those with lower scores on a global cognitive measure. Controlling for *APOE* ε4 did not substantively affect the associations.

Conclusions—These results support further investigation into the relationship between structural AD biomarkers, cognition, genetics, and vascular risk factors in aging American Indians.

Keywords

Alzheimer's disease; American Indians; APOE; Cognition; Magnetic Resonance Imaging; Strong Heart Study

INTRODUCTION

Alzheimer's disease (AD) is the most common of the primary neurodegenerative illnesses. Its rapidly increasing prevalence represents a substantial socioeconomic burden in the U.S. Growing evidence suggests that the neurochemical, molecular, and structural changes associated with AD likely begin many years before the development of mild symptoms of dementia.[1] Current clinical diagnostic criteria from the National Institute on Aging and the Alzheimer's Association recognize AD as a continuum of progressive neuropathologic processes that ultimately result in clinically important cognitive and functional impairments.[2] These criteria support research on biomarkers that reflect such underlying processes for use in early differential diagnosis, along with supporting clinical information. Among potential biomarkers, measures of neuronal injury and the resulting global and regional brain atrophy – especially of the hippocampus – might provide the best sensitivity and specificity to detect subsequent cognitive decline associated with AD.[3] The hippocampus tends to shrink several years before clinical diagnosis of AD dementia, and this reduction in size predicts impending conversion to AD dementia in patients with mild cognitive impairment.[4,5]

Established risk factors for AD, independent of vascular dementia, include cardiovascular disease, obesity, and diabetes. All these chronic conditions are rapidly rising in prevalence in the general U.S. population and, along with early-onset AD, they are also highly prevalent in American Indian populations.[6,7] Comorbid vascular conditions might lead to more rapid progression of AD-related processes, and appropriate treatment could substantially reduce AD prevalence and risk.[8] Despite the mounting disease burden, however, little is known about diagnosed AD in American Indians. In recent years, biomarkers such as hippocampal volume have been extensively examined in the general U.S. population through studies such as the Alzheimer's Disease Neuroimaging Initiative,[9] but these studies included very few American Indian participants. As a result, potential associations between AD-related biomarkers and cognition remain unexplored in American Indians.

This article describes an association linking total brain volume and hippocampal volume, as measured by magnetic resonance imaging (MRI), with cognitive performance in American Indian elders, as measured by standard assessment instruments. Analyses were performed

with data from “Cerebrovascular Disease and its Consequences in American Indians” (CDCAI), a recently completed study.

MATERIALS AND METHODS

Participants

Between 1989 and 1991, the Strong Heart Study enrolled 4,549 American Indian participants aged 45–74 years in communities located in Arizona, Oklahoma, and North and South Dakota.[10] In 2010–2013, eligible surviving members of the Strong Heart cohort were recruited to participate in CDCAI, a study that used cranial MRI to quantify vascular brain injury and brain volume. This project was designated the “Strong Heart Stroke Study” by participating communities and field centers. CDCAI, part of the Strong Heart Study, the largest ongoing cohort of aging American Indians, collected extensive cognitive, neuroimaging, medical, and cultural data. Enrollment criteria and data collection are detailed elsewhere.[11] Participants had to: speak English fluently; be able to complete questionnaires on demographics, medical history, and health behaviors; and be willing to undergo cranial MRI, physical assessments, blood draws, and cognitive testing. DNA had been extracted from whole plasma during a previous study (the Strong Heart Family Study), and *APOE* genotype was assayed as previously described.[12] A total of 1,033 elderly American Indians were enrolled in CDCAI. Among them, 215 participants completed examinations but were removed from analyses because their community withdrew consent to use community members’ data, leaving a preliminary analytic sample of 818. Institutional review boards, local units of the Indian Health Service, and individual tribal councils approved all study procedures, and all participants provided written informed consent.

Within the preliminary sample, 47 participants were excluded for missing cranial MRI data, 69 for self-reported prior stroke, 3 for missing cognitive data, and 1 for missing demographic data (American Indian language proficiency), leaving 698 participants in the final analytic sample (age range 64 – 95, median age 72). Total brain and hippocampal volumes had differing levels of missing data. Missingness was due primarily to movement artifact and to variable sensitivity to image quality in the analytic programs used to estimate volumes. Therefore, separate analytic datasets were constructed for total brain and hippocampal volumes. For total brain volume, 77 participants had missing data, leaving 621 for analysis; for hippocampal volumes, 2 had missing data, leaving 696 for analysis.

Imaging

Details of the cranial MRI examinations are reported elsewhere.[11] Hippocampal volume was measured by using automated segmentation from three-dimensional T1-weighted images with FIRST in the Oxford Centre for Functional MRI of the Brain Software Library (FSL) 5.0 and the ENIGMA1 protocol. Images were checked at key intermediate points, such as after registration and skull stripping, and manual adjustments were made at those points. Intracranial volume (ICV) was estimated by using the ENIGMA1 protocol for FSL. An estimate for total ICV was obtained by linearly aligning each brain with the Montreal Neurological Institute (MNI152) template. The inverse of the determinant of the affine transformation matrix, multiplied by the template size, provides a robust estimate of ICV.[13]

We visually inspected all registrations and edited them as necessary to obtain accurate affine transformations.

