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Vascular Risk Factors and Findings on Brain MRI of Elderly Adult American Indians: The Strong Heart Study

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Abstract

Background: Clinical stroke is prevalent in American Indians, but the risk factors for cerebrovascular pathology have not been well-studied in this population. The purpose of this study was to correlate abnormalities on brain magnetic resonance imaging (MRI) with clinical risk factors in a cohort of elderly American Indians.

Methods: Brain MRI scans from 789 participants of the Strong Heart Study were analyzed for infarcts, hemorrhage, white matter disease, and measures of cerebral atrophy including ventricular and sulcal grade and total brain volume. Clinical risk factors included measures of hypertension, diabetes, and high levels of low-density lipoprotein (LDL) cholesterol. Regression models adjusted for potential confounders were used to estimate associations between risk factors and brain MRI outcomes.

Results: Hypertension was associated with the presence of infarcts ($p = 0.001$), ventricle enlargement ($p = 0.01$), and increased white matter hyperintensity volume ($p = 0.01$). Diabetes was associated with increased prevalence of cerebral atrophy ($p < 0.001$), ventricular enlargement ($p = 0.001$), and sulcal widening ($p = 0.001$). High LDL was not significantly associated with any of the measured cranial imaging outcomes.

Conclusions: This study found risk factors for cerebrovascular disease in American Indians similar to those seen in other populations and provides additional evidence for the important roles of hypertension and diabetes in promoting cerebral infarcts and brain atrophy, respectively.

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Keywords

Brain; Magnetic resonance imaging; Diabetes; Hypertension; Low-density lipoprotein-cholesterol; American Indian; Infarcts

Introduction

Clinical stroke in American Indians, who have an incidence rate of stroke (per 1,000 person-years) as high as 6.85 [1], is substantially more common than in the general US population [2, 3]. Despite progress in the diagnosis and treatment of acute stroke, prevention remains the most effective approach to reducing stroke morbidity. Brain magnetic resonance imaging (MRI) enables early identification of subclinical vascular brain injuries such as infarcts, hemorrhages, white matter hyperintensities (WMH), and cerebral atrophy [4, 5]. Most brain MRI studies have focused primarily on populations of European descent living in Europe and North America and have identified correlations between MRI abnormalities and vascular risk factors, especially hypertension [6, 7]. Some recent studies have demonstrated different associations in other populations. In the United States, for example, African Americans and Hispanics appear to have stronger positive associations between diastolic blood pressure and WMH than do non-Hispanic Whites [8]. Similarly, in the United Kingdom, African Caribbeans appear to have stronger associations linking hypertension and diabetes with WMH and infarcts than do Whites [9, 10]. Given the high prevalence of vascular disease in American Indians [10, 11], an understanding of the associations between vascular risk factors and vascular brain injury in this population is essential to designing effective strategies for prevention and treatment.

Accordingly, the Cerebrovascular Disease and its Consequences in American Indians (CDCAI) study was undertaken to investigate the prevalence and nature of vascular brain injury in elderly American Indians by conducting structural MRI among other clinical examinations. Study procedures included a battery of cognitive, neurological, physical, and laboratory assessments, as well as 1.5T brain imaging. This study reports associations between vascular brain injury and hypertension, diabetes, and high low-density lipoprotein (LDL) cholesterol in the CDCAI study population.

Methods

Participants

The Strong Heart Study was a multicommunity cohort study aimed at better understanding cardiovascular disease in American Indians. Between 1989 and 1991, 4,549 American Indian adults were recruited from 13 tribal communities in the US Southwest, Southern Plains, and Northern Plains [12]. The CDCAI was an ancillary study conducted from 2010 to 2013 to investigate vascular brain injury, its risk factors, and clinical manifestations among surviving members of the Strong Heart cohort [13]. A total of 1,033 participants completed CDCAI examinations; after data collection was complete, one community (n = 215) withdrew consent, and these data were removed from analyses. Of the remaining participants, 29 had unusable MRI scans, leaving 789 for the current study. Institutional

approval for CDCAI study procedures was obtained through appropriate processes from associated tribal councils, the Indian Health Service, and participating institutional IRBs. All participants provided written, informed consent before commencing study activities.

