Educational and Clinical Associations With Longitudinal Cognitive Function and Brain Imaging in American Indians

The Strong Heart Study

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Abstract

Background and Objectives

Little is known about incidence of vascular and Alzheimer dementias in American Indians.

Methods

We conducted a large, heterogeneous, population-based, longitudinal cohort study of brain aging in community-dwelling American Indians aged 64–95 years from 11 tribes across 3 states, with neurologic examinations, 1.5T MRI, and extensive cognitive testing. Visit 1 in 2010–2013 (n = 817) and visit 2 in 2017–2019 (n = 403) included all willing, surviving participants. Standardized cognitive tests at both visits included Modified Mini-Mental Status Examination (MMSE), Wechsler Adult Intelligence Scale digit symbol coding (WAIS), Controlled Oral Word Association (COWA), and California Verbal Learning Test short form (CVLT). Test materials added at follow-up included Wide Range Achievement (reading) Test (WRAT) and National Alzheimer Co-ordinating Center Uniform Data Set cognitive battery (v3 form C2), including Montreal Cognitive Assessment (MoCA). MRI neuroradiologists coded infarcts, hemorrhages, white matter hyper-intensities, sulcal atrophy, and ventricle enlargement.

Results

The mean time between examinations was 6.7 years (SD 1.1, range 3.8–9.1 years). Years of formal education had modest correlation with WRAT reading score ($r = 0.45$). Prevalence and incidence (respectively) of infarcts were 32% and 12.8/1,000 person-years (PYs) hemorrhages 6% and 4.4/1000 PY worsening sulci 74% and 19.0/1000 PY worsening ventricle 79% and 30.1/1000 PY worsening leukoaraiosis 44% and 26.1/1000 PY. Linear losses per year in cognitive scores were 0.6% MMSE, 1.2% WAIS, 0.6% COWA, and 2.2% CVLT. The mean MoCA scores were 18.9 (SD 4.3).

Discussion

These are the first data on longitudinal cognitive and imaging changes in American Indians and first reports of Alzheimer disease–related features. The mean scores in MoCA were similar or lower than standard cutoffs used to diagnose dementia in other racial/ethnic groups, suggesting that standardized cognitive tests may not perform well in this population. Test validation, adaptation, and score adjustment are warranted. Years of education were a poor proxy for premorbid function, suggesting novel methods for cognitive score contextualization is also needed in this population. Evaluation of selective survival suggests attrition from death, and frailty should be accounted for in causal analyses. Overall, these data represent a unique opportunity to examine neurology topics of critical importance to an understudied population.

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Glossary

3MSE = Modified Mini-Mental Status Examination; **AD** = Alzheimer disease; **ADRD** = AD and related dementias; **CDCAI** = Cerebrovascular Disease and its Consequences in American Indians; **CES-D** = Centers for Epidemiologic Studies Depression; **CKD** = chronic kidney disease; **COWA** = Controlled Oral Word Association; **IADL** = Instrumental Activities of Daily Living; **IHS** = Indian Health Service; **MCI** = mild cognitive impairment; **MoCA** = Montreal Cognitive Assessment; **NACC UDS** = National Alzheimer Coordinating Center Uniform Data Set; **NHW** = non-Hispanic White; **SHS** = Strong Heart Study; **VBI** = vascular brain injury; **WAIS** = Wechsler Adult Intelligence Scale; **WRAT** = Wide Range Achievement Test.

Alzheimer disease (AD) is a growing health concern for all older adults, with advancing age the strongest risk factor.[1] Important risk factors for AD include diabetes, social isolation, depression, physical inactivity, obesity, hypertension, traumatic brain injury, and hearing loss,[2] most of which disproportionately affect American Indians.[3,4] Vascular brain injury (VBI)—which includes clinical and subclinical changes detectable by imaging—can accelerate neurodegeneration[5,6] and also unduly affects American Indians.[7,8] Although not defined as clinical syndromes,[9] AD and VBI are leading global causes of cognitive impairment and dementia[10] and frequently present in combination.[11] The U.S. Census Bureau projects the number of American Indians older than 65 years to grow 4-fold over the next 40 years,[12] putting large numbers of people at higher risk, yet little is known about AD and related dementias (ADRDs) in this understudied population.

ADRD studies that include American Indians have thus far been limited by small numbers[13]; nonspecific, indirect, or unvalidated cognitive assessment tools[14,15]; or nonrepresentative sampling.[16,17] In addition, disparities in health, health care, and health care–seeking behaviors have hindered direct comparability among racial/ethnic populations.[18] Furthermore, fundamental cultural, linguistic, educational, and socioeconomic differences influence standardized cognitive assessment, with few standardized tests psychometrically evaluated in American Indians.[19,20] Although some disparities may reflect true population differences, observed contrasts in standardized cognitive testing and dementia research more likely reflect a deeply embedded history of systemic, structural, institutional racism and their long-term consequences. Finally, American Indians—although frequently described as a singular group and often in combination with Alaska Native and other US Indigenous peoples—are not homogeneous with respect to history, culture, language, education, socioeconomics, geographic and local environment, or lived experience rather, and more than 570 federally recognized independent sovereign nations comprise a highly heterogeneous subpopulation, posing unique challenges for public health and epidemiology.

To address these research gaps, we conducted a large, heterogeneous, longitudinal cohort study of vascular and AD-related conditions, cognition, and risk in community-dwelling American Indians over nearly 10 years. In 2010 to 2013, the Cerebrovascular Disease and its Consequences in American Indians (CDCAI) study, an ancillary cohort within the Strong Heart Study, first conducted clinical examination, neuropsychological testing, and cranial MRI in participants aged 64–95 years from 11 tribes across 3 states[21]; in 2017–2019, CDCAI re-examined all available participants to assess clinical, cognitive, and imaging changes over time and new measures related to ADRD. Here, we present this longitudinal, population-based study, with preliminary descriptive analyses of longitudinal cognitive and imaging changes among older American Indians.