Total brain volumes were estimated after skull stripping by using cortical reconstruction implemented in version 5.3 of the Freesurfer image analysis suite. Brain volume measurement included the cerebellum but not the ventricles, cerebrospinal fluid (CSF), or dura. ICV measurement was an estimate based on the Talairach transform.[13] All brain volumes were visually inspected, and participants were removed from analysis if parcellation failed. In all cases, such failure was due to poor image quality or excessive motion artifact. Total brain and hippocampal volumes were standardized and measured as fractions of the ICV.

Cognitive measures

The cognitive measures and performance characteristics of CDCAI participants have previously been described in detail (Verney et al., submitted). The Modified Mini-Mental State Examination (3MSE),[14] a 100-point global cognitive screening measure, was administered to provide a representation of global cognitive status. Measures of five specific cognitive domains were also administered, including the California Verbal Learning Test-II, Short Form (CVLT-II SF),[15] a measure of declarative verbal memory that includes variables for total learning, short-delay recall, and long-delay recall; the Coding subtest from the Wechsler Adult Intelligence Scale-IV (WAIS-IV),[16] a measure of processing speed; and the Controlled Oral Word Association Test (COWAT) using the letters F, A, and S.[17] For all six of these cognitive variables, a higher score reflected better cognitive function.

Covariates

Several covariates were considered for their potential to confound associations. These included age in years, sex, education (any high school, completed high school, any college, completed college degree), study site (North/South Dakota, Oklahoma, and Arizona), American Indian language proficiency (not at all, a little, moderately, very well), marital status, and vascular risk factors. The latter included hypertension, diabetes, and dyslipidemia. Hypertension was defined as systolic blood pressure higher than 140mmHg, diastolic blood pressure higher than 90 mmHg, or a prescription for antihypertensive medication; diabetes was defined as fasting glucose higher than 126 mg/dl or a prescription for insulin or oral hypoglycemic medication; and dyslipidemia was defined as LDL higher than 140 mg/dl or a prescription for statins.

Statistical analyses

We used linear regression models, adjusted for the covariates, to assess the presence of a relationship linking total brain and hippocampal volumes (standardized as a percentage of ICV) with performance on our six cognitive variables. Secondary analyses were run with the addition of *APOE* ε4 status (any ε4 allele) as a covariate. Partial correlations were conducted to further examine the relationships among ε4 allele status, both MRI volumes, and our cognitive variables, adjusted for age, sex, and study site. Additional secondary analyses used a median split to stratify participants into higher- and lower-performing groups according to their scores on the global cognitive measure (3MSE). The purpose of

these analyses was to determine whether the relationship between MRI volumes and cognitive test performance differed according to global cognitive status among study participants. Given the absence of clinical diagnoses of cognitive status, 3MSE scores were used as a proxy for cognitive diagnosis. Given that these models are exploratory in nature, we did not control for multiple comparisons. Statistical tests were two-tailed, with the significance threshold for alpha set at $P = 0.05$. All statistical analyses were performed in R version 3.1.2.

RESULTS

Demographic and clinical characteristics

Table 1 provides data on the two analytic samples (total brain volume versus hippocampal volume) organized according to participant characteristics, MRI volumes, and performance on the six cognitive variables. In the sample with total brain volumes, participants had a mean age of 72.8, and most were female (68%). Twenty-two percent carried an *APOE* ε4 allele. Among vascular risk factors, 80% had hypertension, 48% had diabetes, and 40% had dyslipidemia.

Association between MRI volumetric measurements and cognition

As summarized in Table 2, higher scores on the Coding subtest were significantly associated with larger total brain volumes as well as larger volumes for all hippocampal measurements. Higher 3MSE scores were associated only with larger hippocampal volumes, not with total brain volumes. Total brain volumes were also positively associated with CVLT-II SF performance for total learning, but not for recall trials. Associations between total hippocampal volume and CVLT-II SF measures approached but did not reach statistical significance. When examined separately, left hippocampal volumes had significantly positive associations with total learning and short-delay recall measures on CVLT-II SF, while right hippocampal volumes did not. Positive associations with long-delay recall performance on CVLT-II SF approached but did not reach statistical significance.

Further adjustment by *APOE* ε4 allele status did not change the results for total brain volume or hippocampal volumes. In addition, *APOE* ε4 status did not correlate with any volumetric measurements. Among cognitive variables, *APOE* ε4 was negatively correlated with performance on the Coding subtest ($p<0.001$), but not with the other cognitive measures (data not shown).

Global cognition

In secondary analyses, participants were stratified into two groups according to their 3MSE scores (Table 3). For participants scoring above the median, the associations noted above did not hold. For participants scoring below the median, a positive association was again present between the Coding subtest and all volume measures, and between the 3MSE and all hippocampal volume measures. Hippocampal volume was further positively associated with all CVLT-II SF measures, including delayed recall.