MRI Procedures

CDCAI investigators used 1.5T MRI scanners with image sequences including 5 mm axial-T1-weighted, T2-weighted, and T2* susceptibility-weighted images [14, 15]. For volumetric analysis, 3 mm fluid-attenuated inversion recovery (FLAIR) and 1.5 mm sagittal 3-dimensional T1-weighted volumetric gradient echo images were also obtained. Neuroradiologists who were trained and tested in the study protocols read all scans blinded to participants' age, sex, and clinical information.

Brain infarcts were defined as lesions larger than 2 mm with a characteristic shape, absence of mass effect, and hyperintensity to gray matter on both T2-weighted and FLAIR images. In contrast, perivascular spaces are hypointense on FLAIR images. Lesions within white matter were required to be hypointense on T1- weighted images to distinguish them from focal WMH [15]. Brain hemorrhages were defined as lesions that were hypointense on gradient echo images. Brain infarcts and hemorrhages were characterized by number, size, type, and location. Infarcts between less than 2 cm in maximum dimension and located in the caudate, lenticular nucleus, internal capsule, thalamus, brainstem, cerebellar white matter, centrum semiovale, or corona radiata were defined as "lacunes." The remaining infarcts (larger infarct and similar sized infarcts in other territories) were classified as "non-lacunes" (a somewhat heterogeneous group which would include both large vessel cortical infracts as well as a smaller likely embolic infarcts).

Severity of WMH, sulcal widening, and ventricle enlargement were graded using a semi-quantitative 10-point scale to match participants' images to templates used by the Atherosclerosis Risk in Communities study [16] and the Cardiovascular Health Study [17]. A best fit ranging from grade 0 (absence of disease) to grade 9 (most severe) was determined, with scores of 3 or higher defined as abnormal [18]. WMH volume was calculated by using the Fuzzy Lesion Extractor technique [19] to segment the 3 mm FLAIR images. Total brain volume was measured using the Freesurfer image analysis suite [20, 21]. Intracranial volume, which was estimated using the ENIGMA1 protocol for FMRIB Software Library [22], was used in analyses of hippocampus (HC), WMH, and total brain volume, to adjust for intraindividual variation in head size.

Covariates and Risk Factors

Interviews, clinical examinations, and blood draws were performed within 1 month of the MRI scans. Covariates of interest included age, sex, study site, education, income, cigarette smoking, alcohol use, and body mass index. Main risk factors of interest comprised hypertension, diabetes, and dyslipidemia. Hypertension was defined as seated systolic blood pressure (SBP) >140mm Hg, diastolic blood pressure (DBP) >90 mm Hg, or use of antihypertensive medications. Prevalent diabetes was defined as fasting glucose >126 mg/dL (7 mmol/L) or use of diabetes medications. High LDL was defined as LDL >160 mg/dL based on National Cholesterol Education Program ATP-III guidelines, or use of lipid-

lowering medications. In secondary analyses, associations with continuous fasting glucose, SBP, DBP, and LDL were investigated. History of definite clinical stroke was adjudicated by trained physicians, as previously reported [23].