Methods

Setting

The CDCAI is an ancillary cohort study within the parent Strong Heart Study (SHS). The latter is a 30-year longitudinal cohort that in 1989–1991 recruited 67% of American Indians aged 35–75 years from 13 tribes and communities across the US Northern Plains, Central Plains, and Southwest. The participants of this initial, "parent" cohort were defined as American Indian if they claimed ancestry with any of the original peoples of North, Central, and South America and maintained tribal affiliation or community attachment with any of the original partnering tribes and communities.

As previously described in detail,[21] the first CDCAI study visit (visit 1, 2010–2013) invited all surviving participants from the original SHS cohort. After that visit was completed, 1 tribal community withdrew from all research and has subsequently been removed from data sets and contact rosters. The second CDCAI study visit (visit 2, 2017–2019) included all available, willing participants from CDCAI visit 1. A full description of visit 2 recruitment and examination protocols, including CONSORT diagram, is presented in Supplemental Materials (eFigure 1, links.lww.com/WNL/C410).

Standard Protocol Approvals, Registrations, and Participant Consents

All participating institutional, Indian Health Service (IHS), and tribal review boards approved the study protocols: University of Washington, Oklahoma University Health Sciences Center, Oklahoma City Area IHS, Southern Plains Tribal Health Board (formerly Oklahoma City Area Intertribal Health Board), Great Plains IHS, Cheyenne River Tribe, Oglala Sioux Tribe,

MedStar Health Research Institute, Phoenix Area IHS, and Salt River Pima Maricopa Tribes. None of the study procedures comprised experimental or clinical trials research. All participants provided written informed consent.

MRI Protocols

Collection procedures and protocols for 1.5T MRI have been previously published and are also presented in the Supplement (eMethods, links.lww.com/WNL/C410).[22] The same scanners were used at both visits to collect 6 image sequences in contiguous slices: sagittal T1-weighted localizer coregistered 5-mm axial T1 5-mm axial T2 and T2* susceptibility-weighted images in the anterior commissure/posterior commissure plane 3-mm axial fluid-attenuated inversion recovery and 1.5-mm sagittal T1-weighted volumetric gradient echo. MRI scans were interpreted independently by 2 neuroradiologists blinded to participant data, with adjudication for consensus. Infarcts were defined as lesions ≥3 mm anywhere in the brain with characteristic shape and absence of mass effect. Hemorrhages were defined by the clinical criteria as lesions anywhere in the brain, any size, with hypointensity on gradient echo images. Severity of white matter hyperintensities (WMH; leukoaraiosis), sulcal enlargement, and ventricular dilation were graded on a semiquantitative scale (0–9, with 9 = most severe) based on best visual fit against standard image templates.[23]

Neuropsychological Testing

Trained field staff administered the neuropsychological test battery. Some tests were administered at both visit 1 and visit 2, including Modified Mini-Mental Status Examination (3MSE), a global cognitive screening measure[24]; Wechsler Adult Intelligence Scale Fourth Edition digit symbol coding subtest (WAIS), a measure of visuomotor processing speed and working memory[25]; Controlled Oral Word Association F,A,S Test (COWA), a measure of phonemic fluency and executive function[26]; and California Verbal Learning Test 2nd edition short form (CVLT), assessing learning and memory.[27] The Short Physical Performance Battery (SPPB) measured lower body function by 3 tasks, including chair stand, timed tandem stand, and timed walk.[28]

Cognitive examinations new to visit 2 included the Wide Range Achievement Test version 4 reading test (WRAT),[29] a measure of reading achievement and crystallized function, which may be a sensitive proxy of premorbid function and is not expected to decline or change substantively throughout adulthood[30]; the Functional Activities Questionnaire (FAQ) to assess instrumental Activities of Daily Living (iADL), which represents the capacity of an individual to perform daily tasks of independent living, the loss of which may be indicative of neurodegenerative dementia such as ADRD[31]; and the National Alzheimer Coordinating Center Uniform Data Set (version 3.0, form C2) cognitive test battery (NACC UDS).[32] The NACC UDS included the Montreal Cognitive Assessment (MoCA), a common screening tool covering a broad range of cognitive subdomains of executive function, attention, phonemic and semantic fluency, abstraction, delayed verbal memory, and orientation,[33] as well as other tests from the NACC UDS cognitive battery.

Questionnaire and Examinations

At both visits participants also completed self-reported questionnaires on their neurologic and medical histories, including neurologic symptoms (sudden and temporary loss of speech, loss of vision, double vision, numbness, paralysis, and dizziness), traumatic head injury or concussion with and without loss of consciousness, and prior stroke. The Centers for Epidemiologic Studies Depression (CES-D) Scale assessed symptoms of depression.[34] Participants self-reported age (years); sex (male or female); years of formal education; having smoked more than 100 cigarettes in lifetime (yes or no); alcohol use patterns, including any use in past month (yes or no); bilingual status (self-reported moderate or better ability to speak Native language, in addition to study requirement of English fluency); prior traumatic brain injury both with or without loss of consciousness; and prior stroke. Hypertension was defined based on measured, averaged, seated systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, and/or use of antihypertensive medications; diabetes mellitus by fasting blood glucose ≥126 mg/dL and/or use of antiglycemic medications or insulin; chronic kidney disease (CKD) as estimated glomerular filtration rate <60 mL/minute using the CKD-EPI 2009 equation; and body mass index as weight in kilograms divided by height in meters squared.

