Original Article

Left Ventricular Mass, Brain Magnetic Resonance Imaging, and Cognitive Performance

Results From the Strong Heart Study

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Abstract—Left ventricular mass (LVM) has been shown to serve as a measure of target organ damage resulting from chronic exposure to several risk factors. Data on the association of midlife LVM with later cognitive performance are sparse. We studied 721 adults (mean age 56 years at baseline) enrolled in the Strong Heart Study (SHS, 1993–1995) and the ancillary CDCAI (Cerebrovascular Disease and Its Consequences in American Indians) Study (2010–2013), a study population with high prevalence of cardiovascular disease. LVM was assessed with transthoracic echocardiography at baseline in 1993 to 1995. Cranial magnetic resonance imaging and cognitive testing were undertaken between 2010 and 2013. Generalized estimating equations were used to model associations between LVM and later imaging and cognition outcomes. The mean follow-up period was 17 years. A difference of 25 g in higher LVM was associated with marginally lower hippocampal volume (0.01%; 95% confidence interval, 0.02–0.00; P=0.001) and higher white matter grade (0.10; 95% confidence interval, 0.02–0.18; P=0.014). Functionally, participants with higher LVM tended to have slightly lower scores on the modified mini-mental state examination (0.58; 95% confidence interval, 1.08–0.08; P=0.024). The main results persisted after adjusting for blood pressure levels or vascular disease. The small overall effect sizes are partly explained by survival bias because of the high prevalence of cardiovascular disease in our population. Our findings emphasize the role of cardiovascular health in midlife as a target for the prevention of deleterious cognitive and functional outcomes in later life. **(*Hypertension*. 2017;70:00-00. DOI: 10.1161/HYPERTENSIONAHA.117.09807.)** ● **Online Data Supplement**

Key Words: blood pressure ■ cognitive functioning ■ echocardiography ■ left ventricular mass ■ magnetic resonance imaging

Hypertension, diabetes mellitus, and obesity have been associated with an increased risk of cognitive impairment, with greater risk among those with longer duration and greater severity.[1] Unfortunately, infrequent screening, delayed diagnoses, and poor management of these disease risk factors are common problems particularly among populations without adequate access to healthcare that points to cognitive impairment as a unique burden, especially in medically underserved areas. This disparity underscores the need for clinical markers that capture cumulative risk burden, in order to better identify individuals with excess risk of later cognitive decline.

Left ventricular mass (LVM) has been shown to be able to serve as an easily acquired clinical marker of target organ damage that provides a time-integrated summation of exposure to various risk factors.[2–4] Beyond its association with incident cardiovascular disease (CVD),[4,5] previous results indicate a possible relationship between LVM and later cognitive performance.[6] Specifically, in the Framingham Study, higher LVM was associated with lower cognitive performance over ≈3.5 years of follow-up.[6] However, this association was attenuated with adjustment for cardiovascular risk factors or CVD, suggesting vascular pathology as a mediating factor. Moreover, a relatively short duration of follow-up may have been inadequate to assess the entirety of purported cumulative effects of LVM on cognition. Other studies, including the Helsinki Aging Study, also reported left ventricular hypertrophy to be associated with cognitive decline as assessed by the mini-mental state examination.[7] Additionally, data stemming

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from a small cross-sectional European analysis found LVM to be associated with cognitive decline in elderly subjects, but cognitive and covariate assessment was limited.[8] All together, current evidence suggests a relationship between LVM and cognitive decline, but mediating factors such as vascular brain injury or atrophy are yet unclear as all prior analyses lacked morphological brain data. On the other hand, previous studies only included populations of European ancestry, so generalizability to other populations has not been established. Because genetic components, such as ApoE ε4 allele status, may play an important role in hippocampal atrophy and cognitive decline, risk for nonwhite populations may be different.[9,10]

The objective of this study was to assess the association of midlife LVM with later vascular brain injury and atrophy, and with cognitive performance in elderly American Indians. We hypothesized that higher LVM is associated with abnormal cranial magnetic resonance imaging (MRI) findings and with reduced cognitive performance.

Methods

Study Population

The CDCAI (Cerebrovascular Disease and Its Consequences in American Indians) study recruited surviving members of a 25-year, population-based cohort of American Indians focused on CVD, its risk factors, and its consequences (SHS [Strong Heart Study]).[11] The goals of the CDCAI aim were to characterize the burden, risk factors, and manifestations of vascular brain injury identified via cranial MRI.[11,12] Between 2010 and 2013, the CDCAI enrolled 1033 participants aged ≥64 years from American Indian communities in the Northern Plains, Southern Plains, and Southwestern United States. All participants underwent cranial MRI and cognitive testing according to standardized protocols.[12] For this analysis, 215 participants were removed because 1 community withdrew consent. An additional 74 individuals were excluded from analysis because they were missing LVM data collected at a previous SHS visit. Of the remaining participants (n=744), 23 with a self-reported history of stroke or TIA were excluded from analyses because these conditions are known independent causes and contributors of cognitive dysfunction.[1] The resulting final analytic sample consisted of 721 American Indians. The authorized body of each participating tribe approved the study. Written informed consent was obtained from all participants at enrollment. Written informed consent was obtained from all participants at enrollment.