Statistical Procedures

Participant characteristics were summarized using means and standard deviations or counts and percentages. Poisson regression was used to estimate prevalence ratios (PRs) for associations between risk factors and the common outcomes: presence of infarcts or hemorrhages or abnormal grade (grade ≥3) for WMH, ventricle enlargement, and sulcal widening [24]. Multivariable linear regression was used to estimate risk factor associations with volume of WMH, HC, or total brain, with intracranial volume included as an additional covariate. All models were adjusted for participant age, sex, site, income, education, and the lifestyle risk factors: smoking, alcohol, and body mass index categories. We used robust sandwich errors estimation to estimate valid standard errors for all coefficients. With 10 imaging features and 3 risk factors (30 tests), multiple testing is an important consideration when interpreting results. To control the significance threshold for multiple testing, we used the false discovery rate [25, 26] and set q = 0.05, which reflects the proportion of significant findings that are false positives we are willing to accept. All main results with p values < 0.012, the FDR-corrected critical p value, are indicated with an * and reported as significant. Secondary analysis results were not corrected and are interpreted as exploratory results. Statistical analyses were conducted using Stata (version 14, Stata Corp, College Station, TX, USA).

Results

A description of participants in terms of selected characteristics is included in the online supplementary Table A (for all online suppl. material, see www.karger.com/doi/10.1159/000496343). In general, hypertension (80%) and diabetes (49%) were common in this older aged population, mean age = 73 years. Similarly, MRI findings were also common, with infarcts noted in 33.5% and hemorrhages in 5.7% of participants. With abnormality defined as grade 3 or higher, more than one-third (37.3%) of participants had abnormal WMH grade, while approximately two-thirds had abnormal sulcal widening (66.0%) or abnormal ventricle enlargement (67.5%). A total of 37 (4.7%) of participants had an adjudicated clinical stroke prior to the MRI examination. Of those, 28 (75.7%) were noted as having infarcts on MRI, indicating that the remaining 9 had a history of stroke but no evidence of MRI- defined infarcts 2–20 mm in size. In contrast, among participants with no history of clinical stroke at the MRI visit or self-reported stroke, 29% had infarcts.

Risk Factors and MRI Findings

Both hypertension and diabetes were associated with brain abnormalities, while high LDL or use of lipid-lowering medications was not significantly associated with any findings (Table 1). Hypertension was associated with a 59% (95% CI 20–210%) increased prevalence of infarct (p = 0.001), with positive associations for both non-lacunar only and any lacunar infarcts, though only the subcategory of lacunar infarcts was significant (p = 0.006). Hypertension was also significantly associated with an 18% (95% CI 4–33%) increased

prevalence of ventricle enlargement ($p = 0.01$). Diabetes was associated with increased prevalence of sulcal widening (PR 1.2 [95% CI 1.1–1.3], $p = 0.001$) and ventricle enlargement (PR 1.3 [95 %CI 1.2–1.4], $p < 0.001$). None of the risk factors were significantly associated with hemorrhage or WMH-Grade 3+ abnormalities after FDR adjustment.

In secondary analyses of continuous clinical measures as the exposures (Table 2), each 1 mg/dL increase in fasting glucose was associated with a small (0.1%) increased prevalence of ventricle enlargement ($p = 0.002$). SBP was positively associated with the presence of any infarcts, presence of non-lacunar infarcts, and ventricle enlargement-grade 3+ with elevated prevalence of approximately 0.1–1% for each 1 mm Hg increase in mean SBP.

In models examining brain volumes (Table 3), diabetes was robustly associated with decreased mean total brain volume, $\beta = -16.0$ cm^3 (95% CI −23.6 to −8.5), $p < 0.001$. Hypertension was associated with small increases in WMH volume, $\beta = 1.3$ cm^3 (95% CI 0.3–2.3), $p = 0.01$. No other significant associations with brain volume outcomes were detected. Due to non-normal residuals from WMH volume models, we investigated a binary model of WMH volume (> median and ≤ median) and found a similar positive association between diabetes and increased WMH volume ($p = 0.018$).

In secondary analyses (Table 4), each 1 mm Hg increase in mean SBP was associated with 0.004 cm^3 decrease in HC volume ($p = 0.02$) and 0.03 cm^3 increase in WMH volume ($p = 0.006$). In contrast, DBP was only associated with WMH volume; each 1 mm Hg increase in mean DBP was associated with 0.05 cm^3 increases in mean WMH volume ($p = 0.014$), though it was not significant after FDR correction.