Coding

For these analyses, 3MSE was scored as a summary total (range 0–100), WAIS coding test based on correct items (range 0 – indefinite, visit 1 highest score 91), and COWA as combined correct words (range 0-indefinite, visit 1 highest score 66). CVLT was scored using standard software for short and long delay free recall (range of 0–9) as well as other features such as cued recall, recognition and discrimination, and other standard indices. SPPB was scored by capacity to perform the physical tasks, using standard metrics (range 0–12). In new tests, WRAT was scored as correct answers (range 0–60), and MoCA using standard criteria (range 0–30). For all tests, higher scores denote better function. FAQ/IADL was scored using the Likert scale over 10 items (range 0 = never/normal to 3 dependent on others), with higher scores denoting poorer function. CES-D was scored with the Likert scale over 20 items, with 4 reverse coded items (range 0–60).

Statistical Analyses

Participant characteristics were described using cross-tabulation and summary statistics, including count and percent for dichotomous or categorical variables, and mean and SD, median and interquartile range, and full range for some continuous variables. Data descriptions also used graphical representations, including boxplot, histogram, and modified scatterplot with

Table 1 Comparisons of Participant Categorizations Based on Availability to Follow-up in Sociodemographics and Clinical Features Over 2 Examination Visits of the CDCAI Study

	Visit 1 (1-A): deceased/too frail for follow-up 2010–2013 (N = 268)	Visit 1 (1-B): unavailable at follow-up 2010–2013 (N = 71)	Visit 1 (1-C): refused follow-up 2010–2013 (N = 75)	Visit 1 (1-D): enrolled in follow-up 2010–2013 (N = 403)	Visit 2: follow-up examination (2017–2019) (N = 403)	Mean change from visit 1-visit 2 (N = 403)
Age, y: mean (SD)	75.3 (6.6)	73.7 (6.1)	73.5 (5.8)	71.3 (4.7)	78.0 (4.7)	+6.7 (1.1)
Female sex: n (%)	180 (67.2%)	43 (60.6%)	46 (61.3%)	283 (70.2%)	284 (70.5%)	+0.3%
Years of education: mean (SD)	12.0 (2.6)	13.0 (3.3)	12.4 (3.1)	13.0 (2.5)	13.0 (2.5)	—
Ever smoked (100 + cigarettes): n (%)	167 (62.3%)	51 (71.8%)	43 (57.3%)	279 (69.2%)	248 (61.4%)	−7.8%
Used alcohol within 1 month: n (%)	22 (8.2%)	14 (19.7%)	15 (20.0%)	62 (15.4%)	51 (12.7%)	−2.7%
Hypertensive: n (%)	225 (83.9%)	53 (74.7%)	57 (76.0%)	325 (80.7%)	344 (85.2%)	+4.5%
Diabetic: n (%)	156 (58.2%)	32 (45.1%)	39 (52.0%)	176 (43.7%)	216 (53.5%)	+9.8%
CKD: n (%)	101 (37.7%)	15 (21.1%)	15 (20.0%)	87 (21.6%)	205 (50.7%)	+29.1%
BMI, kg/m^2: mean (SD)	30.2 (6.5)	31.0 (6.1)	32.1 (8.0)	32.2 (6.4)	30.4 (6.9)	−1.9 (4.7)
CES-D score: mean (SD)	15.3 (8.5)	14.8 (6.2)	13.8 (7.6)	13.8 (7.2)	15.5 (7.3)	+1.7 (8.7)
Any prior neurologic symptoms: n (%)	108 (40.3%)	25 (35.2%)	32 (42.7%)	179 (44.4%)	206 (51.2%)	+6.8%
Any prior traumatic brain injury: n (%)	90 (33.6%)	311 (43.7%)	21 (28.0%)	130 (32.3%)	101 (25.2%)	−7.0%
Any self-reported prior stroke: n (%)	31 (11.6%)	8 (11.3%)	8 (10.7%)	22 (5.5%)	29 (7.2%)	+1.5%

Abbreviations: BMI = body mass index; CDCAI = Cerebrovascular Disease and its Consequences in American Indians; CES-D = Centers for Epidemiologic Studies Depression scale; CKD = chronic kidney disease.

hexagonal grouping by count for each data point on the z-axis ("hexplot"). Correlation assessment used Pearson (r) or linear model (β) regression coefficients. For incidence calculation, among those with 2 useable MRIs, estimation of person-time at risk was performed based on cumulative time between examinations for each participant and number of new events was calculated based on the presence of an event at visit 2, among those who did not have said event at visit 1. Overall cognition for each participant was estimated based on individual mean of standardized cognitive test scores (Z-score) for all 5 tests/domains (3MSE, WAIS, COWA, CVLT SF, and CVLT LF). Annualized rate of change in cognitive tests was calculated as difference between visit 1 and visit 2, divided by time between visits so that the population was then categorized based on those >1 SD above mean in annualized rate of change (gain function), those who were within 1 SD of the mean (no change; same function), and those who were 1 SD or more below the mean in annualized rate of change (rapid loss of function). Categories were evaluated using descriptive techniques as above, and tests of association with participant characteristics as of visit 1 were assessed using logistic regression with mutual adjustment (age, sex, education, smoking, alcohol, hypertension, diabetes, CKD, and BMI) in base model, as well as models with individual addition of neurologic symptoms, traumatic brain injury, prior stroke, infarcts, hemorrhage, abnormal sulci, abnormal ventricle, abnormal WMH, bilingual status and CES-D score. Analyses were conducted using STATA version 17 (College Station, TX) or R version 4.0.5 (Vienna, Austria).