Left Ventricular Mass

During the second examination of the SHS in 1993 to 1995 (SHS phase 2), transthoracic echocardiograms were performed using previously described methods.[13,14] Echocardiographic measures of cardiac geometry and function were collected in all participants by expert sonographers and reviewed offline by a highly experienced investigator. Left ventricular internal diastolic diameter, left ventricular posterior wall thickness, and interventricular septal thickness were measured in diastole on 2-dimensional echocardiograms according to American Society of Echocardiography criteria.[15] LVM was calculated by a necropsy-validated formula.[16]

MRI Measurements

Between 2010 and 2013, cranial MRI examinations of study participants were undertaken with methods as described previously in detail.[12,17] In short, MRI scans consisted of 6 MRI sequences undertaken with routine 1.5 T scanners nearby the reservations of American Indians: (1) sagittal T1-weighted localizer, (2) 5 mm axial-T1, (3) 5 mm axial-T2, (4) 5 mm axial-T2* susceptibility-weighted images, (5) 3 mm axial fluid-attenuated inversion recovery images, and (6) 1.5 mm sagittal T1-weighted volumetric gradient echo images.

Table 1. Baseline Characteristics of Strong Heart Study Participants, 1993 to 1995 (n=721)

Variable	
Left ventricular mass (g), mean (SD)	150.1 (32.1)
Age (y) mean (SD)	55.7 (5.6)
Female, n (%)	495 (68.7)
ApoE ε4 allele presence, n (%)	170 (23.6)
Income, n (%)	
<$10 000	195 (33.6)
$10 000 to <$25 000	253 (43.5)
≥$25 000	133 (22.9)
Education (no. of years), mean (SD)	12.4 (2.9)
Study site; n (%)	
Arizona	88 (12.2)
Oklahoma	305 (42.3)
Dakotas	328 (45.5)
Smoking status, n (%)	
Never	202 (28.8)
Ever	263 (37.5)
Current	236 (33.7)
Alcohol use status, n (%)	
Never	137 (19.3)
Ever	339 (47.7)
Current	234 (33.0)
PSS, mean (SD)	10.8 (4.4)
BMI, kg/m^2, mean (SD)	31.5 (5.8)
BMI (CDC), n (%)	
Normal	83 (11.5)
Overweight	234 (32.5)
Obese	402 (55.9)
Systolic blood pressure (mm Hg), mean (SD)	123.3 (16.4)
Diastolic blood pressure (mm Hg), mean (SD)	74.8 (9.3)
Heart disease, n (%)	86 (11.9)
Atrial fibrillation, n (%)	1 (0.1)
Hypertension, n (%)	225 (31.2)
Treatment for hypertension, n (%)	154 (21.4)
Diabetes mellitus, n (%)	211 (29.3)
Treatment for diabetes mellitus, n (%)	
None	589 (92.8)
Oral	0 (0.0)
Insulin	44 (6.9)
Oral/insulin	2 (0.3)

ApoE indicates apolipoprotein E; and BMI, body mass index.

Neuroradiologists trained in the study protocols and blinded to participant information read and graded all scans. A primary reader scored all MRI features, and a secondary reader independently scored for the infarcts, hemorrhages, or other focal lesions. Both neuroradiologists

reviewed any scans with discrepant readings until a consensus was reached. A quality control committee oversaw the conduct and evaluation of study procedures.[12,17]

Quantitative volumetric brain data were estimated using automated software, including FLEX for white matter hyperintensity (WMH) volume[18]; FIRST in FSL 5.0 and the ENIGMA1 protocol for the hippocampal volumes[19–21]; and FreeSurfer for total brain volume.[22] Brain and hippocampal, and WMH volumes were normalized to the total intracranial volume. Brain infarcts were defined as lesions 3 mm or larger (including both lacunes and larger cortical infarcts) with characteristic shape, absence of mass effect, and hyperintensity to gray matter on both T2-weighted images and fluid-attenuated inversion recovery to contrast with perivascular spaces, which have characteristic location and shape and demonstrate cerebrospinal fluid intensity on all sequences.[17,23] Lesions within white matter were required to be hypointense on T1-weighted images to distinguish them from focal WMH.[17,23–25] Severity of WMH was graded using a semiquantitative 10-point scale based on previously validated image standards for fluid-attenuated inversion recovery images for WMH.[17,26–29] Performing visual scoring based on a semiquantitative grading system was done because elderly patients often have a difficult time holding their head still in the scanner and because 3D volumetric scans and subsequent image processing with segmentation are relatively vulnerable to motion artifacts.[29–32] As this was a study of volunteers without acute symptoms, diffusion imaging was not performed for the detection of acute infarcts. Infarcts were scored for acuity based on the presence of edema or mass effect on the fluid-attenuated inversion recovery and T2 images. Brain hemorrhages were defined as lesions hypointense on gradient echo images (sequence 4), which are sensitive to even small amount of old blood in the brain tissue.[17,33] Both microhemorrhages and larger hemorrhages were recorded.