In sensitivity analyses, individuals with a history of stroke were excluded to determine whether relationships were consistent among those with “subclinical” MRI findings in Tables B and C in the online supplementary material. Similar associations were identified for diabetes and hypertension, although hypertension was no longer significantly associated with increased WMH volume ($p = 0.06$).

Discussion

In this study, hypertension was associated with the presence of more infarcts, enlargement of ventricles, and increased volume of WMH. Diabetes was associated with increased prevalence of cerebral atrophy, including ventricular enlargement and sulcal widening. High serum LDL was not significantly associated with any of the measured cranial imaging outcomes.

The prevalence of infarcts in our study sample (34%) may appear higher than that reported in studies of people of European descent (21%) and African Caribbean heritage (22%) [9], but similar to that of a racially mixed group of Americans (31%) in a study involving participants of similar age and MRI scans with similar scoring [9, 27]. The prevalence of abnormal WMH (37%) was higher than that of similarly aged people of European descent (33%), but not the African Caribbeans (43%) in the same study [9]. The prevalence of hemorrhages was 5.7%, somewhat lower than in other population-based studies of European

descent [28, 29]. Hypertension was common in our sample (80.6%) and was associated with the presence of one or more brain infarcts. Hypertension was also associated with ventricle enlargement (a measure of cerebral atrophy), while elevated SBP was associated with larger WMH volume. Both associations have been reported in prior studies of middle-aged and elderly US White [30, 31] and African Caribbean [9] populations. In addition, higher SBP, but not DBP, was associated with higher prevalence of infarcts and ventricle enlargement and decreased hippocampal volume. Others have observed associations between ventricle enlargement and SBP, but not DBP [32]. On more detailed analysis of infarct subtypes, increases in SBP were associated with the presence of non-lacunar infarcts, while hypertension trended toward association with both subtypes, though only the subtype including any lacunar infarct was significant. The differing degrees of significance in the association of infarcts with SBP versus hypertension are uncertain. We did not detect an association between hypertension and hemorrhage, but this null result might reflect limited statistical power due to the low prevalence (5.7%) of MRI-defined hemorrhage in our sample.

Diabetes is highly prevalent in American Indians, representing a major public health problem [10, 33, 34]. Indeed, almost half of the study population had diabetes or impaired fasting glucose. Among our brain MRI findings, the strongest associations with diabetes appeared in measures of brain atrophy, including sulcal widening, ventricle enlargement, and reduced overall brain volume. Similar associations have been reported in several other studies [35–41], including studies of middle-aged African Americans [41, 42] and Asians [43, 44]. The underlying mechanism remains unclear, but in addition to microvascular disease, both hydration status and direct neurodegeneration might be involved [45, 46].

Although dyslipidemia is relatively common in American Indians [47, 48], we did not identify any associations between high LDL and brain abnormalities on MRI. This null result might reflect the complex relationships among LDL levels, decisions to treat with lipid-lowering medications, and the actual state of disease in our study sample. For example, people receiving treatment might also receive better health care than those who remain untreated. Others have reported associations linking higher continuous LDL levels with reduction in WMH and larger brain volumes in multiethnic US samples [49, 50] and in an outpatient sample in Japan [51]. The mechanism underlying this somewhat paradoxical relationship is uncertain, but it might be related to the special role of cholesterol in the repair and metabolism of white matter [52, 53].

As reported in other studies [54, 55], most MRI-defined infarcts (85.9%) are clinically covert, particularly in people with no history of clinically defined stroke. A relatively large number of our participants (29%) who did not have a history of clinical stroke or self-reported stroke had infarcts on MRI. Hypertension had a relatively strong correlation with non-lacunar infarcts in our sample, while neither diabetes nor high LDL was robustly associated with any type of infarct.

