Lifestyle Risk Factors and Findings on Brain Magnetic Resonance Imaging of Older Adult American Indians: The Strong Heart Study

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Keywords

Brain magnetic resonance imaging · Smoking · Alcohol · Body mass index · American Indian · Infarcts

Abstract

Background: Clinical stroke is prevalent in American Indians, but the lifestyle risk factors for vascular brain injury have not been well-studied in this population. The purpose of this study was to correlate brain magnetic resonance imaging (MRI) findings with obesity, alcohol use, and smoking behaviors in elderly American Indians from the Strong Heart Study. **Methods:** Cranial MRI scans ($n = 789$) were analyzed for dichotomous measures of infarcts, hemorrhages, white matter hyperintensities (WMH), and cerebral atrophy and continuous measures of total brain, WMH, and hippocampal volume. Poisson regression was used to estimate prevalence ratios, and linear regression was used to estimate measures of association for continuous outcomes. Models were adjusted for the risk factors of interest as well as age, sex, study site, income, education, hypertension, diabetes, and low-density li-

poprotein cholesterol. **Results:** Smoking was associated with increased hippocampal atrophy ($p = 0.002$) and increased prevalence of sulcal widening ($p < 0.001$). Relative to non-smokers, smokers with more than 25 pack-years of smoking had a 27% (95% CI 7–47%) increased prevalence of high-grade sulci, $p = 0.005$. Body mass index was inversely associated with prevalence of nonlacunar infarcts and sulcal widening (all $p = 0.004$). Alcohol use was not significantly associated with any of the measured MRI findings. **Conclusions:** This study found similar associations between smoking and vascular brain injury among American Indians, as seen in other populations. In particular, these findings support the role of smoking as a key correlate for cerebral atrophy.

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Introduction

The prevalence of stroke in American Indians as noted in the Strong Heart Study (SHS) nearly twice that of Americans of European descent (5.8 vs. 3.0%) [1–3].

Despite progress in acute stroke diagnosis and treatment, prevention remains the most effective approach to reducing morbidity and mortality. Cranial magnetic resonance imaging (MRI) enables early identification of subclinical or covert vascular brain injury, such as infarcts, hemorrhages, white matter hyperintensities (WMH), and cerebral atrophy [4, 5]. Prior studies, primarily conducted in populations with European heritage, have found correlation of both overt clinical stroke and these covert MRI findings with obesity, cigarette smoking, and alcohol use [6, 7]. Some recent studies have demonstrated different associations in other populations. For example, worsening WMH has been associated with continued smoking in those of European but not African descent [8]. Similarly, whites may have stronger associations between WMH and alcohol consumption than African Caribbeans [9]. Given the high prevalence of vascular disease and its risk factors in American Indians [10, 11], understanding the association between lifestyle risk factors and brain injury is critical. The Cerebrovascular Disease and its Consequences in American Indians (CDCAI) study [12] was undertaken to determine the prevalence and severity of brain abnormalities on brain MRI in this high-risk population and correlate them with risk factors and clinical manifestations. CDCAI involves the surviving members of the SHS cohort of American Indians aged 64 years and older from 3 geographic regions (Northern Plains, Southern Plains, and Southwest) and includes a battery of cognitive, neurological, physical, and laboratory assessments along with cranial MRI scans. The purpose of this study is to extend the prior assessment of vascular risk factors [13] to examine associations of body mass index (BMI), smoking, and alcohol use with brain injury using data acquired from the CDCAI study.

Methods

Participants and Procedures

The SHS is a longitudinal, multicommunity cohort study aimed at better understanding cardiovascular disease in American Indians. Between 1989 and 1991, 4,549 American Indians were recruited from 13 tribes in the U.S. Southern Plains, Northern Plains, and Southwest [14]. The CDCAI study is an ancillary study conducted between 2010 and 2013 and focused on vascular brain injury, its risk factors, and clinical manifestations among surviving participants from the original SHS [12]. Human subjects research committees from the communities, tribal councils, Indian Health Service, and partner institutions approved the study procedures, and all participants gave written, informed consent. After data collection was complete, 209 participants who completed cranial MRI

scans were removed from analyses because one community withdrew consent to use their data. Ultimately, 789 completed usable MRI scans and were included in these analyses.