Data Availability

These data are the intellectual property of the sovereign tribes and communities from whom they were collected and are not directly shareable without the express permission and consent of those entities. Researchers interested in using CDCAI study data may propose secondary analyses using the standard Strong Heart Study (SHS) procedures, per tribal data use agreements. These processes are outlined on the SHS website: strongheartstudy.org.

Results

CDCAI visit 1 (2010–2013) had 86% successful recruitment,[21] with N = 817 available for analysis and follow-up. The time between visit 1 and visit 2 (2017–2019) ranged from 3.8 to 9.1 years, with a mean 6.7 (SD: 1.1). Of the 817 who participated in visit 1, 71 (8.7%) were not available or lost to follow-up and 232 (28.4%) died before they could enroll and/or complete study activities, leaving 515 successfully invited to participate in the follow-up visit 2 examination. Of the 515 recruited, 75 (14.6%) refused, withdrew, or were no shows to their scheduled appointments and 36 (7.0%) were determined by field staff to be unable to either consent or undergo study procedures because of frailty, cognitive status, or similar concerns. Of

Figure 1 Formal vs Achieved Education Among American Indian Elders at CDCAI Visit 2 (2017–2019 Aged Mean 78.1 Years [SD4.7] Range 71–94 Years)
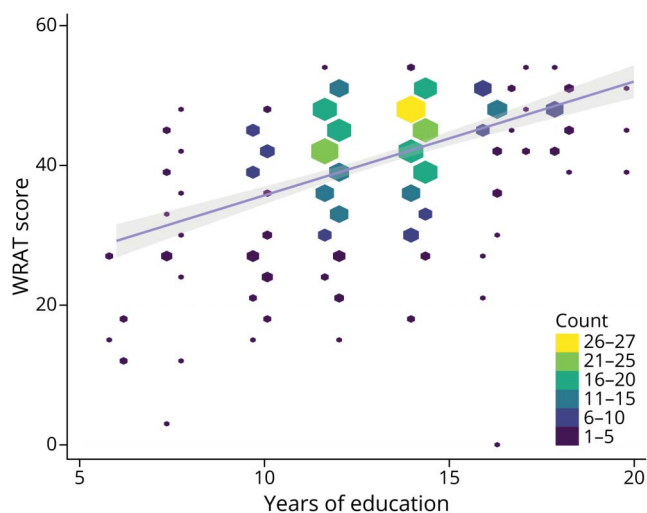
Modified scatterplot (hexplot) of the Wide Range Achievement Test (WRAT) score on y-axis and years of formal education received on x-axis. Count indicated by hexagon groupings, shown using color scale at each data point (z-axis) and by size of hexagon. Fractional linear fit line (lilac) and 95% CI (gray shaded region) multiple polynomial fit line were also assessed, with no marked difference from linear fit. Pearson correlation coefficient for WRAT score with continuous years of education: r = 0.45. Abbreviations: CDCAI = Cerebrovascular Disease and its Consequences in American Indians.

the 586 nondeceased and 515 contacted, 403 (68.8% and 78.2%, respectively) were successfully enrolled (Supplemental Materials, eFigure 1, links.lww.com/WNL/C410). Of the 403 enrolled in visit 2, 335 (83.1%) had complete, useable MRI data, 4 participants did not complete the MRI sequences, 12 MRIs had inadequate image quality, 32 individuals were ineligible for MRI, and 19 refused to undergo an MRI. Of note, 3 of the participants who consented and underwent MRI died before completing other study procedures and are thus included in "deceased" count, although their MRI data are still available for analysis. Further technical details about MRI are included below.

The 414 participants who participated in visit 1 but did not participate in visit 2 were categorized based on reasons for nonparticipation, including death or frailty (N = 268), unavailable (N = 71), or refusal (N = 75). Features associated with selection and survival (Table 1) are presented, with summary visit 1 data for the group with no follow-up data (N = 414), stratified by reason for nonparticipation, summary visit 1 data for those who did later enroll in the follow-up (N = 403), and summary visit 2 data from those at the follow-up (N = 403). Participants who died or became too frail for follow-up (1A) were older and more depressed than those who were unavailable (1B), refused (1C), or did later participate in the follow-up (1D). However, the differences across categories were within 1 SD for all features. No clear pattern was detected among groups or over time comparing visit 1 with visit 2, by sex, years of education, BMI, or smoking. Participants who later died or became too frail (1A) were less likely to be alcohol drinkers than any other group and were also more likely to be hypertensive, diabetic, or have CKD compared with other visit 1 participants (1B, 1C, and 1D). Neurologic symptoms were not different among groups at visit 1 but did increase over time (visit 1 vs visit 2). The history of traumatic brain injury was more common among those not available for follow-up (1B vs 1D) and less likely to be reported at follow-up (visit 1 vs visit 2). Self-reported stroke was higher among participants who did not attend the follow-up (1A, 1B, and 1C) and increased over time (visit 1 vs visit 2). Additional analyses examining completion/noncompletion of MRI did not detect any significant group differences (data not shown).