Neuropsychological Test Performance

Cognitive testing was completed at a clinic visit within 30 days of the MRI scan, typically the same day or the following day. Trained examiners evaluated general cognitive function using the 100-point modified mini-mental state (3MSE); processing speed using the Wechsler Adult Intelligence Scale Fourth Edition (WAIS-IV) Coding test[34]; phonemic fluency and executive functioning using the Controlled Oral Word Association test[35,36]; and verbal learning, immediate, and both immediate and delayed memory using the California Verbal Learning Test-Second Edition Short Form (CVLT-II SF).[37,38] For the purpose of this analysis, mild cognitive impairment was defined as 3MSE <78 points.[39]

Covariates

All study participants underwent clinic examination at both the LVM visit and the cognitive examination visit, which included personal interview, physical examination, and medication review.[11] Blood pressure status was assessed by the average of 2 seated blood pressure readings at clinic examination. Hypertension was defined as a self-report of current antihypertensive therapy or clinic measurement of systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg.[40] Body mass index (BMI) was calculated as body weight divided by height squared (kg/m^2). Diabetes mellitus was evaluated based on American Diabetes association criteria of fasting glucose ≥140 mg/dL, 2-hour postchallenge glucose ≥200 mg/dL, or use of oral hypoglycemic medication or insulin.[41,42] History of CVD (coronary heart disease, heart failure, TIA, or stroke) was determined based on self-report, and by adjudication procedures using systematic review of medical records.[43] Cohen Perceived Stress Scale (PSS) was used to describe the level of general stress.[44] ApoE ε4 allele status was assayed by immunoblot.[45–47]

Statistical Analysis

Descriptive statistics of demographic characteristics and covariates are presented as mean (SD) or frequency (%; Table 1; Table S1). Generalized Estimating Equations were used to assess associations between LVM, cranial MRI findings, and cognitive performance (Table 2). An initial model adjusted for age, sex, education (continuously as number of years), income (<10K, 10 to <25K, and ≥25K annually per household), BMI (normal, overweight, and obese), presence of at least 1 ApoE ε4 allele, and study site. A second model additionally adjusted for BMI, alcohol use (never, ever, and

Table 2. Associations of LVM With Neuroimaging and Neurocognitive Findings (per 25 g Difference of Left Ventricular Mass)

	Basic Adjustment		Full Adjustment	
Neuroimaging findings	Coefficient (95% CI)	*P* value	Coefficient (95% CI)	*P* value
Brain volume (%)	−0.287 (−0.618 to 0.043)	0.088	−0.321 (−0.656 to 0.013)	0.060
Hippocampal volume (%)	−0.009 (−0.014 to −0.003)	0.003*	−0.010 (−0.015 to −0.004)	0.001*
White matter grade	0.102 (0.026 to 0.178)	0.008*	0.098 (0.020 to 0.176)	0.014*
White matter hyperintensity volume (%)	0.028 (−0.005 to 0.062)	0.095	0.026 (−0.009 to 0.061)	0.152
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Infarcts	1.134 (0.971 to 1.324)	0.112	1.116 (0.951 to 1.308)	0.178
Hemorrhage	0.761 (0.493 to 1.173)	0.216	0.748 (0.474 to 1.179)	0.211
Neurocognitive findings	Coefficient (95% CI)	*P* value	Coefficient (95% CI)	*P* value
3MSE	−0.632 (−1.124 to −0.140)	0.012*	−0.576 (−1.075 to −0.077)	0.024
WAIS-IV Coding	−0.356 (−1.159 to 0.446)	0.384	−0.225 (−1.053 to 0.602)	0.593
COWA	−0.779 (−1.482 to −0.075)	0.030	−0.693 (−1.410 to 0.024)	0.058
CVLT-II learning	−0.038 (−0.344 to 0.269)	0.810	−0.043 (−0.361 to 0.274)	0.788
CVLT-II short recall	−0.064 (−0.201 to 0.074)	0.364	−0.077 (−0.218 to 0.065)	0.289
CVLT-II long recall	0.001 (−0.145 to 0.147)	0.987	0.000 (−0.150 to 0.151)	0.997