MRI Procedures

As described in detail previously [15], 1.5T MRI scanners used image sequences including axial T1, T2, and T2*-weighted images [16, 17]. For volumetric analysis, 3 mm fluid-attenuated inversion recovery (FLAIR) and 1.5 mm sagittal 3D T1-weighted gradient echo images were also obtained.

Brain infarcts were identified as lesions of a characteristic shape, absence of mass effect, and hyperintensity to gray matter on both T2-weighted and FLAIR images (to distinguish them from perivascular spaces which are hypointense on FLAIR) and were required to >2 mm in size on both T2-weighted and FLAIR images. White matter infarcts were distinguished from WMH by their focality and distinct low signal on the T1-weighted and high signal on the FLAIR images. Lesions matching these criteria <2 cm in maximum dimension and located in the caudate, lenticular nucleus, internal capsule, thalamus, brainstem, cerebellar white matter, centrum semiovale, or corona radiata regions were defined as “lacunes.” The remaining infarcts (either larger or in other territories) were classified as non-lacunes.

Brain hemorrhages were hypointense with “blooming” on gradient echo images. Severity of WMH, sulcal widening, and ventricle enlargement were graded using a 10-point scale, with 0 being the least and 9 the most severe [16]. As in prior analyses [18], a grade of 3 or more was considered abnormal. WMH volume was calculated by segmenting the 3 mm FLAIR images using the Fuzzy Lesion Extractor technique [19]. Total brain volume was measured using the Freesurfer image analysis suite [20, 21]. Hippocampal volume was measured using automated segmentation from the 3D T1-weighted images with FIRST in FSL 5.0 [22] and the ENIGMA1 protocol [23]. Intracranial volume was estimated using the ENIGMA1 protocol for FSL [24].

Covariates and Risk Factors

Interviews, clinical examination, and blood draws were performed within 1 month of the MRI scans. All models were adjusted for age, gender, study site, education, income, hypertension defined as systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or use of antihypertensive medications, diabetes defined as fasting glucose >126 mg/dL (7 mmol/L) or use of diabetes medications, and high levels of low density lipoprotein cholesterol (LDL) >160 mg/dL or use of lipid-lowering medications. The associations of hypertension, diabetes, and high LDL cholesterol with the MRI findings in this population are the topic of a companion paper [13]. Risk factors of interest comprised BMI in kg/m², alcohol use, and lifetime smoking, as defined and categorized in Table 1. BMI was categorized as normal = 18.5–24.9 kg/m²; overweight = 25–29.9 kg/m²; obese = 30+ kg/m² (note: one individual with BMI <18.5 was included in the normal category). Alcohol use was categorized as: never drinker; former drinker: last drink >1 year ago; current light drinker: <2 drinks/week; current moderate drinker: 2–14 drinks/week or binge drinking once/year; and current heavy drinker: 14+ drinks/week or binge drinking 2+ times/year. Smoking was categorized in terms of lifetime pack-years: never smoker; smoker with <10 pack-years; smoker with 10 to >25 pack-years and smoker with 25+ pack years.