DISCUSSION

This study takes the first step toward describing the relationships among aging, cognition, and brain volumes in American Indians, an underserved and understudied population. Our analyses were based on the largest longitudinal cohort of elderly American Indians ever assembled, and our findings demonstrate an association in this population between common cognitive performance measures and global as well as regional brain volumes. Within the full study sample, all volumes (total brain and total, left, and right hippocampal) were associated with processing speed. Total brain volume was positively associated with verbal learning, but not with verbal recall. Conversely, left hippocampal volume was associated with both verbal learning and recall, as well as with performance on a global cognitive measure (3MSE). Notably, the addition of *APOE* ε4 status to our analytic model did not substantially change our results. When findings were examined separately in participants with higher and lower 3MSE scores, all results were enhanced in the lower-performing group, and absent in the higher-performing group.

Reductions in whole brain volume occur in normal aging, beginning in late adolescence and hastening in older age.[18] Brain atrophy typically precedes the onset of AD,[19] and is also independently associated with other factors, such as depression, type 2 diabetes, and hypertension.[20] In AD, a larger whole brain volume, in conjunction with lifestyle factors, might confer protection against disease progression. For example, in a sample of older adults with high CSF concentrations of tau and phosphorylated tau who were cognitively normal at baseline, both whole brain volume and education moderated the time to onset of clinically important cognitive impairment.[21] With regard to specific cognitive abilities, whole brain volume has been found to be positively associated with global cognition and non-memory measures, and particularly with measures of processing speed.[22,23]

Our results demonstrate an association between smaller total brain volume and reductions in learning and processing speed, but not in declarative recall. Reduced processing speed is considered a sensitive yet nonspecific proxy for accelerated brain aging.[23] The consistent association in our sample between reductions in all volumetric measurements of the brain and slower processing speed suggests that declines in this domain warrant further investigation of cognitive risk factors, along with appropriate clinical treatment, as needed. Nevertheless, regional volumetric analyses may provide greater specificity than measures of whole brain volumes in detecting neuropathologic changes related to AD.

In the subset of participants with data on hippocampal volume, poor performance on the measure for recall of verbal information was associated with smaller left hippocampal volumes, but not with reductions in total brain volume. This finding is consistent with current models of hippocampal function, in which the hippocampus plays a prominent role in memory storage and retrieval. Decline in declarative memory is a cardinal feature of typical AD, and studies have repeatedly demonstrated that hippocampal size is associated with declarative memory, and that a decline in hippocampal volume predicts a decline in memory.[24,25] Reductions in the volume of the left hippocampus might precede reductions in the right hippocampus, and therefore might herald the onset of clinical AD dementia.[5] Although the hippocampus is notably susceptible to pathological insults, injuries associated

with abnormal $A\beta_{42}$ accumulation could be especially important for memory in the context of AD. For example, one study found an association between hippocampal volume and memory performance among participants who were amyloid-positive on a PET scan using Pittsburgh compound B (PiB+), but not among participants whose scans were amyloid negative (PiB−).[26] Others have demonstrated that reductions in CSF $A\beta_{42}$ are associated with smaller hippocampal volumes and reduced episodic memory.[27]

Given the associations observed in other studies among $A\beta_{42}$ accumulation, hippocampal atrophy, and reduced memory performance, we wanted to know whether the association between cognitive performance and volumetric measurements in our study cohort differed by degree of cognitive impairment. Some studies have reported a link between cognitive test performance and hippocampal volumes in non-demented older adults,[28,29] but this association might be more prominent in elders with clinical manifestations of disease.[30] One study found an association between left hippocampal volumes and reductions in verbal recall in a sample with AD, as well as in a sample with amnestic mild cognitive impairment, whereas right hippocampal volumes were associated with verbal recall only in the AD sample. No correlations were observed between left or right hippocampal volumes and memory indices, either at baseline or after two years of follow-up, in participants who remained cognitively normal.[31] Furthermore, some elders might maintain a high level of cognitive function for several years despite the presence of hippocampal atrophy, possibly because of cognitive reserve.[18,32] Unfortunately, we had no detailed information on histories of cognitive symptoms or performance of activities of daily living among our participants, nor are appropriate normative data available to determine normal vs. impaired cognition in American Indians. As a result, we could not clinically characterize our sample in terms of cognitive diagnosis. Therefore, in secondary analyses, we used a median split to divide the group into high and low global functioning, as measured by the 3MSE. We found that our results were driven primarily by participants with lower levels of global cognitive function, and that associations between hippocampal volume and recall measures were much more pronounced in this group. Although this result could be attributed to the smaller range of scores in the higher-performing group, it might also reflect findings that hippocampal atrophy tracks more closely with cognition as cognitive impairment increases. However, the extent of AD pathology in our study sample is unknown, and we could not assign clinical diagnostic categories. Therefore, future research should use a longitudinal design that incorporates careful diagnostic evaluation of American Indian elders in order to determine whether the association between brain volume and cognitive test performance in this population correlates with diagnostic categories.