WRAT reading score mean was 40.7 (SD 9.2, range 0–54). Years of formal education ranged from 6 to 20 at visit 2, with mean > 12 years, although responses were not consistent over time—even among those with repeated visits. Pearson coefficient showed moderate correlation of WRAT reading score with years of formal education ($r = 0.45$). Linear regression with bootstrapped standard errors for Z-score transformed (standardized) WRAT and education variables estimated $\beta = 0.48$ (95% CI, CI: 0.37–0.59). WRAT scores were moderately positively associated with years of education (Figure 1), but with substantial residual

Table 2 Change in Selected MRI Findings Related to Vascular Injury and Atrophy Among American Indian Elders Over 2 CDCAI Examination Visits

	Visit 1 (1-D) 2010–2013 with useable MRI data (N = 389), n (%)	Visit 2 2017–2019 with useable MRI data (N = 335), n (%)	New events: n Cases	Incidence: n Cases/1000 PY
Any Infarcts, n (%)	102 (26.2%)	106 (31.6%)	29	12.8
Hemorrhages, n (%)	12 (3.1%)	19 (5.7%)	10	4.4
Abnormal sulcal grade, n (%)	238 (61.2%)	247 (73.7%)	43	19.0
Abnormal ventricle grade, n (%)	238 (61.2%)	263 (78.5%)	68	30.1
Abnormal WMH grade, n (%)	111 (28.5%)	148 (44.2%)	59	26.1

Abbreviations: CDCAI = Cerebrovascular Disease and its Consequences in American Indians; PY = person-year; WMH =: white matter hyperintensities.
Abnormal grades defined as ≥3.
Total person time at risk: 2,257.4 person-years, among n = 335 with MRI at both time points.

Table 3 Change in Cognitive and Functional Test Scores Among American Indian Elders Over 2 CDCAI Examination Visits

	Visit 1 (1-D) 2010–2013 (N = 403)	Visit 2 2017–2019 (N = 403)	Change from visit 1–visit 2	Annualized rate of change* visit 1–visit 2
3MSE	91.3 (6.7)	87.1 (9.5)	−4.2 (7.1)	−0.6 (1.1)
WAIS Coding	49.2 (13.4)	41.9 (14.1)	−7.4 (9.7)	−1.1 (1.5)
COWA	26.9 (11.1)	24.3 (11.1)	−2.6 (7.5)	−0.4 (1.2)
CVLT short free	6.4 (1.8)	5.4 (2.1)	−1.1 (1.9)	−0.2 (0.3)
CVLT long free	6.0 (2.0)	4.7 (2.4)	−1.4 (2.1)	−0.2 (0.3)
SPPB	6.1 (2.4)	4.5 (2.7)	−1.6 (3.1)	−0.2 (0.5)
Overall cognition	0.3 (0.6)	0.0 (0.7)	−0.3 (0.5)	−0.04 (0.07)

Abbeviations: CDCAI = Cerebrovascular Disease and its Consequences in American Indians; COWA = Controlled Oral Word Association; CVLT = California Verbal Learning Test; 3MSE = Modified Mini-Mental Status Examination; SPPB = Short Physical Performance Battery; WAIS = Wechsler Adult Intelligence Scale. All features provided as mean (SD). Intraindividual rate of change (annualized loss) calculated as individual difference in score divided by time elapsed between examinations, in years. Overall cognitive score based on individual average of Z-scores over the 5 primary cognitive test scores (excluding SPPB). Scores on a Z-scale.

variability, most data centered between 12 and 14 years of formal education, with WRAT scores showing a large range in variance throughout these categories.

The number of participants who had complete, quality MRI data at both visits were lower than the total number who were able to participate in each visit, respectively (Supplemental Materials, eMethods, links.lww.com/WNL/C410). Of the N = 818 at visit 1 (2010–2013) and N = 403 at visit 2 (2017–2019), respectively, n = 20 (2.4%) and n = 51 (12.6%) refused MRI because of contraindications, frailty, or claustrophobia, leaving N = 798 and N = 352 with completed MRI image sequences, respectively. A few of the completed sets of MRIs had technical or image quality errors, such as reconstruction artifacts, incomplete sequence, excess motion artifact, or inadequate field of view: n = 13 (1.6%) and n = 17 (4.8%), resulting in N = 785 and N = 335 full sets of useable MRI data, respectively. Incidental findings from visit 1 MRI have been described previously.[22] Of the n = 335 with full sets of readable MRI at visit 2, 13 (3.9%) had at least 1 new incidental finding, including 6 meningioma, 1 hygroma, 1 varix, 1 hydrocephalus, 1 cyst, 1 craniopharyngioma, 1 schizencephaly, 1 aneurysm, and 1 acute finding of uncertain nature.

As with reports of the prior visit 1, approximately one-third of participants at visit 2 had imaging findings consistent with VBI and approximately two-thirds had imaging findings consistent with atrophy or volumetric loss (Table 2). Change in MRI findings between visit 1 and visit 2 included substantive increases in infarcts, hemorrhage (hematoma), WMH, proportion with abnormal sulcal widening, and proportion with abnormal ventricle enlargement. Person-time between examinations was a cumulative 2,257.4 person-years (PYs), among the N = 335 with both MRIs. Incidence of previously undetected (new) infarcts was 12.8/1000 PY and new hemorrhages was 4.4/1000 PY. Newly abnormal ventricle enlargement was 19.0/1000 PY, sulcal

widening was 30.1/1000 PY, and worsening white matter disease (leukoaraiosis) was 26.1/1000 PY.

As with sociodemographics, MRI, and neurologic history, cognitive test scores (Table 3) were generally better at the earlier visit. On average, losses per year were as follows: 3MSE 0.6 points (out of possible 100), WAIS coding test 1.1 points (highest score 91), COWA 0.4 words (highest score 66), CVLT short and long free recall 0.2 words each (out of possible score 9), and SPPB 0.2 points (out of possible score 12, Table 3, Supplemental Materials, eFigure 2, links.lww.com/WNL/C410). Mean rate of change in overall cognition was 0.04 points per year (Z-scale). Between 12%-19% of the population had cognitive test scores >1 SD above the mean in annualized rate of change, with highest gains in CVLT short free recall; for overall cognition, 11% had such gains (Table 4, Supplemental Materials, eTable 1). Similarly, between 10-17% of the population had annualized rate of change in cognitive test scores more than 1 SD below mean, suggesting rapid loss of function, with the worst losses in CVLT long free recall and SPPB (lower body physical function); 14% had rapid loss in overall cognition.