Table 1. Selected participant characteristics in the CDCAI study at the time of the MRI examination (2010–2013), $n = 789$

Age, years, mean $\pm$ SD	73.0 $\pm$ 5.8	Current smoker	164 (20.8)
Gender, female	533 (67.6)	Diabetes (physician diagnosis, medication or high fasting glucose)	389 (49.3)
Study site		Fasting visit glucose, mg/dL, mean $\pm$ SD)	124.0 $\pm$ 53.3
North and South Dakota	357 (45.2)	Hypertension (physician diagnosis, medication, or high visit BP)	636 (80.6)
Oklahoma	336 (42.6)	SBP, mm Hg, mean $\pm$ SD)	136 $\pm$ 21
Arizona	96 (12.2)	DBP, mm Hg, mean $\pm$ SD)	68 $\pm$ 11
Household income		High LDL (medication or high visit LDL), mean (SD)	275 (33.6)
USD <10,000/year	238 (30.2)	LDL, mg/dL, mean $\pm$ SD	98.2 $\pm$ 34.8
USD 10–20,000/year	229 (29.0)	Prior clinical stroke	34 (4.7)
USD 20–35,000/year	173 (21.9)	Infarct, 3–20 mm	263 (33.5)
USD >35,000/year	149 (18.9)	Any lacunar infarcts	181 (23.0)
Education		Only non-lacunar infarcts	82 (10.4)
Some high school	155 (19.6)	Hemorrhage	45 (5.7)
High school graduate	197 (25.0)	WMH grade 3+	292 (37.3)
Any college	317 (40.2)	Sulcal grade 3+	515 (66.0)
College graduate	120 (15.2)	Ventricle grade 3+	527 (67.5)
Adiposity (BMI)		Intracranial volume in cm ³ , mean (SD)	1214.28 (138.25)
Normal, <25 kg/m ² *	119 (15.2)	Hippocampal volume in cm ³ , mean (SD)	6.61 (1.01)
Overweight, 25–30 kg/m ²	240 (30.6)	Brain volume in cm ³ , mean (SD)	937.12 (101.28)
Obese, >30 kg/m ²	425 (54.2)	WMH volume in cm ³ , mean (SD)	7.52 (6.96)
Alcohol use		Values given as n (%) unless otherwise noted. * One underweight individual was included in the “normal” BMI weight category.	
Never	191 (24.2)		
Former	461 (58.4)	MRI, magnetic resonance imaging; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; WMH, white matter hyperintensities; CDCAI, cerebrovascular disease and its consequences in American Indians; BMI, body mass index.	
Current light drinker	46 (5.8)		
Current moderate drinker	27 (3.4)		
Current heavy drinker	64 (8.1)		
Lifetime smoking			
Never	272 (34.5)		
<10 pack-years	240 (30.4)		
10–24 pack-years	132 (16.7)		
25+ pack-years	145 (18.4)		

Statistical Procedures

Participant characteristics were summarized using means and SDs or count and percentages. Poisson regression was used to estimate prevalence ratios (PR) for associations between risk factors and the presence of infarcts or hemorrhages or abnormal grade (grade ≥ 3) for WMH, ventricle enlargement, and sulcal widening. Multivariable linear regression was used to estimate risk factor associations with WMH, hippocampus, or total brain volume, with intracranial volume included as an additional covariate. All models were adjusted for participant age, sex, study site, income, education, diabetes, hypertension, high LDL, and the lifestyle risk factors of interest: smoking, alcohol, and BMI categories. Omnibus Wald tests were used to test the global significance of the categorical risk factor variables; for each risk factor, we tested the null hypothesis that the β coefficients for all categories were jointly equal to zero. We used robust sandwich errors estimation to estimate valid standard errors for coefficients in the regression models. Because we examined 10 imaging features and 3 risk factors (30 individual tests), multiple testing is a concern [25]. We adjusted for multiple testing using the false discovery rate (FDR) [26] and set $q = 0.05$, which reflects the proportion of false positive significant findings that we are willing to accept. All main results with p values

<0.0067, the FDR-corrected critical p value, are indicated with an * and reported as significant. Statistical analyses were conducted using Stata (version 14, Stata Corp., College Station, TX, USA).

Results

Participants

Participant characteristics are noted in Table 1. These elderly adult American Indian participants had a mean age of 73 years and 68% were women. Over half were obese and had a history of alcohol consumption and cigarette smoking. Vascular risk factors were common with about 80% of participants having hypertension, almost 50% having diabetes, and about 40% having high LDL or use of lipid-lowering medications. Evidence of vascular brain injury on MRI was also common – 33.5% had infarcts and 37.3% had abnormal WMH grade.

Lifestyle Risk Factors and MRI Findings

Lifetime smoking was significantly associated with the presence of sulci-grade 3+, $p = 0.0007$. Relative to never smokers, smokers with 25 or more pack years had an increased PR of 27% (8–48%), $p = 0.005$ (Table 2). Potential effects were observed for even low reported levels of smoking; smokers with <10 pack-years also had increased prevalence compared with never smokers, PR (95% CI) 1.31 (1.15–1.48). Smoking was also associated with hippocampal volume, $p = 0.002$, but no other volume measures (Table 3). Relative to never smokers, smokers with 10–24 pack years had slightly reduced hippocampal volume, β (95% CI) -0.3 (-0.5 to -0.1) cm^3 . Interestingly, the reduction was not statistically significant in heavier smokers, though the trend was similar. BMI was inversely associated with the presence of nonlacunar infarcts ($p = 0.004$) and sulci-grade 3+ ($p = 0.004$). Relative to normal weight individuals, obese individuals had significantly lower risks of these outcomes after adjustment for other lifestyle factors and covariates. No significant associations were observed for alcohol use.

Residuals from linear regression models of WMH were not normally distributed, so in sensitivity analyses, we investigated relationships between risk factors and a binary variable reflecting participants above and below the median WMH volume of 5.95 cm^3 . Results from these models were also not statistically significant at the FDR significance threshold.

Discussion

In our population of elderly American Indians, obesity was highly prevalent at 54%, as in other studies of American Indian populations [27, 28], and was associated with decreased prevalence of brain abnormalities. Studies assessing obesity as a risk factor for brain atrophy have had variable findings. For example, 2 studies [29, 30] found obesity associated with increased risk of silent infarcts, while 3 studies [31–33] found reduced risk of infarcts. Similarly, BMI is positively associated with WMH burden in some studies [34], but negatively associated with WMH burden in others [35–37]. While increased weight loss with cognitive decline in the elderly [37] is a potential explanation for these findings, it is likely that relationships between brain atrophy measures and BMI are complex and may vary by age [35, 38], and these effects may also be confounded by survival bias. Furthermore, these relationships may be difficult to interpret from cross-sectional studies, since body weight (or chang-

Table 2. Associations between lifestyle factors and categorical brain abnormalities detected by structural cranial MRI in elderly American Indians

	Any infarct vs. no infarct	Lacunar infarct vs. no infarct	Non-lacunar infarct only vs. no infarct	Hemorrhage vs. none	WMH grade 3+ vs. WMH grade 1–2	Sulci grade 3+ vs. sulci-grade 1–2	Ventrite grade 3+ vs. ventrite grade 1–2
	PR (95% CI)	PR (95% CI)	PR (95% CI)	PR (95% CI)	PR (95% CI)	PR (95% CI)	PR (95% CI)
Adiposity (BMI)							
Normal (<25)	Referent	Referent	Referent	Referent	Referent	Referent	Referent
Overweight (25–29)	0.93 (0.71–1.22)	1.00 (0.70–1.42)	0.68 (0.39–1.18)	1.08 (0.50–2.3)	0.87 (0.70–1.08)	0.99 (0.87–1.12)	0.94 (0.82–1.06)
Obese (30+)	0.81 (0.61–1.06)	0.97 (0.69–1.35)	0.40 (0.22–0.71)	0.84 (0.37–1.89)	0.70 (0.56–0.89)	0.83 (0.72–0.96)	0.87 (0.76–0.99)
Alcohol use							
Never	Referent	Referent	Referent	Referent	Referent	Referent	Referent
Former	0.81 (0.64–1.03)	0.74 (0.55–1.01)	0.89 (0.49–1.60)	0.56 (0.26–1.20)	0.91 (0.73–1.13)	0.94 (0.83–1.07)	0.98 (0.86–1.11)
Current/light	0.92 (0.57–1.46)	0.73 (0.37–1.43)	1.40 (0.60–3.25)	0.57 (0.12–2.69)	1.01 (0.65–1.57)	1.12 (0.9–1.39)	1.10 (0.89–1.37)
Current/moderate	0.72 (0.36–1.44)	0.60 (0.24–1.5)	0.82 (0.22–3.06)	1.44 (0.45–4.66)	1.17 (0.70–1.96)	1.08 (0.84–1.40)	1.11 (0.89–1.40)
Current/heavy	0.95 (0.63–1.44)	1.10 (0.64–1.88)	0.75 (0.29–1.94)	1.12 (0.37–3.41)	1.06 (0.72–1.56)	1.01 (0.83–1.23)	1.18 (1.00–1.40)
Smoking							
Never	Referent	Referent	Referent	Referent	Referent	Referent	Referent
<10 pack-years	0.94 (0.73–1.22)	0.82 (0.58–1.17)	1.19 (0.70–2.03)	1.63 (0.72–3.70)	0.92 (0.73–1.16)	1.31 (1.15–1.49)	0.92 (0.81–1.05)
10–24 pack-years	1.04 (0.77–1.41)	1.16 (0.80–1.70)	0.79 (0.38–1.64)	2.28 (1.00–5.21)	0.88 (0.66–1.17)	1.19 (1.03–1.39)	1.04 (0.91–1.20)
25+ pack-years	0.98 (0.72–1.34)	1.05 (0.71–1.55)	0.71 (0.37–1.39)	1.33 (0.51–3.44)	0.99 (0.75–1.30)	1.27 (1.07–1.47)	1.11 (0.97–1.27)

* FDR-corrected critical p value (significant).
One underweight individual was included in the “normal” BMI weight category. Models adjusted for age, sex, study site, income, education, diabetes, hypertension, high LDL, smoking, alcohol, and BMI.
Global p values for exposures reflect a joint test of all variable coefficients; within exposure variable results reflect the risk for the category relative to the referent category.
MRI, magnetic resonance imaging; WMH, white matter hyperintensities; PR, prevalence ratio; BMI, body mass index.

Table 3. Associations between lifestyle factors and volumetric measures from structural cranial MRI in elderly American Indians

	Hippocampal volume, cm ³		WMH volume, cm ³		Brain volume, cm ³	
	β (95% CI)	<i>p</i> value	β (95% CI)	<i>p</i> value	β (95% CI)	<i>p</i> value
Adiposity (BMI)		0.88		0.01		0.65
Normal (<25)	Referent		Referent		Referent	
Overweight (25–29)	0.05 (–0.17 to 0.28)	0.64	–1.88 (–3.58 to –0.18)	0.03	4.82 (–5.75 to 15.40)	0.37
Obese (30+)	0.05 (–0.16 to 0.26)	0.63	–2.40 (–4.00 to –0.80)	0.003	4.23 (–6.55 to 15.01)	0.44
Alcohol use		0.28		0.56		0.59
Never	Referent		Referent		Referent	
Former	–0.01 (–0.19 to 0.17)	0.92	–0.68 (–1.89 to 0.52)	0.27	–5.65 (–15.28 to 3.98)	0.25
Current/light	0.07 (–0.20 to 0.33)	0.62	0.32 (–2.00 to 2.63)	0.79	–11.76 (–28.29 to 4.76)	0.16
Current/moderate	–0.37 (–0.97 to 0.24)	0.23	1.02 (–2.28 to 4.33)	0.54	–16.65 (–48.41 to 15.10)	0.30
Current/heavy	–0.23 (–0.55 to 0.09)	0.15	0.03 (–1.98 to 2.03)	0.98	–6.12 (–23.66 to 11.43)	0.49
Smoking		0.002*		0.91		0.33
Never	Referent		Referent		Referent	
<10 pack-years	0.09 (–0.10 to 0.28)	0.34	–0.12 (–1.35 to 1.11)	0.85	–0.79 (–10.62 to 9.05)	0.88
10–24 pack-years	–0.27 (–0.50 to –0.05)	0.02	–0.23 (–1.59 to 1.14)	0.74	–0.57 (–12.30 to 11.17)	0.92
25+ pack-years	–0.15 (–0.38 to 0.08)	0.19	0.29 (–1.20 to 1.77)	0.70	–10.83 (–23.30 to 1.63)	0.09

* FDR-corrected critical *p* value (significant).

One underweight individual was included in the “normal” BMI weight category.

Models adjusted for age, sex, study site, income, education, diabetes, hypertension, high LDL, smoking, alcohol, BMI and IC volume.

Global *p* values for exposures reflect a joint test of all coefficients; within exposure variable results reflect the mean difference in volume for the category relative to the referent category.

MRI, magnetic resonance imaging; WMH, white matter hyperintensities; BMI, body mass index.

es in weight) may be an early indicator of brain disease, or a potential causal factor [39].

Alcoholism has been reported as being relatively prevalent in the American Indian population [40, 41] yet 12-month alcohol dependence [42] in our population of older adult American Indians was similar to national rates. Only 10.5% reported having alcohol within the past week. Recent alcohol use (as categorized by use within the past week) was associated with ventricular and sulcal enlargement (measures of cerebral atrophy) and hippocampal volume loss (data not shown) – both findings have been reported in prior studies of European descent [43, 44] and African American [43] populations. Although they likely represent largely chronic changes, these findings may also reflect a component of subacute volume loss from hydration status. Studies in animals suggest that acute alcohol intoxication and recovery causes fluid redistribution in the brain – resulting in rapid ventricular volume changes [45].

Lifetime smoking is relatively prevalent in the study population with 18% having a >25 pack-year history and 17% reporting a 10–25 pack-year history and represents a major health problem [46] although in our population 41.6% reported having never smoked. The predominant brain MRI findings associated with smoking in our study

were measures of brain atrophy including increased sulci widening and decreased hippocampal volume. These associations have been reported in a number of other studies [8, 47, 48] including African Americans [47] and Asians [47, 49], and animal studies have consistently linked hippocampal neuronal damage to nicotine exposure [48]. The mechanism remains unclear, but may relate to microvascular disease [48].

When compared with similar studies on other populations, these results on an American Indian population demonstrate that although the prevalence of lifestyle-related risk factors may be somewhat higher than other groups, associations with brain abnormalities are relatively similar.

Our study is not without limitations. As discussed, the temporality and causality of associations cannot be examined using these cross-sectional data; however, we discuss their consistency with previously reported relationships in the literature as well as biological plausibility. Although we controlled for clinical vascular risk factors (hypertension, diabetes, and high LDL), there may be residual confounding or measurement error. For example, we had detailed dose information for current drinkers, but not former drinkers. There is also the concern that some of these lifestyle factors may mediate their effects via the clinical

risk factors and there may be over-controlling in some of our analyses. While lifestyle risk factors hold much promise as being modifiable, our study was unable to address the impact of lifestyle changes with respect to brain injury and aging. Future studies might examine whether interventions for stopping smoking or alcohol use are able to reduce the progression of brain atrophy; for example, one study [50] has found evidence for reversibility of alcohol-related brain atrophy, possibly related to rehydration. The apparent negative association of obesity with the presence of non-lacune infarcts and sulcal widening bears further investigation.

Conclusion

This is the first large cohort study of older adult American Indian examining lifestyle risk factors for vascular brain injury based upon MRI findings. Independen-

dent of vascular risk factors, smoking was associated with measures of cerebral and hippocampal atrophy. Although similar findings have been reported in other populations, our results underscore the importance of lifestyle factors to reduce the prevalence of vascular brain injury, especially in this high risk, vulnerable population.

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