When compared with similar studies on other populations, these results on an American Indian population demonstrate that although the prevalence of both vascular risk factors and brain MRI defined infarcts and white matter disease may in some instances be higher than

that of other previously studied groups, the associations were relatively consistent and may have similar mechanisms of pathogenesis. This underscores the importance in lowering risk factors in this relatively vulnerable population with a high burden of diabetes and hypertension in an attempt to reduce infarcts, white matter microvascular changes, and brain atrophy.

Our study has certain limitations. First, the temporality of associations cannot be examined by using cross-sectional data. Nevertheless, strong biological support exists for a unidirectional relationship among most of the associations we examined, and our findings are consistent with other population studies of European and US Whites, Asians, and people of African descent. We were unable to address the impact of medications, therapies, or adherence to medications or therapies on vascular brain injury. Future studies are advised to examine whether earlier or stricter interventions for hypertension or diabetes can reduce MRI-defined infarcts or WMH.

Conclusion

This was the first large cohort study among elderly American Indians to obtain brain MRIs and examine risk factors for vascular brain injury. In our study sample, hypertension was associated with the presence of infarcts, and SBP was associated with increased volume of WMH, and diabetes was associated with measures of cerebral atrophy. Although similar findings have been reported in other populations, our results underscore the importance of diagnostic, monitoring, and preventive measures to reduce the prevalence of vascular brain injury – especially in a vulnerable, high-risk population such as American Indians.

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Table 1.

Associations of clinical cardiovascular risk factors with findings of brain abnormalities from 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 grades 1–2		Sulcal grade 3+ vs. sulcal grades 1–2		Ventricle grade 3+ vs. ventricle grades 1–2	
	PR (95% CI)	***p* value**	**PR (95% CI)**	***p* value**	**PR (95% CI)**	***p* value**	**PR (95% CI)**	***p* value**	**PR (95% CI)**	***p* value**	**PR (95% CI)**	***p* value**	**PR (95% CI)**	***p* value**
Hypertension	1.59 (1.20–2.10)	0.001 *	1.67 (1.16–2.40)	0.006 *	1.71 (1.01–2.90)	0.046	0.61 (0.32–1.15)	0.12	1.27 (1.01–1.60)	0.04	1.07 (0.96–1.19)	0.23	1.18 (1.04–1.33)	0.011 *
Diabetes	1.23 (1.00–1.51)	0.045	1.18 (0.91–1.53)	0.21	1.52 (1.01–2.30)	0.045	0.97 (0.55–1.71)	0.91	1.14 (0.95–1.37)	0.16	1.19 (1.08–1.31)	0.001 *	1.27 (1.16–1.40)	<0.001 *
High LDL	1.04 (0.84–1.28)	0.75	1.01 (0.77–1.33)	0.93	1.17 (0.75–1.83)	0.49	1.24 (0.66–2.33)	0.51	0.97 (0.79–1.18)	0.74	1.02 (0.91–1.13)	0.75	1.10 (0.99–1.21)	0.08

Models adjusted for age, sex, site, income, education, smoking, alcohol, and BMI.

* Denotes statistical significance after false discovery rate based correction for multiple comparisons.

MRI, magnetic resonance imaging; WMH, white matter hyperintensities; PR, prevalence ratio; LDL, low-density lipoprotein.

Table 2.