Participant characteristics significantly associated with rapid loss, compared with no change in function, included age and hemorrhages (Table 5), but only age surpassed the stringent Bonferroni cutoff to address the influence of multiple comparisons. None of the features examined was associated with gain in function. Features that were only measured at the second examination visit included the NACC UDS with the MoCA, which had a mean score 18.9 (SD 4.3, median 19, range 3–29, Figure 2). The FAQ (iADLs) score was highly skewed, with 191 participants scoring 0 (normal) and mean score 5.6 (SD 5.3) and 35 participants scoring ≥9 (consistent with dependency on >3 iADLs), among those with scores >0.

Table 4 American Indian Participants, Categorized by Annualized Rate of Change in Cognitive Test Scores

	Loss: >1 SD below mean annualized rate of change, n (%)	Same: within 1 SD of mean annualized rate of change, n	Gain: >1 SD above mean annualized rate of change, n (%)
3MSE	60 (15%)	293	46 (12%)
WAIS Coding	61 (15%)	282	52 (13%)
COWA	51 (13%)	301	49 (12%)
CVLT short free	38 (10%)	265	69 (19%)
CVLT long free	63 (17%)	258	51 (14%)
SPPB	65 (16%)	291	48 (12%)
Overall cognition	51 (14%)	272	40 (11%)

Abbreviations: COWA = Controlled Oral Word Association; CVLT = California Verbal Learning Test; 3MSE = Modified Mini-Mental Status Examination; SPPB = Short Physical Performance Battery; WAIS = Wechsler Adult Intelligence Scale.
Overall cognitive change defined based on individual averages of 5 standardized (Z-score) cognitive test scores (excluding SPPB).

Discussion

In this study, we report the first longitudinal estimates of cognitive and neuroimaging features in a population-based cohort of American Indians. This study was undertaken over 10 years, using complete recruitment and case ascertainment strategies, and these data are representative of individuals older than 65 years from 11 tribes and communities across 3 US regions.

Little is known about the incidence of VBI or atrophy from neurodegenerative conditions, such as AD, in this population. The findings described in this report suggest that both the vascular and neurodegenerative changes are of particular concern for aging American Indians. We detected prevalence of cerebral infarcts at 26% of American Indians age 65-95 and 32% among those same individuals 7 years later, with an estimated incidence 12.8/1000 PY. Previous reports of similarly aged non-Hispanic Whites (NHWs) detected similar prevalence of infarcts (28%), but lower incidence of strokes (9% in those without prior infarct).[35] Similarly, we also found substantial worsening leukoaraiosis in 44% of all visit 2 participants and with an incidence of 26/1000 PY, in contrast with 27% of NHWs.[36] These factors, associated with elevated blood pressure and other key risk factors found in most of our population, warrant future analyses both for outcomes such as stroke and opportunities for risk reduction and prevention.

Population-based score ranges, normative profiles, and diagnostic standards for most standardized cognitive assessments have not been established for American Indians. Our longitudinal analysis, in combination with our prior publications on cross-sectional

Table 5 Logistic Regression Associations of Selected Factors in American Indians, Comparing Those With Loss or Gain in Cognitive Function to Those With No Change