Basic models adjust for age, sex, education, income, site, ApoE ε4 allele carrier status, and BMI. Full models adjust additionally for smoking, alcohol use, PSS, previous atrial fibrillation, diabetes mellitus, and hypertension. Statistically significant results are indicated by * and are corrected for multiple comparisons using the Benjamini–Hochberg procedure to obtain a false discovery rate of 0.10. 3MSE indicates modified mini-mental state examination; ApoE, apolipoprotein E; BMI, body mass index; CI, confidence interval; COWA, Controlled Oral Word Association Test; CVLT-II, California Verbal Learning Test-II Short Form; *P* value, *P* value (unadjusted for multiple comparisons); PSS, Perceived Stress Scale; and WAIS-IV, Wechsler Adult Intelligence Scale Fourth Edition.

current), smoking status (never, ever, and current), PSS, CVD, atrial fibrillation, diabetes mellitus status, and hypertension at the time of echocardiogram. Sensitivity analyses for the main models were undertaken by additionally adjusting for systolic blood pressure and diastolic blood pressure at follow-up (Table 3) and by adjusting for self-reported vascular disease at the time of neurocognitive examination (Table 4). Multiple testing was addressed using the false discovery rate, set at the 0.10 α level using the Benjamani–Hochberg procedure for each set of neuroimaging and neurocognitive analyses.[48] Multiple imputation by chained equations was used to handle missing covariate data, and results were pooled using Rubin rules for model-based statistics and directly pooling resampling.[49] Additional analyses were undertaken to test for effect modification by sex (Table S2) and stratified by ApoE ε4 carrier status (Table S3). Finally, to assess whether associations between LVM and cognitive function were attributable to MRI findings, we applied mediation analyses using Sobel statistic, which is interpreted as the average causally mediated effect, along with a bias-corrected percentile bootstrap to obtain 95% confidence intervals (CIs) and *P* values (Table S4).[50] Statistical analyses were conducted using R version 3.3.3 and packages mice and sandwich.[49,51,52]

Results

Baseline characteristics of study participants at the second examination of SHS (1993–1995) are presented in Table 1. At the time of LVM assessment, the mean age of the study population was ≈56 years, predominantly female with a mean of 12 years of education. Risk factors for vascular disease were markedly elevated: mean BMI was 31.5 kg/m^2, prevalence of hypertension was 31%, and prevalence of diabetes mellitus was 29%. Prevalence of self-reported current alcohol use was 33% and current smoking status was 34%. Responses to the perceived stress scale indicated an average value of 10.8 and a small fraction (4.0%) had stress >20, which is considered high stress. Mean LVM was 150 g (142 g in women and 169 g in men).

Characteristics of study participants at the time of neurocognitive examination (2010–2013), an average of 17.3 years after the second examination of SHS, are presented in Table S1. The mean age of the study population was 73 years. The burden of cardiovascular risk factors deteriorated. Most notably, diabetes mellitus prevalence escalated to 52%, hypertension prevalence to 80%, whereas mean BMI was still 31.5 kg/m^2. Incident vascular events (ie, stroke, congestive heart failure, or myocardial infarction) were self-reported by 13% of participants. Mild cognitive impairment was present in 10% of study participants.

Regression coefficients and 95% CI expressing associations for LVM, per 25 g difference, with cranial MRI findings and cognitive performance are presented in Table 2. Among MRI findings, a 25 g difference in LVM was statistically significantly associated with a 0.009% lower hippocampal volume adjusting for age, sex, education, site, income, BMI, and ApoE ε4 allele carrier status (95% CI, −0.014% to −0.003%; *P*=0.003) and a slightly higher grade of WMHs (0.10; 95% CI, 0.026–0.178; *P*=0.008). These associations were also statistically significant after further control of smoking, alcohol use, PSS, atrial fibrillation, diabetes mellitus, and hypertension (−0.01%; 95% CI, −0.015% to −0.004%; *P*=0.001 and 0.10; 95% CI, 0.02 to 0.176; *P*=0.014, respectively). Associations with WMH volume, brain volume, hemorrhage, and infarcts

Table 3. Blood Pressure–Adjusted Associations of Left Ventricular Mass With Neuroimaging and Neurocognitive Findings (per 25 g Difference of Left Ventricular Mass)

	Basic Adjustment		Full Adjustment	
Neuroimaging findings	Coefficient (95% CI)	*P* value	Coefficient (95% CI)	*P* value
Brain volume, %	−0.291 (−0.628 to 0.046)	0.091	−0.318 (−0.657 to 0.021)	0.066
Hippocampal volume, %	−0.009 (−0.015 to −0.003)	0.003*	−0.010 (−0.016 to −0.004)	0.001*
White matter grade	0.078 (0.002 to 0.155)	0.045	0.077 (−0.001 to 0.155)	0.052
White matter hyperintensity volume, %	0.017 (−0.017 to 0.051)	0.334	0.019 (−0.017 to 0.054)	0.301
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Infarcts	1.093 (0.930 to 1.286)	0.281	1.098 (0.933 to 1.293)	0.261
Hemorrhage	0.755 (0.481 to 1.186)	0.223	0.735 (0.457 to 1.181)	0.203
Neurocognitive findings	Coefficient (95% CI)	*P* value	Coefficient (95% CI)	*P* value
3MSE	−0.586 (−1.084 to −0.087)	0.021	−0.569 (−1.076 to −0.061)	0.028
WAIS-IV Coding	−0.333 (−1.161 to 0.495)	0.431	−0.229 (−1.063 to 0.604)	0.590
COWA	−0.753 (−1.473 to −0.033)	0.041	−0.700 (−1.421 to 0.021)	0.057
CVLT-II learning	−0.032 (−0.347 to 0.283)	0.843	−0.035 (−0.355 to 0.286)	0.832
CVLT-II short recall	−0.054 (−0.195 to 0.087)	0.452	−0.057 (−0.198 to 0.085)	0.433
CVLT-II long recall	0.017 (−0.133 to 0.166)	0.828	0.020 (−0.133 to 0.172)	0.802

Basic models adjust for age, sex, education, income, site, BMI, ApoE ε4 allele carrier status, duration of follow-up, systolic and diastolic blood pressures at left ventricular mass and neurocognitive assessment. Full models adjust additionally for smoking status, alcohol use, PSS, previous atrial fibrillation, diabetes mellitus, and hypertension. Statistically significant results are indicated by * and are corrected for multiple comparisons using the Benjamini–Hochberg procedure to obtain a false discovery rate of 0.10. 3MSE indicates modified mini-mental state examination; ApoE, apolipoprotein E; BMI, body mass index; CI, confidence interval; CVLT-II, California Verbal Learning Test-II Short Form; COWA, Controlled Oral Word Association Test; *P* value, *P* value (unadjusted for multiple comparisons); PSS, Perceived Stress Scale; and WAIS-IV, Wechsler Adult Intelligence Scale Fourth Edition.

Table 4. Vascular Disease-Adjusted Associations of Left Ventricular Mass With Neuroimaging and Neurocognitive Findings (per 25 g Difference of Left Ventricular Mass)

	Basic Adjustment		Full Adjustment	
Neuroimaging findings	Coefficient (95% CI)	*P* value	Coefficient (95% CI)	*P* value
Brain volume, %	−0.288 (−0.620 to 0.044)	0.089	−0.324 (−0.660 to 0.012)	0.059
Hippocampal volume, %	−0.009 (−0.015 to −0.003)	0.002*	−0.010 (−0.016 to −0.004)	0.001*
White matter grade	0.102 (0.026 to 0.178)	0.008*	0.098 (0.020 to 0.177)	0.013*
White matter hyperintensity volume, %	0.028 (−0.005 to 0.062)	0.097	0.026 (−0.009 to 0.061)	0.152
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Infarcts	1.131 (0.969 to 1.321)	0.119	1.114 (0.950 to 1.306)	0.185
Hemorrhage	0.767 (0.498 to 1.179)	0.227	0.754 (0.481 to 1.184)	0.221
Neurocognitive findings	Coefficient (95% CI)	*P* value	Coefficient (95% CI)	*P* value
3MSE	−0.620 (−1.110 to −0.131)	0.013*	−0.565 (−1.063 to −0.067)	0.026
WAIS-IV coding	−0.328 (−1.130 to 0.475)	0.424	−0.208 (−1.037 to 0.621)	0.622
COWA	−0.760 (−1.465 to −0.055)	0.035	−0.685 (−1.403 to 0.033)	0.061
CVLT-II learning	−0.034 (−0.341 to 0.272)	0.827	−0.038 (−0.355 to 0.279)	0.815
CVLT-II short recall	−0.063 (−0.200 to 0.075)	0.371	−0.075 (−0.216 to 0.066)	0.300
CVLT-II long recall	0.001 (−0.146 to 0.147)	0.991	0.000 (−0.151 to 0.151)	0.998