Of note, the addition of *APOE* ε4 status to the model did not appreciably change our results. Furthermore, despite findings in predominantly White samples that *APOE* ε4 status is typically correlated with brain volume or episodic memory,[33] we did not observe such a correlation in our sample. Nevertheless, a small but significant negative association was present between *APOE* ε4 status and processing speed. The presence of an *APOE* ε4 allele is a well-established risk factor for late-onset AD in predominantly non-Hispanic White populations, but less is known about dementia risk in non-White populations. Among Choctaw Indians, studies have reported that the incidence of the *APOE* ε4 allele in elders with clinically diagnosed AD is significantly lower than in Whites, while *APOE* ε4 is

associated with AD diagnosis only in elders with a relatively low percentage of Choctaw ancestry.[34,35] However, these results were based on small samples, and other studies have shown that genotype frequencies in American Indians are similar to those in Whites.[36] More recent research has reported a higher frequency of *APOE* ε2 (a possible protective factor against late-onset AD) in a larger group of American Indians.[37] The relevance of *APOE* to the development of AD in American Indians remains uncertain, warranting further, detailed study of the genetic mechanisms of AD risk in this population.

The strong association between vascular risk factors and dementia reported in American Indians might indicate that vascular risk outweighs genetic risk for late-onset AD, or that the negative effects of vascular risk might precede the effects of other risk factors, such as the *APOE* ε4 allele. Indeed, such inference is supported by recent evidence that rates of early-onset AD in American Indians are double those in Whites.[7,37,38] In particular, vascular risk factors are substantially overrepresented in American Indians.[6] As an example, 80% of our study sample had hypertension and nearly 50% had diabetes. Vascular comorbidity might thus represent a mediating factor for AD, such that AD progresses more rapidly in the presence of vascular pathology.[39] Both animal models and findings in humans suggest that treatment of vascular risk factors and other comorbidities can modify hippocampal atrophy and reduce AD risk.[8,40] Treatment of vascular risk factors might therefore represent an important point of intervention. Notably, the present study could not determine the extent to which pathology leading to smaller brain volumes was related to AD or to vascular pathology. Thus, future studies are needed to determine the extent to which true AD pathology occurs among American Indian elders.

This study has certain limitations. First, participants lacked cognitive diagnoses, constraining our ability to understand the role of disease stage in the relationship between hippocampal size and cognition. Second, MRI scans were performed at multiple sites, and comparisons between scanners introduced noise in our analyses that might have obscured results. To mitigate this factor, analyses included study site as a covariate. Third, rates of movement artifact and poor imaging resulted in differential sample sizes for participants with data on total brain volume versus those with data on hippocampal volume. Nevertheless, the demographic and clinical differences between these two subgroups were not substantial. Fourth, cognitive testing in our sample was limited, omitting visual memory, language, spatial abilities, and aspects of attention and executive function. Finally, in unpublished work, we have found that normative data on the U.S. all-races population is inappropriate for use with elderly American Indians, as it might overestimate the degree of cognitive impairment in this population. This limitation restricted our ability to describe the study sample in terms of true cognitive deficit and prevented us from evaluating the implications of cognitive data. Despite these limitations, the present study is unique in terms of sample size and scope of data collection, and its findings can guide both ongoing and future efforts to better describe this underserved population.

Our results are based on the largest sample of elderly American Indians ever assembled for collection of data on global and regional brain volumes and cognitive function. Vascular risk factors were highly prevalent among study participants. Analyses demonstrated a strong association between measures of brain volume and measures of processing speed,

independent of age and other potential confounders. We also report an association between hippocampal volumes and verbal recall, while *APOE* ε4 status apparently had little impact on cognitive performance. These findings raise questions about the relative strength of the associations linking smaller brain volumes with vascular versus AD pathology. Future longitudinal research on the progression of atrophy and cognitive decline among clinically well-characterized American Indian elders will significantly enhance our understanding of the relationships linking global and regional brain volumes with cognition, genetics, and vascular risk factors in this population.

Acknowledgments

Sources of support: This work was supported by the National Heart, Lung, and Blood Institute (HL093086), the National Institute on Aging (P50AG005136), and the National Institute of Neurological Disorders and Stroke (P50NS062684).

This work was supported by the National Heart, Lung, and Blood Institute (HL093086), the National Institute on Aging (P50AG005136), and the National Institute of Neurological Disorders and Stroke (P50NS062684). We sincerely thank all study participants for their important contributions. We also acknowledge editing assistance from Raymond M. Harris, PhD. The opinions expressed in this paper are those of the authors and do not necessarily reflect the views of the IHS.