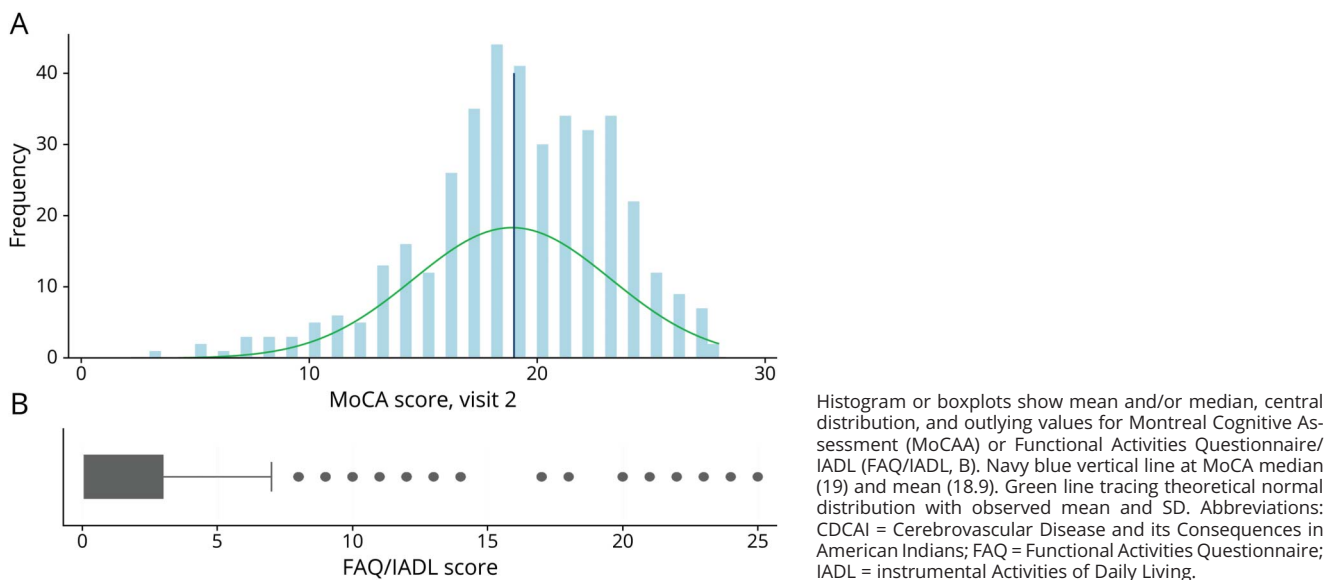|	OR (95% CI)	*p* Value
Loss (n = 51) compared to no change (n = 272)		
Age (y)[a]	2.0 (1.4, 2.9)	<0.001
Sex[a]	1.3 (1.0, 1.8)	0.080
Education (yrs)[a]	1.3 (0.9, 1.8)	0.109
Ever smoking[a]	0.8 (0.6, 1.1)	0.265
Recent alcohol use[a]	0.9 (0.7, 1.3)	0.690
Hypertension[a]	1.0 (0.7, 1.3)	0.895
Diabetes[a]	1.1 (0.8, 1.6)	0.394
CKD[a]	1.0 (0.7, 1.4)	0.883
BMI (kg/m²)[a]	0.8 (0.6, 1.2)	0.324
Neuro sympt[b]	1.1 (0.8, 1.5)	0.614
TBI[b]	1.2 (0.9, 1.6)	0.299
Stroke[b]	0.7 (0.4, 1.2)	0.215
Infarcts[b]	1.0 (0.8, 1.4)	0.831
Hemorrhage[b]	1.4 (1.1, 1.9)	0.010
Abnormal sulci[b]	1.1 (0.8, 1.5)	0.529
Abnormal vent[b]	1.1 (0.8, 1.5)	0.613
Abnormal WMG[b]	1.2 (0.8, 1.7)	0.312
Gain (n = 40) compared with no change (n = 272)		
Age (y)[a]	0.8 (0.5, 1.3)	0.337
Sex[a]	1.2 (0.8, 1.6)	0.420
Education (y)[a]	1.3 (0.9, 1.8)	0.113
Ever smoking[a]	1.1 (0.8, 1.7)	0.498
Recent alcohol use[a]	0.9 (0.7, 1.3)	0.707
Hypertension[a]	1.1 (0.8, 1.5)	0.699
Diabetes[a]	1.1 (0.7, 1.5)	0.744
CKD[a]	0.9 (0.6, 1.4)	0.799
BMI (kg/m²)[a]	0.6 (0.4, 1.0)	0.067
Bilingual[b]	0.9 (0.6, 1.3)	0.569
CES-D[b]	0.7 (0.5, 1.1)	0.102

Abbreviaitions: BMI = body mass index; ; CES-D = Centers for Epidemiologic Studies Depression; CKD = chronic kidney disease.
[a] Variables all mutually adjusted, all standardized (z-scale).
[b] Variables added individually to mutually adjusted model.

cognitive assessments,[19,37] adds novel information on unadjusted cognitive score distributions and typical rate of change for each measured cognitive domain in American Indians from 3 major

Figure 2 Distributions of Scoring for Selected New Instruments Measuring Cognitive and Functional Status Among American Indian Elders at CDCAI Visit 2 (2017–2019 Aged Mean 78.1 Years, Range 71–94 Years)

Histogram or boxplots show mean and/or median, central distribution, and outlying values for Montreal Cognitive Assessment (MoCAA) or Functional Activities Questionnaire/IADL (FAQ/IADL, B). Navy blue vertical line at MoCA median (19) and mean (18.9). Green line tracing theoretical normal distribution with observed mean and SD. Abbreviations: CDCAI = Cerebrovascular Disease and its Consequences in American Indians; FAQ = Functional Activities Questionnaire; IADL = instrumental Activities of Daily Living.

geographic regions. Normal cognitive aging involves some degree of cognitive decline over time,[38] including processing speed and some more complex attention, memory, visuospatial, and executive function capacities. Future research may examine how adjustment for age, sex or gender, education, and health status relate to variance in cognition, to change in cognition, or to predictive capacity of baseline cognition with respect to later cognition.

Future research should more closely examine how participant characteristics may be associated with gain and loss in cognitive test scores over time. In particular, specific domains may be selectively affected by different exposures and disease conditions. In addition, although test-retest gain in function is not usually expected over a multiyear delay in older individuals, the possibility that inexperience with standardized testing, text anxiety, and psychological sequelae of traumatic early educational experiences remains unexplored.

These data on MoCA (mean 18.9, SD 4.3) represent wholly new information, with no prior information among American Indians. Conventional MoCA cutoff for screening possible impairment, including mild cognitive impairment (MCI) and dementia, is < 26 for NHWs.[33] More recent reports have found that lower cutoffs are appropriate for non-Hispanic African American or Hispanic/Latino populations—24 and 25 for MCI and 16 and 19 for dementia, respectively.[39] Our study mean scores were below most of these screening or diagnostic thresholds. It is unlikely that approximately half of the CDCAI study population is truly impaired, so it follows that either the cognitive assessments or the thresholds are functionally unsuitable to this population.

In previous studies to psychometrically evaluate the Mini-Mental State Examination and the Consortium to Establish a Registry for AD tests,[20,40] albeit with smaller numbers of participants, American Indian participant scores were compared with age-adjusted and education-adjusted normative data from NHW,[41] with 11% of American Indians scoring below threshold. In addition, previous research has shown that education length, quality, and degree of achievement are associated with variance and validity on MoCA (and 3MSE) testing, with high score variance in low educational settings.[42-45] Altogether, these findings suggest that MoCA and other standard tests may have poor test performance and discrimination capacity in American Indians, compared with other population settings.

Future work may establish cognitive case categorizations in this study population, distinguished either algorithmically or by case review and adjudication, to establish normative and impaired score ranges for these standardized tests. Furthermore, once gold standard cognitive assessment categorizations are available, relative test performance characteristics comparing different cutoffs for MCI and dementia should be defined for each test. Finally, psychometric validation for cognitive tests should be completed, both overall as well as by region and by sex or gender, assess population strata and within-group heterogeneity.

In this work, we detected low correlation and substantial residual variability comparing years of formal education—the de facto metric for educational achievement most commonly used to adjust, normalize, or standardize cognitive assessments—with WRAT reading score. In studies among

NHW and African Americans, quality of education explained much of the racial variance in association between years of formal education and WRAT scores (Pearson $r = 0.60$).[46] In our analyses, the correlation coefficient was substantively lower (Pearson $r < 0.4$), suggesting that refinement in tools used to contextualize cognitive scores in baseline function are needed. In particular, measurement of achieved education in this population may need to account for both the formal and informal sources of learning.[47] Additional quantification and adjustment may be needed regarding test anxiety or confusion which may manifest because of a legacy of generations of residential or boarding school attendance and the consequent trauma, distress, and anxiety.[48,49]

In these analyses, we identified common symptoms of depression, which may influence test scores. Previous studies in this cohort have found that approximately 20% of older American Indians met criteria consistent with clinical depression (CES-D score >16)[34] and that depressive symptoms were associated with poorer processing speed, verbal fluency, general cognition, and lower body motor function, independent of age, sex, education, income, married status, alcohol use, smoking, hypertension, diabetes, and stroke. Our research group also found that 12 of the 20 questions had adequate psychometric properties.[50] Future analyses may build on this work, to assess the influence of depressive symptoms on newly collected cognitive test domains, on biological or clinical outcomes, such as AD or dementia, and relationships with trauma and stress.

We evaluated participants by the participation history in the initial and follow-up CDCAI examinations based on key sociodemographics, clinical comorbidities, neuroimaging features, neurologic history, and cognition. We found that participants who participated in the first examination only presented poorer health profiles compared with those who participated in both examinations, suggesting greater likelihood of mortality in this group and possibility of selective survival. These differences were more extreme than previous sensitivity analyses focused on possible selection related to cardiovascular features between the baseline SHS examination (1989–1991) and the visit 1 CDCAI examination (2010–2013). One interpretation for these findings is that selection may be more evident in features related to cognition, brain imaging, and neurologic history. Another interpretation is that attrition from mortality is accelerating in this cohort, now aged >70 years. Future research using these data will need to account for selection, such as with inverse probability weighting. Additional inquiry may also examine whether particular population strata are at extreme risk for mortality or other adverse events and thus represent ideal targets for primary and secondary prevention efforts.

The SHS and CDCAI studies have had consistently high recruitment and retention, comprehensive data collection, standardized clinical and neurologic examinations, and detailed neuropsychological batteries in an understudied population. We attribute a large degree of this success to field staff dedication and involvement with the communities. Prioritization of community-based participatory research standards hiring community members as community-facing research staff and maintenance of two-way communications through Community Advisory Boards are all key to development and maintenance of positive relationships and mutual respect.

Our data highlight issues including loss to follow-up, attrition, and frailty in the SHS and CDCAI cohort. Risk profiles of participants in the follow-up examination were similar to those who would not be available for follow-up, based on their data collected an average of 7 years earlier. These findings suggest that aging is a significant mechanism responsible for attrition and loss in this cohort population, with some aging earlier or more rapidly than others. If so, then, population stratification and risk prediction may be possible and critically important. The goal of precision medicine was to establish highly specified groups which may be a high priority for future public health efforts, including prevention and intervention. Future research should examine the role of population stratification, prediction, and prevention, with mortality and frailty related to vascular and neurodegenerative dementia as key outcomes.

In this report, we describe the methods used to recruit and examine a well-characterized population-based sample of community-dwelling older American Indians, with a focus on longitudinal analysis of 2 examination visits separated by a mean of 6.7 years. These neuroimaging and neuropsychology data, with a follow-up expanded to include behavioral and neuropsychological testing related to ADRD, encompass a unique opportunity to examine change over time in both structure and function in an understudied population.

Disclosure
The authors report no relevant disclosures.Go to Neurology.org/N for full disclosures.

Appendix Authors

Name	Location	Contribution
Astrid M. Suchy-Dicey, PhD	Elson S. Floyd College of Medicine, Washington State University, Seattle	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data; oversaw all aspects of data collection, scientific direction, and data harmonization; contributed to neuropsychological test score review panel
Kyra Oziel, BS	Elson S. Floyd College of Medicine, Washington State University, Seattle	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; oversaw all aspects of data collection, scientific direction, and data harmonization
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Amanda M. Fretts, PhD	Department of Epidemiology, School of Public Health, University of Washington, Seattle	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; oversaw all aspects of data collection, scientific direction, and data harmonization
Jason G. Umans, MD	MedStar Health Research Institute, Washington, DC	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; oversaw all aspects of data collection, scientific direction, and data harmonization

Appendix *(continued)*

Name	Location	Contribution
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W. T. Longstreth, Jr, MD	Department of Epidemiology, School of Public Health, and Department of Neurology, School of Medicine, University of Washington, Seattle	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
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Dedra S. Buchwald, MD	Elson S. Floyd College of Medicine, Washington State University, Seattle	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; oversaw all aspects of data collection, scientific direction, and data harmonization
Thomas J. Grabowski, MD	Neurology, School of Medicine, University of Washington	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; oversaw all aspects of data collection, scientific direction, and data harmonization

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