Basic models adjust for age, sex, education, income, site, BMI, ApoE ε4 allele carrier status, duration of follow-up and vascular disease at follow-up. Full models adjust additionally for smoking, alcohol use, PSS, previous atrial fibrillation, diabetes mellitus, and hypertension. Statistically significant results are indicated by * and are corrected for multiple comparisons using the Benjamini–Hochberg procedure to obtain a false discovery rate of 0.10. 3MSE indicates modified mini-mental state examination; ApoE, apolipoprotein E; BMI, body mass index; CI, confidence interval; CVLT-II, California Verbal Learning Test-II Short Form; COWA, Controlled Oral Word Association Test; *P* value, *P* value (unadjusted for multiple comparisons); PSS, Perceived Stress Scale; and WAIS-IV, Wechsler Adult Intelligence Scale Fourth Edition.

were not statistically significant. Among measures of cognitive performance, a 25 g of LVM difference was statistically significantly associated with a slightly lower 3MSE score adjusting for age, sex, education, income, site, BMI, and presence of at least 1 ApoE ε4 allele (0.63; 95% CI, −1.124 to −0.14; *P*=0.012), whereas no statistically significant associations with Controlled Oral Word Association test, WAIS-IV coding, CVLT-II SF total learning scoring, and CVLT-II SF immediate and delayed free recall scoring were observed. Further control of comorbidities and risk factors rendered the 3MSE association nonsignificant. When we conducted sensitivity analyses with adjustment for systolic blood pressure and diastolic blood pressure (Table 3), only associations with hippocampal volume remained statistically significant in our fully adjusted models. Further sensitivity analyses with adjustment for self-reported vascular events, including stroke, myocardial infarction, or congestive heart failure, are presented in Table 4. In models adjusting for demographic factors as well as comorbidities and risk factors, associations with hippocampal volume and white matter grade were statistically significant.

No models showed effect modification by sex (Table S2). In models stratified by ApoE ε4 allele carrier status (Table S3), no associations were statistically significant; however, this may owe to a smaller effective sample size, particularly among ApoE ε4–positive participants (n=170). Mediation analyses found a statistically significant average causal-mediated effect relating LVM to 3MSE scores via hippocampal volume after adjusting for age, sex, education, income, site, duration of follow-up, BMI and presence of at least 1 ApoE ε4 allele (Table S4). Hippocampal volume had a −0.137 average causal-mediated effect relating LVM to 3MSE (95% bootstrap CI, −0.275 to −0.034; *P*=0.03). White matter grade had a −0.100 average causal-mediated effect relating LVM to 3MSE (95% bootstrap CI, −0.236 to −0.011; *P*=0.07).

Discussion

These findings, from a population-based cohort study of middle-aged and elderly American Indians, suggest that higher LVM in midlife is associated with a slightly lower general cognitive performance in later life. These functional changes are accompanied by lower hippocampal volume and greater severity of WMHs, which may play an explanatory role. In fact, mediation analyses suggest that LVM may lead to hippocampal atrophy, which in turn could lead to impaired cognition. However, overall effect sizes are small. This lack of clinical significance can, on the one hand, be explained by survival bias because of the high prevalence of CVD and concomitant risk factors in our study population, on the other hand, by the multifactorial nature of cognitive decline.

Vascular risk factors, such as hypertension, are known to play a significant role in accelerating structural brain aging and cognitive decline.[1,53] Landmark studies, such as the Honolulu Asia Aging Study, have shown a long-term relationship of midlife blood pressure levels to late-life cognitive function.[54] In the same study, β-amyloid plasma levels started decreasing

≥15 years before Alzheimer Disease was diagnosed, and the association of β-amyloid with Alzheimer disease was mediated by midlife blood pressure.[55] Similarly, an active blood pressure lowering regimen has been shown to alter the progression of WMHs, a key finding in this study.[56] Our observed associations of LVM with cognitive performance can hence be partially explained by adverse effects of cardiovascular risk factors (in particular, blood pressure) on the microcirculatory system of the hippocampal region leading to atrophy and its consequent functional deficits. We, therefore, performed additional sensitivity analyses adjusting for blood pressure levels. Our main results did not change. These findings seem to suggest that CVD—predicted by higher LVM—may indeed explain, in part, some morphological brain changes which supports a role in increased brain aging.[57] Nonetheless, whether the relationship of LVM with lower cognitive performance is because of residual factors or unmeasured confounding leading to functional deficits, some other process, or whether the occurrence of LVM and cognitive decline are independent but convergent disease processes remains uncertain. However, although, on the one hand, the concomitant occurrence of LVM and dementia may synergize and increase the risk of poor cognition in later life,[58] it may, on the other hand, open a window of opportunity for future prevention through early detection and intervention.[59,60]

These analyses are the first to assess the association of midlife LVM with later vascular brain injury and atrophy, and with cognitive performance in American Indians. Other strengths of this study include a large, well-characterized cohort with standardized, rigorous assessment of echocardiographic measures of LVM, MRI findings, and cognitive performance. However, there are also noteworthy limitations. Survival bias may have significantly influenced our findings as more than half of participants from the baseline SHS phase I examination died before the CDCAI study. This bias may have led to an underestimation of our findings. Furthermore, cognitive ability and brain morphology were not evaluated at baseline, preventing analyses of longitudinal changes in such measures. This limitation is shared with previous investigations that partly relied on cross-sectional data.[6,8] In addition, cognitive dysfunction has not been validated in American Indians, hence the degree of clinical significance for loss in these performance measures is yet unclear.[61] Finally, as this was a study of volunteers without acute symptoms nearby the reservations of American Indians, more advanced imaging techniques such as diffusion tensor imaging or perfusion imaging which we might have done in a university medical center setting could not be performed. Thus, we may have underestimated the burden of small-vessel disease in our population.

Perspectives

Higher LVM in middle-aged American Indians is associated with slight morphological brain changes and decreased cognitive performance in later years. As elderly American Indians are one of the fastest growing segments of the US population, and because patients with CVD are surviving longer, our findings warrant further research into clinical outcomes of CVD and related conditions as possible targets for prevention and intervention to ameliorate deleterious cognitive and functional outcomes.[62]

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Disclosures

None.

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Novelty and Significance

What Is New?

- Data on the association of midlife left ventricular mass with later cognitive performance are sparse and all previous analyses lacked morphological brain data.

What Is Relevant?

- In brain magnetic resonance imaging assessments, a 25 g increase in left ventricular mass in midlife was associated with marginally lower hippocampal volume and higher white matter grade at later age. Functionally, individuals with higher left ventricular mass tended to have lower scores in the modified mini-mental state examination.

Summary

Higher left ventricular mass in middle-aged American Indians was associated with slightly decreased cognitive performance in later years. The small overall effect sizes are partly explained by survival bias because of the high prevalence of cardiovascular disease in our population. These findings emphasize the role of cardiovascular health in midlife as a target for the prevention of deleterious cognitive and functional outcomes in later life.

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Left ventricular Mass, Brain MRI and Cognitive Performance: Results from the Strong Heart Study

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Short title: Left ventricular mass, Brain MRI and Cognitive Functioning

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Supplementary Table S1. Characteristics of study participants at time of neurocognitive assessment, 2010 to 2013 (n = 721)

Variable		
Age (years); *mean (sd)*	73.0	(5.7)
Elapsed time from LVM assessment (years); *mean (sd)*	17.3	(1.1)
Body mass index (kg/m^2); *mean (sd)*	31.5	(6.7)
Self-reported myocardial infarction; *n (%)*	91	(12.6)
Self-reported stroke; *n (%)*	44	(6.1)
Self-reported congestive heart failure; *n (%)*	54	(7.5)
Self-reported vascular disease; *n (%)*	93	(12.9)
Self-reported diabetes; *n (%)*	372	(51.6)
Self-reported hypertension; *n (%)*	575	(79.8)
Systolic blood pressure (mmHg); *mean (sd)*	135.4	(21.6)
Diastolic blood pressure (mmHg); *mean (sd)*	68.2	(11.4)
Mild cognitive impairment (3MSE <78); *n (%)*	70	(10.2)

Supplementary Table S2. Effect modification tests for sex by left ventricular mass

Neuroimaging findings	Basic adjustment				Full adjustment			
	Coefficient	95% CI	p-value	sig.	Coefficient	95% CI	p-value	sig.
Brain volume (%)	-0.112	(-0.692, 0.468)	0.704		-0.107	(-0.688, 0.475)	0.719	
Hippocampal volume (%)	0.001	(-0.010, 0.011)	0.915		0.000	(-0.011, 0.011)	0.997	
White matter grade	-0.035	(-0.183, 0.113)	0.644		-0.048	(-0.198, 0.101)	0.524	
White matter hyperintensity volume (%)	0.013	(-0.053, 0.080)	0.693		0.008	(-0.058, 0.073)	0.818	
	Odds Ratio	95% CI	p-value		Odds Ratio	95% CI	p-value	
Infarcts	1.213	(0.889, 1.655)	0.224		1.217	(0.886, 1.671)	0.225	
Hemorrhage	1.244	(0.546, 2.830)	0.603		1.275	(0.554, 2.931)	0.568	
Neurocognitive findings	Coefficient	95% CI	p-value	sig.	Coefficient	95% CI	p-value	sig.
3MSE	-0.229	(-1.165, 0.708)	0.632		-0.218	(-1.166, 0.730)	0.652	
WAIS-IV Coding	-0.111	(-1.592, 1.370)	0.883		-0.199	(-1.685, 1.287)	0.793	
COWA	-0.465	(-1.848, 0.918)	0.510		-0.454	(-1.848, 0.939)	0.523	
CVLT-II Learning	-0.430	(-1.021, 0.161)	0.154		-0.421	(-1.017, 0.175)	0.166	
CVLT-II Short recall	-0.159	(-0.424, 0.106)	0.239		-0.154	(-0.418, 0.110)	0.254	
CVLT-II Long recall	-0.257	(-0.543, 0.029)	0.078		-0.249	(-0.535, 0.037)	0.088	

Coefficient estimated from linear and logistic models adjusting for a product term between sex and left ventricular mass.
Basic models adjust for age, education, income, site, duration of follow-up, BMI and ApoE ε4 allele carrier status.
Full models additionally adjust for smoking, alcohol use, PSS, prior atrial fibrillation, diabetes, and hypertension.
95% CI, 95% confidence interval; p, p-value (unadjusted for multiple comparisons)
Statistical significant results are indicated by * and are corrected for multiple comparisons using the Benjamini Hochberg procedure to obtain a false discovery rate of 0.10.
3MSE, Modified Mini-Mental State Examination
WAIS-IV, Wechsler Adult Intelligence Scale Fourth Edition
COWA, Controlled Oral Word Association Test
CVLT-II, California Verbal Learning Test-II Short Form

Supplementary Table S3. Association of left ventricular mass with later neuroimaging/ neurocognitive measures stratified by ApoE ε4 carrier status

	ApoE ε4 positive				ApoE ε4 negative			
Neuroimaging findings								
	Coefficient	95% CI	p-value	sig.	Coefficient	95% CI	p-value	sig.
Brain volume (%)	-0.542	(-1.172, 0.087)	0.091		-0.173	(-0.534, 0.188)	0.348	
Hippocampal volume (%)	-0.006	(-0.017, 0.006)	0.353		-0.009	(-0.016, -0.003)	0.006	
White matter grade	0.229	(0.058, 0.400)	0.009		0.083	(0.001, 0.164)	0.048	
White matter hyperintensity volume (%)	0.059	(-0.003, 0.120)	0.061		0.029	(-0.013, 0.071)	0.177	
	Odds Ratio	95% CI	p-value		Odds Ratio	95% CI	p-value	
Infarcts	1.249	(0.912, 1.711)	0.167		1.109	(0.916, 1.343)	0.290	
Hemorrhage	0.916	(0.434, 1.937)	0.819		0.729	(0.433, 1.228)	0.235	
Neurocognitive findings	Coefficient	95% CI	p-value	sig.	Coefficient	95% CI	p-value	sig.
3MSE	-0.179	(-1.292, 0.935)	0.753		-0.690	(-1.284, -0.095)	0.023	
WAIS-IV Coding	-0.104	(-1.865, 1.656)	0.908		-0.262	(-1.156, 0.632)	0.565	
COWA	-1.361	(-2.994, 0.272)	0.102		-0.785	(-1.577, 0.007)	0.052	
CVLT-II Learning	0.141	(-0.494, 0.775)	0.664		-0.081	(-0.457, 0.294)	0.671	
CVLT-II Short recall	-0.043	(-0.283, 0.197)	0.725		-0.039	(-0.207, 0.129)	0.647	
CVLT-II Long recall	0.039	(-0.246, 0.323)	0.790		0.009	(-0.190, 0.209)	0.927	

Models adjust for age, sex, education, income, site, duration of follow-up, and BMI.
95% CI, 95% confidence interval; p, p-value (unadjusted for multiple comparisons)
Statistical significant results are indicated by * and are corrected for multiple comparisons using the Benjamini Hochberg procedure to obtain a false discovery rate of 0.10.
3MSE, Modified Mini-Mental State Examination
WAIS-IV, Wechsler Adult Intelligence Scale Fourth Edition
COWA, Controlled Oral Word Association Test
CVLT-II SF, California Verbal Learning Test-II Short Form

Supplementary Table S4. Causal mediation of left ventricular mass and modified mini mental state exam findings

	Coefficient	95% CI	p-value
Hippocampal volume			
Average direct effect	-0.503	(-1.044, 0.039)	0.069
Total effect	-0.647	(-1.189, -0.105)	0.019
Average causally mediated effect	-0.137	(-0.275, -0.034)	0.0282
White matter grade			
Average direct effect	-0.555	(-1.097, -0.014)	0.044
Total effect	-0.647	(-1.189, -0.105)	0.019
Average causally mediated effect	-0.100	(-0.236, -0.011)	0.0702

Coefficients estimated from linear regression models.
All models control for age, duration of follow-up, sex, education, income, site, BMI, and ApoE ε4 allele carrier status.
95% CIs and p-values were obtained from multiple imputed models using robust sandwich error estimation and pooled by Rubin's Rules.
Average causally mediated effect (95% CIs and p-values) was calculated from bias corrected percentile bootstrap and direct pooling of multiple imputed datasets.