References

1. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & dementia: the journal of the Alzheimer's Association. May; 2011 7(3):280–292.
2. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & dementia: the journal of the Alzheimer's Association. May; 2011 7(3):263–269.
3. Toledo JB, Weiner MW, Wolk DA, et al. Neuronal injury biomarkers and prognosis in ADNI subjects with normal cognition. Acta Neuropathol Commun. 2014; 2:26. [PubMed: 24602322]
4. Risacher SL, Saykin AJ, West JD, et al. Baseline MRI predictors of conversion from MCI to probable AD in the ADNI cohort. Current Alzheimer research. Aug; 2009 6(4):347–361. [PubMed: 19689234]
5. Bernard C, Helmer C, Dilharreguy B, et al. Time course of brain volume changes in the preclinical phase of Alzheimer's disease. Alzheimer's & dementia: the journal of the Alzheimer's Association. Mar; 2014 10(2):143–151. e141.
6. Lee ET, Cowan LD, Welty TK, et al. All-cause mortality and cardiovascular disease mortality in three American Indian populations, aged 45–74 years, 1984–1988. The Strong Heart Study. Am J Epidemiol. Jun 1; 1998 147(11):995–1008. [PubMed: 9620042]
7. Panegyres PK, Chen HY. Coalition against Major D. Early-onset Alzheimer's disease: a global cross-sectional analysis. European journal of neurology. Sep; 2014 21(9):1149–1154. e1164–1145. [PubMed: 24780092]
8. Burns JM, Cronk BB, Anderson HS, et al. Cardiorespiratory fitness and brain atrophy in early Alzheimer disease. Neurology. Jul 15; 2008 71(3):210–216. [PubMed: 18625967]
9. Yang X, Tan MZ, Qiu A. CSF and brain structural imaging markers of the Alzheimer's pathological cascade. PloS one. 2012; 7(12):e47406. [PubMed: 23284610]
10. Lee ET, Welty TK, Fabsitz R, et al. The Strong Heart Study. A study of cardiovascular disease in American Indians: design and methods. Am J Epidemiol. Dec; 1990 132(6):1141–1155. [PubMed: 2260546]
11. Suchy-Dicey AM, Shibata D, Best LG, et al. Cranial Magnetic Resonance Imaging in Elderly American Indians: Design, Methods, and Implementation of the Cerebrovascular Disease and Its

Consequences in American Indians Study. Neuroepidemiology. Sep 8; 2016 47(2):67–75. [PubMed: 27603047]

12. North KE, Goring HH, Cole SA, et al. Linkage analysis of LDL cholesterol in American Indian populations: the Strong Heart Family Study. Journal of lipid research. Jan; 2006 47(1):59–66. [PubMed: 16264198]
13. Buckner RL, Head D, Parker J, et al. A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: reliability and validation against manual measurement of total intracranial volume. NeuroImage. Oct; 2004 23(2):724–738. [PubMed: 15488422]
14. Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. The Journal of clinical psychiatry. Aug; 1987 48(8):314–318. [PubMed: 3611032]
15. Delis, DC., Kramer, JH., Kaplan, E., Ober, BA. California Verbal Learning Test - Second Edition. San Antonio, TX: Pearson; 2000.
16. Wechsler, D. Wechsler Adult Intelligence Scale - Fourth Edition. San Antonio, TX: Pearson; 2008.
17. Spreen, O., Strauss, EA. A Compendium of Neuropsychological Tests. NY: Oxford University Press; 1991.
18. Fotenos AF, Mintun MA, Snyder AZ, Morris JC, Buckner RL. Brain volume decline in aging: evidence for a relation between socioeconomic status, preclinical Alzheimer disease, and reserve. Archives of neurology. Jan; 2008 65(1):113–120. [PubMed: 18195148]
19. Fotenos AF, Snyder AZ, Girton LE, Morris JC, Buckner RL. Normative estimates of cross-sectional and longitudinal brain volume decline in aging and AD. Neurology. Mar 22; 2005 64(6): 1032–1039. [PubMed: 15781822]
20. Akinyemi RO, Mukaetova-Ladinska EB, Attems J, Ihara M, Kalaria RN. Vascular risk factors and neurodegeneration in ageing related dementias: Alzheimer's disease and vascular dementia. Current Alzheimer research. Jul; 2013 10(6):642–653. [PubMed: 23627757]
21. Roe CM, Fagan AM, Grant EA, et al. Cerebrospinal fluid biomarkers, education, brain volume, and future cognition. Archives of neurology. Sep; 2011 68(9):1145–1151. [PubMed: 21911695]
22. MacLullich AM, Ferguson KJ, Deary IJ, Seckl JR, Starr JM, Wardlaw JM. Intracranial capacity and brain volumes are associated with cognition in healthy elderly men. Neurology. Jul 23; 2002 59(2):169–174. [PubMed: 12136052]
23. Rabbitt P, Scott M, Thacker N, et al. Losses in gross brain volume and cerebral blood flow account for age-related differences in speed but not in fluid intelligence. Neuropsychology. Sep; 2006 20(5):549–557. [PubMed: 16938017]
24. Vyhnalek M, Nikolai T, Andel R, et al. Neuropsychological correlates of hippocampal atrophy in memory testing in nondemented older adults. Journal of Alzheimer's disease: JAD. 2014; 42(Suppl 3):S81–90. [PubMed: 24670399]
25. Wang PN, Liu HC, Lirng JF, Lin KN, Wu ZA. Accelerated hippocampal atrophy rates in stable and progressive amnestic mild cognitive impairment. Psychiatry research. Mar 31; 2009 171(3):221–231. [PubMed: 19217759]
26. Oh H, Madison C, Villeneuve S, Markley C, Jagust WJ. Association of gray matter atrophy with age, beta-amyloid, and cognition in aging. Cerebral cortex. Jun; 2014 24(6):1609–1618. [PubMed: 23389995]
27. Wang L, Benzinger TL, Hassenstab J, et al. Spatially distinct atrophy is linked to beta-amyloid and tau in preclinical Alzheimer disease. Neurology. Mar 24; 2015 84(12):1254–1260. [PubMed: 25716355]
28. Mortimer JA, Gosche KM, Riley KP, Markesbery WR, Snowdon DA. Delayed recall, hippocampal volume and Alzheimer neuropathology: findings from the Nun Study. Neurology. Feb 10; 2004 62(3):428–432. [PubMed: 14872025]
29. Zimmerman ME, Pan JW, Hetherington HP, et al. Hippocampal neurochemistry, neuromorphometry, and verbal memory in nondemented older adults. Neurology. Apr 29; 2008 70(18):1594–1600. [PubMed: 18367703]
30. Kohler S, Black SE, Sinden M, et al. Memory impairments associated with hippocampal versus parahippocampal-gyrus atrophy: an MR volumetry study in Alzheimer's disease. Neuropsychologia. Sep; 1998 36(9):901–914. [PubMed: 9740363]

31. Peng GP, Feng Z, He FP, et al. Correlation of hippocampal volume and cognitive performances in patients with either mild cognitive impairment or Alzheimer's disease. CNS neuroscience & therapeutics. Jan; 2015 21(1):15–22. [PubMed: 25146658]
32. Sole-Padulles C, Bartres-Faz D, Junque C, et al. Brain structure and function related to cognitive reserve variables in normal aging, mild cognitive impairment and Alzheimer's disease. Neurobiology of aging. Jul; 2009 30(7):1114–1124. [PubMed: 18053618]
33. Liu Y, Yu JT, Wang HF, et al. APOE genotype and neuroimaging markers of Alzheimer's disease: systematic review and meta-analysis. Journal of neurology, neurosurgery, and psychiatry. Feb; 2015 86(2):127–134.
34. Henderson JN, Crook R, Crook J, et al. Apolipoprotein E4 and tau allele frequencies among Choctaw Indians. Neuroscience letters. May 10; 2002 324(1):77–79. [PubMed: 11983299]
35. Weiner MF, Hynan LS, Rossetti H, et al. The relationship of cardiovascular risk factors to Alzheimer disease in Choctaw Indians. The American journal of geriatric psychiatry: official journal of the American Association for Geriatric Psychiatry. May; 2011 19(5):423–429. [PubMed: 20808139]
36. Rosenberg RN, Richter RW, Risser RC, et al. Genetic factors for the development of Alzheimer disease in the Cherokee Indian. Archives of neurology. Oct; 1996 53(10):997–1000. [PubMed: 8859062]
37. Chen HY, Panegyres PK. The Role of Ethnicity in Alzheimer's Disease: Findings From The C-PATH Online Data Repository. Journal of Alzheimer's disease: JAD. Feb 6; 2016 51(2):515–523. [PubMed: 26890783]
38. Jacklin KM, Walker JD, Shawande M. The emergence of dementia as a health concern among First Nations populations in Alberta, Canada. Canadian journal of public health = Revue canadienne de sante publique. Jan-Feb;2013 104(1):e39–44.
39. Villeneuve S, Reed BR, Madison CM, et al. Vascular risk and Abeta interact to reduce cortical thickness in AD vulnerable brain regions. Neurology. Jul 1; 2014 83(1):40–47. [PubMed: 24907234]
40. Zhu N, Jacobs DR Jr, Schreiner PJ, et al. Cardiorespiratory fitness and brain volume and white matter integrity: The CARDIA Study. Neurology. Jun 9; 2015 84(23):2347–2353. [PubMed: 25957331]

Table 1

Characteristics of older American Indians in the Cerebrovascular Disease and its Consequences in American Indians (CDCAI) study

	Total brain volume sample (N = 621)	Hippocampal volume sample (N = 696)
Demographic Information		
Study site n (%)		
Northern plains	254 (40.9)	311 (44.7)
Southern plains	281 (45.2)	297 (42.7)
Southwest	86 (13.8)	88 (12.6)
Age mean (sd)	72.8 (5.7)	72.8 (5.7)
Sex n (%)		
Female	425 (68.4)	469 (67.4)
Male	196 (31.6)	227 (32.6)
Education n (%)		
Up to/any high school	107 (17.2)	128 (18.4)
High school graduate	159 (25.6)	182 (26.1)
Any college	255 (41.1)	280 (40.2)
College graduate	100 (16.1)	106 (15.2)
Marital status n (%)		
Single	32 (5.2)	36 (5.2)
Married/partner	245 (39. 5)	267 (38.4)
Divorced/separated/widowed	344 (55.4)	393 (56.5)
American Indian language proficiency n (%)		
Not at all	217 (34.9)	227 (32.6)
A little	172 (27.7)	198 (28.4)
Moderately	84 (13.5)	92 (13.2)
Very well	148 (23.8)	179 (25.7)
Any *APOE* ε4 allele n (%)	145 (23.3)	154 (22.1)
Vascular risk factors		
Hypertension n (%)	498 (80.2)	558 (80.2)
Diabetes n (%)	292 (47.0)	335 (48.1)
Dyslipidemia n (%)	259 (41.7)	283 (40.7)
Cranial MRI Measurements		
Left hippocampal volume, mm^3 *mean (sd)*	3235.5 (541.6)	3218.8 (564.4)
Right hippocampal volume, mm^3 *mean (sd)*	3399.7 (527.5)	3387.0 (528.8)
Total hippocampal volume, mm^3 *mean (sd)*	6641.1 (979.8)	6605.8 (1019.5)
Brain volume, mm^3 *mean (sd)*	939234.5 (101132.6)	939211.2 (101291.4)
Intracranial volume, mm^3 *mean (sd)*	1213148.5 (134890.8)	1215370.5 (136616.1)
Cognitive Measurements		
3MSE *mean (sd)*	89.1 (8.6)	88.9 (8.7)
CVLT-II SF total learning *mean (sd)*	22.6 (5.2)	22.6 (5.2)
CVLT-II SF short-delay free recall *mean (sd)*	5.9 (2.0)	5.9 (2.0)

	Total brain volume sample (N = 621)	Hippocampal volume sample (N = 696)
CVLT-II SF long-delay free recall *mean (sd)*	5.5 (2.2)	5.5 (2.2)
WAIS-IV Coding *mean (sd)*	45.4 (14.6)	45.1 (15.1)
Verbal fluency *mean (sd)*	25.0 (11.4)	24.8 (11.4)

Abbreviations: 3MSE = Modified Mini Mental State Examination; *APOE* = apolipoprotein E; CVLT-II SF = California Verbal Learning Test-2nd edition, Short Form; sd = standard deviation; WAIS-IV = Wechsler Adult Intelligence Scale, 4th edition.

Table 2

Association between MRI volumetric measures and performance on cognitive tests in older American Indians

	Regression model			
	n	**beta**	**Confidence interval**	**p-value**
Total brain volume				
3MSE	595	0.04	(−0.02, 0.10)	0.253
CVLT-II SF total learning	613	0.08	(0.01, 0.15)	**0.022**
CVLT-II SF short-delay free recall	613	0.18	(−0.01, 0.37)	0.069
CVLT-II SF long-delay free recall	613	0.09	(−0.08, 0.26)	0.280
WAIS-IV Coding	621	0.04	(0.01, 0.07)	**0.007**
Phonemic verbal fluency	621	0.03	(−0.00, 0.07)	0.087
Hippocampal volume				
3MSE	666	1.37	(0.40, 2.34)	**0.006**
CVLT-II SF total learning	686	1.20	(−0.12, 2.51)	0.076
CVLT-II SF short-delay free recall	686	2.80	(−0.25, 5.86)	0.072
CVLT-II SF long-delay free recall	686	2.88	(−0.02, 5.77)	0.051
WAIS-IV Coding	696	0.76	(0.24, 1.28)	**0.004**
Phonemic verbal fluency	696	0.12	(−0.50, 0.74)	0.713
Left hippocampal volume				
3MSE	667	0.84	(0.28, 1.40)	**0.003**
CVLT-II SF total learning	687	0.77	(0.04, 1.49)	**0.039**
CVLT-II SF short-delay free recall	687	1.97	(0.16, 3.77)	**0.032**
CVLT-II SF long-delay free recall	687	1.58	(−0.08, 3.24)	0.063
WAIS-IV Coding	697	0.39	(0.11, 0.68)	**0.007**
Phonemic verbal fluency	697	0.17	(−0.17, 0.51)	0.338
Right hippocampal volume				
3MSE	667	0.52	(−0.00, 1.05)	**0.050**
CVLT-II SF total learning	687	0.58	(−0.18, 1.34)	0.132
CVLT-II SF short-delay free recall	687	1.18	(−0.51, 2.87)	0.171
CVLT-II SF long-delay free recall	687	1.55	(−0.01, 3.12)	0.052
WAIS-IV Coding	697	0.43	(0.13, 0.73)	**0.004**
Phonemic verbal fluency	697	−0.00	(−0.34, 0.33)	0.977

All models are adjusted for age, sex, study site, language, marital status, education, and comorbid diabetes, hypertension, and hypercholesterolemia. Total, left, and right hippocampal volumes are defined as 100,000 times the fraction of volume to intracranial volume. Brain volume is defined as a fraction of intracranial volume.

Abbreviations: 3MSE = Modified Mini Mental State Examination; CVLT-II SF = California Verbal Learning Test-2nd edition, Short Form; MRI = magnetic resonance imaging; WAIS-IV = Wechsler Adult Intelligence Scale, 4th edition.

Table 3

Association between MRI volumetric measures and performance on cognitive tests in older American Indians, stratified by median score on 3MSE

	3MSE ≤ 90				3MSE > 90			
	n	**Beta**	**Confidence interval**	**p-value**	**n**	**Beta**	**Confidence interval**	**p-value**
Total brain volume								
3MSE	274	0.02	(−0.07, 0.10)	0.696	321	−0.16	(−0.35, 0.02)	0.086
CVLT-II SF total learning	269	0.09	(−0.02, 0.20)	0.129	318	0.05	(−0.04, 0.14)	0.310
CVLT-II SF short-delay free recall	269	0.13	(−0.18, 0.45)	0.406	318	0.12	(−0.11, 0.36)	0.309
CVLT-II SF long-delay free recall	269	0.15	(−0.11, 0.41)	0.260	318	−0.06	(−0.28, 0.15)	0.562
WAIS-IV Coding	274	0.07	(0.02, 0.11)	**0.003**	321	0.01	(−0.03, 0.05)	0.649
Phonemic verbal fluency	274	0.05	(−0.01, 0.12)	0.105	321	−0.01	(−0.05, 0.04)	0.787
Hippocampal volume								
3MSE	313	1.95	(0.60, 3.29)	**0.005**	353	−1.42	(−4.48, 1.65)	0.365
CVLT-II SF total learning	308	2.06	(0.14, 3.98)	**0.035**	348	0.19	(−1.65, 2.03)	0.840
CVLT-II SF short-delay free recall	308	5.52	(1.00, 10.03)	**0.017**	348	0.56	(−3.89, 5.02)	0.804
CVLT-II SF long-delay free recall	308	6.72	(2.40, 11.04)	**0.002**	348	−1.38	(−5.37, 2.60)	0.496
WAIS-IV Coding	313	1.50	(0.70, 2.29)	**<0.001**	353	−0.13	(−0.91, 0.64)	0.732
Phonemic verbal fluency	313	0.89	(−0.15, 1.93)	0.093	353	−0.92	(−1.66, −0.18)	**0.015**
Left hippocampal volume								
3MSE	313	1.21	(0.39, 2.03)	**0.004**	354	−0.51	(−2.23, 1.20)	0.558
CVLT-II SF total learning	308	1.01	(−0.09, 2.10)	**0.071**	349	0.49	(−0.50, 1.47)	0.335
CVLT-II SF short-delay free recall	308	3.36	(0.60, 6.13)	**0.017**	349	1.09	(−1.38, 3.56)	0.388
CVLT-II SF long-delay free recall	308	3.27	(0.71, 5.83)	**0.012**	349	−0.10	(−2.32, 2.13)	0.933
WAIS-IV Coding	313	0.80	(0.36, 1.24)	**<0.001**	354	−0.10	(−0.52, 0.32)	0.634
Phonemic verbal fluency	313	0.54	(−0.04, 1.11)	0.067	354	−0.33	(−0.75, 0.09)	0.127
Right hippocampal volume								
3MSE	313	0.73	(0.04, 1.43)	**0.038**	354	−0.50	(−2.22, 1.23)	0.575
CVLT-II SF total learning	308	1.05	(0.05, 2.06)	**0.040**	349	0.08	(−1.09, 1.26)	0.890
CVLT-II SF short-delay free recall	308	2.15	(−0.09, 4.40)	0.060	349	0.46	(−2.47, 3.40)	0.758
CVLT-II SF long-delay free recall	308	3.45	(1.29, 5.61)	**0.002**	349	−0.61	(−2.99, 1.78)	0.619
WAIS-IV Coding	313	0.70	(0.28, 1.11)	**0.001**	354	0.16	(−0.34, 0.67)	0.529

	3MSE ≤ 90				3MSE > 90			
	n	**Beta**	**Confidence interval**	**p-value**	**n**	**Beta**	**Confidence interval**	**p-value**
Phonemic verbal fluency	313	0.35	(−0.20, 0.91)	0.215	354	−0.49	(−0.90, −0.07)	**0.022**

All stratified models are adjusted for age, sex, study site, language, marital status, education, and comorbid diabetes, hypertension, and hypercholesterolemia. Total, left, and right hippocampal volumes are defined as 100,000 times the fraction of volume to intracranial volume. Brain volume is defined as a fraction of intracranial volume.

Abbreviations: 3MSE = Modified Mini Mental State Examination; CVLT-II SF = California Verbal Learning Test-2nd edition, Short Form; MRI = magnetic resonance imaging; WAIS-IV = Wechsler Adult Intelligence Scale, 4th edition.