Secondary associations of clinical cardiovascular measures with findings of brain abnormalities from 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 grades 1–2		Sulcal grade 3+ vs. sulcal grades 1–2		Ventricle grade 3+ vs. ventricle grades 1–2	
	PR (95% CI)	***p* value**	**PR (95% CI)**	***p* value**	**PR (95% CI)**	***p* value**	**PR (95% CI)**	***p* value**	**PR (95% CI)**	***p* value**	**PR (95% CI)**	***p* value**	**PR (95% CI)**	***p* value**
Fasting glucose, mg/dL	1.00 (0.99–1.00)	0.47	1.00 (0.99–1.00	0.79	1.00 (0.99–1.01)	0.30	1.00 (0.99–1.01)	0.33	1.00 (0.99–1.00)	0.16	1.00 (0.99–1.00)	0.23	1.001 (1.001–1.002)	0.002
SBP, mm Hg	1.01 (1.00–1.01)	0.003	1.00 (1.00–1.01)	0.14	1.01 (1.01–1.02)	0.001	1.00 (0.99–1.01)	0.81	1.00 (0.99–1.01)	0.10	1.00 (0.99–1.00)	0.35	1.002 (1.000–1.004)	0.04
DBP, mm Hg	1.00 (0.99–1.01)	0.51	1.00 (0.99–1.02)	0.58	1.01 (0.99–1.03)	0.55	0.99 (0.97–1.02)	0.70	1.01 (0.99–1.02)	0.08	1.00 (0.99–1.01)	0.42	1.00 (0.99–1.01)	0.52
LDL, mg/dL	1.00 (0.99–1.00)	0.33	1.00 (0.99–1.00)	0.08	1.00 (0.99–1.01)	0.71	1.00 (0.99–1.01)	0.98	1.00 (0.99–1.00)	0.06	0.99 (0.99–1.00)	0.28	0.99 (0.99–1.00)	0.27

Models adjusted for age, sex, site, income, education, smoking, alcohol, and BMI.

MRI, magnetic resonance imaging; WMH, white matter hyperintensities; PR, prevalence ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein.

Table 3.

Associations of clinical cardiovascular risk factors with estimated brain volumes from structural cranial MRI in elderly American Indians

	Hippocampal volume, per cm^3		WMH volume, per cm^3		Brain volume, per cm^3	
	β (95% CI)	***p* value**	**β (95% CI)**	***p* value**	**β (95% CI)**	***p* value**
Hypertension	0.06 (−0.10 to 0.23)	0.45	1.32 (0.30 to 2.34)	0.01 *	0.27 (−9.85 to 10.39)	0.96
Diabetes	−0.07 (−0.21 to 0.06)	0.28	0.47 (-0.39 to 1.34)	0.28	−16.04 (−23.61 to −8.48)	<0.001 *
High LDL	0.08 (−0.05 to 0.21)	0.22	0.22 (-1.11 to 0.68)	0.64	−5.64 (−13.64 to 2.36)	0.17

Models adjusted for age, sex, site, income, education, smoking, alcohol BMI, and IC volume.

* Statistical significance after false discovery rate based correction for multiple comparisons.

MRI, magnetic resonance imaging; WMH, white matter hyperintensities; LDL, low-density lipoprotein.

Table 4.

Secondary associations of clinical cardiovascular measures with estimated brain volumes from structural cranial MRI in elderly American Indians

	Hippocampal volume, per cm^3		WMH volume, per cm^3		Brain volume, per cm^3	
	β (95% CI)	*p* value	β (95% CI)	*p* value	β (95% CI)	*p* value
Fasting glucose, mg/dL	−0.008 (−0.002 to 0.001)	0.22	0.002 (−0.01 to 0.01)	0.58	−0.04 (−0.12 to 0.04)	0.30
SBP, mm Hg	−0.004 (−0.007 to −0.001)	0.02	0.03 (0.01 to 0.06)	0.006	−0.08 (−0.25 to 0.10)	0.39
DBP, mm Hg	−0.001 (−0.008 to 0.005)	0.67	0.05 (0.01 to 0.10)	0.01	−0.03 (−0.40 to 0.34)	0.87
LDL, mg/dL	−0.0004 (−0.002 to 0.001)	0.68	−0.01 (−0.02 to 0.005)	0.22	0.08 (−0.03 to 0.19)	0.14

Models adjusted for age, sex, site, income, education, smoking, alcohol BMI, and IC volume

MRI, magnetic resonance imaging; WMH, white matter hyperintensities; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein.