

Associations of Echocardiography Markers and Vascular Brain Lesions: The ARIC Study

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Background—Associations between subtle changes in cardiac and cerebral structure and function are not well understood, with some studies suggesting that subclinical cardiac changes may be associated with markers of vascular brain insult.

Methods and Results—Data from the ARIC (Atherosclerosis Risk in Communities) Study (5th ARIC visit; 2011–2013; N=1974) were used to explore relationships between abnormalities of cardiac structure/function and subclinical brain disease and to test specific associations between those cardiac and vascular brain changes that share a common mechanism. In adjusted models white matter hyperintensities were 0.66 cm³ greater (95% confidence interval [CI] 0.08–1.25) for every 1-mm increase in left ventricular LV wall thickness and 0.64 cm³ greater (95% CI 0.19–1.08) for every 10 g/m² increase in LV mass index, both markers of LV structure. Odds of brain infarction also increased with greater LV wall thickness (odds ratio 1.11, 95% CI 1.01–1.23 per 1 mm) and larger LV mass (odds ratio 1.08, 95% CI 1.00–1.17 per 10 g/m²). Higher ejection fraction (per 5%), a marker of systolic function, was significantly associated with decreased odds of overall infarct (odds ratio 0.85, 95% CI 0.77–0.95), but not with cortical infarction (odds ratio 0.92, 95% CI 0.78–1.08).

Conclusions—Among elderly participants in a large cohort study, subclinical markers of LV structure and LV systolic dysfunction were associated with increased odds of brain infarction and more white matter hyperintensities, independent of other vascular risk factors. This suggests end-organ dysfunction occurs in the heart and brain in parallel, with further studies needed to determine causality. (*J Am Heart Assoc.* 2018;7:e008992. DOI: 10.1161/JAHA.118.008992)

Key Words: brain infarction • cardiology • echocardiography • white matter disease

Heart failure (HF) is a significant public health problem, affecting over 5 million individuals with the estimated cost of nearly \$35 billion.¹ Both the prevalence and incidence of HF are greatest among the elderly. Subclinical cardiac dysfunction (ACC/AHA Stage B HF) is present in up to 44% of elderly people, predominantly occurs despite preserved left ventricular ejection fraction (LVEF), and is associated with a higher risk of incident HF or death.² This large burden of subclinical cardiac dysfunction may also be associated with

brain changes and risk for subclinical brain injury in the elderly, ranging from subclinical stroke to more chronic changes such as white matter injury or white matter hyperintensities (WMH). Mechanisms of these brain changes in patients with clinical or subclinical HF include strokes from reduced systolic function, a secondary arrhythmia, or possibly subtle hypoperfusion even in the setting of only modestly reduced ejection fraction (EF). Importantly, co-occurrence of cardiac and brain dysfunction could result from shared cardiovascular risk factors. For example, systemic hypertension can result in increased left ventricular (LV) mass and left atrial (LA) volume due to chronically increased cardiac afterload load,^{3–5} and is also associated with an increased incidence of lacunar infarction and WMH.^{6,7}

We hypothesize that there are shared mechanisms by which subclinical alterations in cardiac structure and function associate with subclinical brain lesions. Specifically, we hypothesize that echocardiographic features indicative of chronically increased cardiac load are associated with vascular changes in the brain such as lacunar infarcts and WMH. We believe that these associations will be independent of other vascular risk factors, including the presence of hypertension. In contrast, we hypothesize that echocardiographic

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Clinical Perspective

What Is New?

- Subclinical changes in cardiac structure and function occur in parallel with markers of cerebrovascular brain insult; specifically, subclinical changes in left ventricular mass were associated with greater odds of infarction and size of white matter hyperintensities even when controlling for hypertension.

What Are the Clinical Implications?

- These findings emphasize the importance of control of shared risk factors and may suggest a direct link between cardiac function and potential for neurologic sequelae.

indices of abnormal LV function indicate increased embolic risk and thus will more strongly associate with embolic-appearing brain infarcts. In this study we define the cross-sectional associations of cardiac structure, systolic function, and diastolic function, and subclinical brain markers in nearly 2000 elderly participants in the community-based ARIC (Atherosclerosis Risk in Communities) Study attending the fifth study visit.

Methods

The ARIC Study initially recruited 15 792 people in 1987-1989 from 4 US communities: Washington County, MD; Forsyth County, NC; the suburbs of Minneapolis, MN; and the suburbs of Jackson, MS. Participants have been studied in person for a total of 5 visits, with the most recent visit (ARIC visit 5; 2011-2013) including the ARIC-NCS (ARIC Neurocognitive Study), which provided detailed cognitive assessment, brain magnetic resonance imaging (MRI) in a subset of participants (N=1974), as well as echocardiography (N=6118).⁸ As reported previously,⁹ participants for brain MRI were selected from the larger ARIC-NCS cohort on the basis of having no MRI contraindications and any of the following: having had a prior research brain MRI in the ARIC Study, having impaired cognition, or being chosen from a sample of normals. The prevalence of dementia in the ARIC-NCS Study was 9.0%.⁸ Of the participants who then had a research brain MRI, 5.4% (N=114) had a diagnosis of dementia. The sampling frame and weights for the ARIC Study have also been previously described.¹⁰ The study was approved by the institutional review boards at all institutions involved in the study, and informed consent was obtained from all participants. The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure in accordance with ARIC policies.

Brain MRI

All 4 field centers included brain imaging with a 3-T MRI scanner with the following sequences: MP RAGE, Axial T2* GRE, Axial T2 FLAIR, and Axial DTI. All scans were evaluated for protocol compliance and scan quality by a trained MRI image analyst, and these data were tracked through the coordinating center. MP RAGE images were preprocessed to correct intensity inhomogeneity and gradient nonlinearity using methods developed by the Mayo Aging and Dementia Imaging Research Laboratory and previously published.¹¹ For rating of cerebrovascular lesions, MRI images were read centrally at the Mayo Aging and Dementia Imaging Research Laboratory by experienced image analysts with confirmation by neuroradiologists. Studies were evaluated for presence, size (in multiple axes), and location of infarcts in the central gray matter, hemispheric cortical infarctions, and hemispheric white matter lacunar infarctions (Figure). Infarcts were classified as cortical if they extended to the cortical surface (cortical gray and could include underlying white matter) and were hyperintense on fluid-attenuated inversion recovery sequences as previously described.⁹ Lacunar infarcts were defined as subcortical infarcts between 3 and 20 mm in maximum diameter, as has been defined previously in ARIC.⁹ Infarcts were either present or absent, and the number of each infarct type was considered in a separate analysis. Quantitative measures of WMH volume were derived from the axial FLAIR images using a semiautomated algorithm developed by the Mayo Aging and Dementia Imaging Research Laboratory.¹² Following segmentation, WMH volumes were calculated in different anatomic compartments using an atlas-based parcellation technique. Estimated total intracranial volume was quantified from the MPRAGE pulse sequences using Freesurfer (version 5.1). All analyses including the WMH data included estimated total intracranial volume as a covariate in statistical models.

Echocardiography

Echocardiograms were performed during ARIC Visit 5 (2011-2013). All echocardiograms were performed using dedicated Philips iE33 ultrasound systems (Bothell, WA) with Vision 2011 and X5-1 xMatrix transducer for 2-dimensional, Doppler, and 3-dimensional data acquisition, purchased specifically for use in the ARIC Study. Details of the design and procedures for echocardiography at the fifth ARIC visit have been previously published, including reproducibility metrics. Coefficients of variation for measures of LV structure, systolic function, and diastolic function were consistently $\leq 10\%$.¹³ LV dimensions and wall thickness were measured from the parasternal long-axis view according to the recommendations of the American Society of Echocardiography.¹⁴ LV mass was calculated from LV linear dimensions and indexed to body surface area as recommended by the American Society of Echocardiography

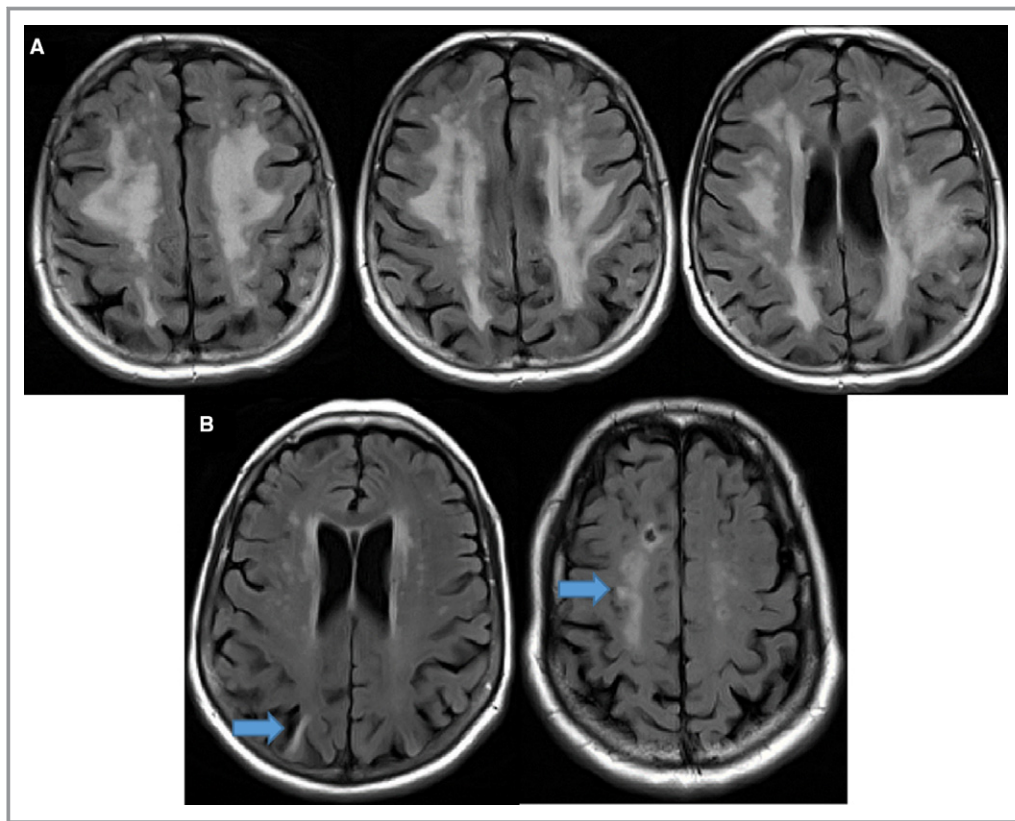


Figure. **A**, Sample MRI demonstrating white matter hyperintensity (WMH) in a participant. The total calculated WMH volume demonstrated in this axial fluid-attenuated inversion recovery (FLAIR) is 101.2 cm³, and the total percentage of normal white matter that includes WMH is 19.36%. **B**, Sample participant's axial FLAIR sequences demonstrating cortical infarction (left arrow) and lacunar infarction (right arrow) as defined by study criteria. MRI indicates magnetic resonance imaging.

guidelines. All tissue Doppler imaging was acquired with the following ARIC protocol defaults: sweep speed 100 cm/s; sample volume length 5 mm; and filter setting 100 Hz. The parameters chosen for our analysis were indicative of (1) LV structure: LV end-diastolic diameter (cm), mean LV wall thickness (mm), and LV mass index (per 10 g/m²); (2) LV systolic function: LV ejection fraction (per 5%), and longitudinal strain (%); and (3) LV diastolic function: tissue Doppler-based early diastolic lateral mitral annular relaxation velocity (cm/s), Early diastolic transmitral flow velocity to early diastolic lateral mitral annular relaxation velocity (E-Em lateral ratio) (cm/s), and LA volume index (per 5 mL/m²). LV mass was also indexed to height (per 10 g/m^{2.7}) (Tables S1 and S2).

Covariate Assessment

Covariates were defined based on status at the time of the 2011-2013 visit. Blood pressure was measured using a random-zero sphygmomanometer, with the average of the second and third of 3 measured values used in analysis. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg,

antihypertensive drug use, or prior history of hypertension. Diabetes mellitus was defined as self-report of a physician diagnosis of diabetes mellitus, fasting glucose ≥ 126 mg/dL, nonfasting glucose ≥ 200 mg/dL, or use of medications for diabetes mellitus. Body mass index was measured as the weight (kilograms) divided by the square of measured height (meters), and hypercholesterolemia was defined as a measured total cholesterol >200 mg/dL. Smoking status was self-reported. Race was self-reported at the ARIC baseline visit, and a combined race-center variable was defined based on a combination of racial group and field center. Level of educational attainment was defined at ARIC baseline, as was sex.

Statistical Analysis

Baseline characteristics were examined by the presence of white or black race. Categorical variables were reported as percentages, and continuous variables were recorded as mean (SD). The χ^2 method was used to compare differences for categorical variables, and the equivalence t test was used for continuous variables. Due to right skewness, WMH volume

was modeled by generalized linear models with γ families and identity links; thus, results are presented as increases (or decreases) per 1-unit increase in each predictor variable. Likewise, logistic regression was used to estimate the odds ratio (OR) of the presence of infarcts. Data were weighted using ARIC sampling fractions to weight back to the visit 5 cohort. Modeling of the numbers of cortical and lacunar infarcts was done with negative binomial regression with mean dispersion and log links, and results are reported as rate ratios (RR). Interaction terms were included where appropriate to examine racial disparities, and linear combinations of these models were constructed to give race-specific estimates. Participants with heart failure (N=59) or atrial fibrillation (N=105) were excluded for the primary outcomes of interest: WMH, infarction, and cortical/lacunar infarcts. All models were adjusted for age, sex, estimated total intracranial volume (for WMH analyses), education, hypertension, diabetes mellitus, low-density lipoprotein, smoking, alcohol, body mass index, and history of myocardial infarction. Participants with a history of myocardial infarction (N=80) were also excluded in a sensitivity analysis (Tables S3 and S4). Covariates were chosen on the basis of clinical relevance and prior knowledge of their potential to confound associations rather than solely on univariate associations with the outcome of interest. The models were structured to evaluate each variable in a separate model with inclusion of the covariates but not with inclusion of other cardiac markers due to concern for collinearity. A sensitivity analysis with different modeling strategies was performed (Table S5). All models were checked for linearity and homoscedasticity in primary predictors, and neither of these assumptions was violated. All statistical analyses were performed with Stata v14.1 (StataCorp, College Station, TX).

Results

Demographics

The analysis sample included 1829 ARIC participants with brain MRI imaging and available echocardiographic data who did not have heart failure or atrial fibrillation (Table 1). Echocardiographic measures were grouped according to those reflective of LV structure and systolic and diastolic function. The majority of the participants had a preserved LV ejection fraction, normal LA volume index and normal LV mass index (LVMI).

Cardiac Structure and Function and White Matter Hyperintensities

Greater LVMI was significantly associated with greater WMH, an association driven by greater LV wall thickness but not

Table 1. Demographic Features of Study Participants

	Overall (N=1829)
Age (y), mean (SD)	76.42 (5.35)
Female	1180 (60%)
Education	
< High school	285 (14%)
High school or vocational school	809 (41%)
College, graduate or professional school	878 (45%)
History of hypertension	1334 (68%)
History of diabetes mellitus	565 (29%)
Body mass index (kg/m ²), mean (SD)	28.47 (5.65)
Current smoking	102 (5%)
Current alcohol use	887 (45%)
History of heart failure	59 (3%)
History of myocardial infarction	102 (5%)
WMH (adj TIV) (cm ³), mean (SD)	17.58 (2.80)
Cortical infarcts	205 (10%)
Lacunar infarcts	366 (19%)
Microhemorrhages	478 (24%)
Myocardial infarction	80 (5%)
Ejection fraction, mean (SD)	65.68 (6.40)
LVEF <35%	2 (<1%)
Mean LV wall thickness (cm), mean (SD)	0.99 (0.14)
LV mass index (g/m ²), mean (SD)	78.67 (19.54)
Average peak longitudinal strain	−18.00 (2.46)
Lateral early diastolic myocardial velocity (cm/s), mean (SD)	7.01 (2.07)
LA volume index (mL/m ²), mean (SD)	26.20 (8.71)

Values are N (%) unless otherwise specified. adj TIV indicates adjusted total intracranial volume; LA, left atrial; LV, left ventricular; LVEF, LV ejection fraction; WMH, white matter hyperintensities.

greater LV chamber size (Table 2). Every 10 g/m² increase in LVMI was associated with 0.64 cm³ (95% confidence interval [CI] 0.19–1.08) greater WMH, and every 1-mm increase in mean LV LVMI wall thickness was associated with 0.66 cm³ (95% CI 0.08–1.25) greater WMH. LV mass was also indexed to height to account for obesity-induced bias with similar results (Table S1). Worse longitudinal strain, but not LVEF, was suggestive of greater WMH (β =0.35, 95% CI 0.07–0.64) but did not achieve statistical significance (P =0.08). Markers of LV diastolic function were not significantly associated with WMH. The association of LA volume index with WMH was the only cardiac predictor that could potentially be modified by race, with a larger effect seen in blacks (0.85 cm³, 95% CI 0.05–1.65) than in whites (0.01 cm³, 95% CI −0.49 to 0.47) per 5 mL/m² increase, at P <0.1 (Table S6).

Table 2. Cardiac Predictors of Brain Structures (N=1829)

	WMH β Coefficients*	95% CI	P Values
LV structure			
End-diastolic left ventricular diameter, cm	1.47	−0.31 to 3.24	0.11
Mean LV wall thickness, mm	0.66	0.08-1.25	0.03
LV mass index (10 g/m ²)	0.64	0.19-1.08	<0.01
LV systolic function			
Ejection fraction (per 5%)	−0.25	−0.80 to 0.30	0.38
Average peak longitudinal strain, %	0.31	−0.04 to 0.65	0.08
LV diastolic function			
Lateral early diastolic myocardial velocity, cm/s	−0.08	−0.39 to 0.23	0.61
E-Em lateral ratio, cm/s	0.15	−0.07 to 0.36	0.18
LA volume index (5 mL/m ²)	0.18	−0.25 to 0.61	0.42
	Presence of Infarct Odds Ratios*	95% CI	P Values
End-diastolic left ventricular diameter, cm	1.21	0.88-1.68	0.24
Mean LV wall thickness, mm	1.11	1.01-1.23	0.04
LV mass index, 10 g/m ²	1.08	1.00-1.17	0.04
LV systolic function			
Ejection fraction, per 5%	0.85	0.77-0.95	<0.01
Average peak longitudinal strain, %	1.04	0.98-1.10	0.24
LV diastolic function			
Lateral early diastolic myocardial velocity, cm/s	0.94	0.87-1.01	0.08
E-Em lateral ratio, cm/s	1.00	0.97-1.04	0.82
LA volume index, 5 mL/m ²	1.06	0.97-1.16	0.19

BMI indicates body mass index; CI, confidence interval; E-Em lateral ratio, early diastolic transmitral flow velocity to early diastolic lateral mitral annular tissue velocity; LA, left atrial; LDL, low-density lipoprotein; LV, left ventricular.

*Adjusted for age, sex, estimated total intracranial volume, education, hypertension, diabetes mellitus, smoking, alcohol, BMI, LDL, and history of myocardial infarction. Participants with heart failure or atrial fibrillation were excluded.

Cardiac Structure and Function and Cerebral Infarction

Greater LVMI and greater mean LV wall thickness were both associated with higher odds of having any brain infarct (OR 1.08, 95% CI 1.00-1.17 per 10 g/m² and OR 1.11, 95% CI 1.01-1.23) per 1-mm increase in LV wall thickness, respectively) (Table 2). When indexed to height, the effect estimate for LVMI was similar (OR 1.14, 95% CI 0.98-1.33) but did not achieve statistical significance ($P=0.09$). No association was noted with LV chamber size. Average peak longitudinal strain, a marker of LV systolic function, was not associated with brain infarcts; however, a higher EF (per 5% increase) was associated with a decreased odds of infarction (OR 0.85, 95% CI 0.77-0.95). The association of a higher EF with decreased odds of infarction remained significant when there was adjustment for a history of myocardial infarction (Table 2). The effect estimate minimally changed when excluding participants with myocardial infarction and also remained statistically significant (Table S3; OR 0.87,

95% CI [0.78, 0.96]). Race did not significantly modify these associations (Table S6).

Cardiac Structure and Function and Subtype of Infarct

Markers of LV structure, LV diastolic function, or LV systolic function were not associated with cortical or lacunar infarcts, with the exception of EF (Table 3). Higher EF (per 5%) was associated with decreased rates of lacunar infarcts (RR 0.89, 95% CI [0.80, 1.00]) but no association was found with cortical infarcts. This association was not modified by race (Table S7), and the direction and size of the effect estimate remained similar when excluding those with prior history of myocardial infarction, although decreased power resulted in widening of the CI and loss of statistical significance (Table S4; RR 0.92, 95% CI 0.82-1.03). Although average peak longitudinal strain was not associated with cortical infarction in the study sample overall, race significantly

Table 3. Cardiac Predictors of Rates of Cortical and Lacunar Infarcts (N=1829)

	Cortical Infarcts Rate Ratios*	95% CI	P Values
LV structure			
End-diastolic left ventricular diameter, cm	1.35	0.83-2.21	0.23
Mean LV wall thickness, mm	1.12	0.97-1.28	0.12
LV mass index, 10 g/m ²	1.08	0.99-1.17	0.09
LV systolic function			
Ejection fraction, per 5%	0.92	0.78-1.08	0.29
Average peak longitudinal strain, %	1.00	0.91-1.10	0.97
LV diastolic function			
Lateral early diastolic myocardial velocity, cm/s	0.99	0.89-1.09	0.77
E-Em lateral ratio, cm/s	1.00	0.94-1.05	0.9
LA volume index (5 mL/m ²)	1.03	0.91-1.17	0.66
	Lacunar Infarcts Rate Ratios*	95% CI	P Values
LV structure			
End-diastolic left ventricular diameter, cm	0.96	0.68-1.36	0.83
Mean LV wall thickness, mm	1.05	0.94-1.17	0.4
LV mass index, 10 g/m ²	1.02	0.94-1.11	0.65
LV systolic function			
Ejection fraction, per 5%	0.89	0.80-1.00	0.04
Average peak longitudinal strain, %	1.03	0.97-1.10	0.27
LV diastolic function			
Lateral early diastolic myocardial velocity, cm/s	0.96	0.90-1.03	0.28
E-Em lateral ratio, cm/s	0.99	0.95-1.03	0.73
LA volume index, 5 mL/m ²	1.07	0.99-1.16	0.09

CI indicates confidence interval; E-Em lateral ratio, early diastolic transmitral flow velocity to early diastolic lateral mitral annular tissue velocity; LA, left atrial; LV, left ventricular. *Adjusted for age, sex, estimated total intracranial volume, education, hypertension, diabetes mellitus, smoking, alcohol, body mass index, low-density lipoprotein, and history of myocardial infarction. Participants with heart failure or atrial fibrillation were excluded.

modified this association such that a higher percentage strain was associated with higher rates of cortical infarction (RR 1.18, 95% CI 1.03-1.35) in blacks compared with whites (RR 0.93, 95% CI 0.82-1.05; *P* interaction=0.01).

Discussion

Our study defined the vascular neurologic correlates, as detected on MRI, of subclinical alterations in cardiac structure and function assessed by comprehensive echocardiography in a cohort of elderly people in the community. Greater LVMI, indicative of chronically increased afterload, was associated with greater WMH and prevalence of infarction. Importantly, this association was driven by the association of greater LV wall thickness with these brain phenotypes and not by greater LV chamber size. Additionally, higher participant EF was associated with a decreased odds of infarction. These associations were, importantly, found in a cohort excluding participants with prevalent HF or atrial fibrillation and

accounting for sampling strategy so that they might be reflective of the population.

White matter changes in the brain are associated with long-standing hypertension,¹⁵ which itself is one of the most powerful risk factors for HF. Similarly, cardiac changes that are common in long-standing hypertension, including LV hypertrophy, are known to be independently associated with new atherothrombotic brain infarction¹⁶ as well as silent cerebrovascular disease.¹⁷ Addition of LVMI has been shown to improve traditional cardiovascular disease risk prediction models.¹⁸ When cardiac MRI has been used, LV mass was found to be associated with incident coronary heart disease but was no longer significant when adjustment was made for blood pressure.¹⁹ The association between greater LVMI and greater WMH and higher odds of infarct has been previously reported, with this study confirming these prior results while differing in the magnitude of the association, potentially suggesting a higher risk than previously cited. Our work also supports prior work in demonstrating that the odds of

infarction are increased among those with changes in LV structure while data are controlled for hypertension. It is still likely that, despite the persistence of results after adjustment for hypertension and other risk factors, the observed associations are due to shared risk factors. However, it is possible that there are other subtle forms of injury to the brain that result more directly from these cardiac abnormalities, due to either hypoperfusion or microemboli; our data do not allow us to speculate further about the likelihood of these other mechanisms. We acknowledge that our findings may not directly translate to similar relationships in individuals with clinical HF, but these findings suggest that such associations may exist among people with even subtle cardiac structural changes.

EF plays a central role in the stratification and management of patients with HF, and increased rates of stroke and cardiovascular death are well documented in patients with decreased EF.²⁰ We found an association between higher EF and decreased odds of overall infarction but did not find an association when we looked specifically at the rates of cortical infarcts. It is worth noting that the strongest relationship with stroke is with EF $\leq 15\%$,²⁰ and an LVEF $< 50\%$ is rare in our cohort, which might limit our ability to detect any possible associations of EF with stroke subtype. We acknowledge that our findings are not reflective of the lower range of EF but rather EF across a relatively narrow and healthy range. Lacunar infarcts, in contrast, have traditionally been considered a disease of a single penetrating artery and are more susceptible to the effects of chronic hypertension. As a result, markers of increased cardiac load (LV mass) would be hypothesized to be more closely associated with increased rates of lacunar disease. These findings may be reflective of decreased power, or it may be that several other disease processes may also affect the cerebral small vessels and lead to lacunae, perhaps explaining our lack of association with these measures. There has been prior work demonstrating a high prevalence of subclinical cerebral infarction in patients with HF with a preserved EF,²¹ but this question is distinct from our work, as our population was mostly healthy, with mild degrees of cardiac impairment.

We did not find an association between odds of infarction and longitudinal strain, which some might consider a more sensitive marker for systolic dysfunction. LVEF has formed the foundation for establishing and diagnosing heart failure and remains an important clinical measure. There is growing recognition of the importance of echocardiography with strain, in addition to LVEF, in particular in understanding beat-to-beat perturbation, early valve disease, and subclinical LV systolic function.²² LVEF and longitudinal strain are importantly reflective of different entities and should be used together in assessing LV systolic function. Although LVEF is an integral part of the assessment of LV function, this

measure can be influenced by variability secondary to image quality, the axis of the image, and measurement error.²³ Echocardiography with strain uses speckle-tracking technology to examine myocardial fiber deformation, and longitudinal strain in particular represents shortening and lengthening of the subendocardial and subepicardial myocardium, which are thought to be more sensitive to subendocardial ischemia.²⁴ A particular advantage to global longitudinal strain, therefore, is using it for prognosis when LVEF is normal or nearly normal.²³ The ARIC Study, a cohort of mostly healthy older adults, is ongoing and provides an opportunity to reexamine these relationships in the future.

The biracial structure of our cohort allows for examination of relationships stratified by race. We did find differences in some cardiac parameters by race, although generally these did not have differential effects on WMH or infarcts. The variables suggestive of significance for effect modification by race, at a $P < 0.1$, were 2 measures of LV diastolic dysfunction and 1 measure of LV systolic function. Specifically, increasing LA volume index, which is a marker of chronic LV diastolic pressure, appeared to be associated with a greater increase in WMH in blacks than in whites. There also appeared to be differences in the rates of cortical infarction between whites and blacks per unit increase in lateral early diastolic myocardial velocity. It is notable that longitudinal strain, a marker of LV systolic function, was not associated with a greater odds of infarction and did not impact the prevalence of cortical infarction among our participants until we accounted for potential differences in race with suggestion of increased rates of cortical infarcts in blacks compared with whites. Racial differences have been previously explored with prior work also suggesting a modification of the association between cardiac and cerebrovascular subclinical disease,^{17,25} and we suggest that such differences may also have an impact on infarction outside of traditional cardiovascular risk factors. Our large sample size uniquely allows for separate analyses in whites and blacks, although the effect sizes between whites and blacks were similar, without evidence of effect modification by race, so we interpret any slight differences cautiously.

We have shown that mild decreases in cardiac function are associated with neuroimaging changes, even when data are controlled for independently associated factors such as hypertension. Our findings demonstrate that participants with mild cardiac structure/function changes, considered "normal" by standard clinical definitions, have brain parenchyma damage evidenced by WMH and infarcts. It is likely that the association between brain and subclinical cardiac dysfunction is at least partly due to shared risk for end-organ damage from hypertension and other underlying risk factors, although we attempted to reduce some of this potential confounding in our adjustment for these risk factors. Given the association between these imaging findings and cognitive impairment,

and an increase in mortality in HF accompanied by cognitive impairment,²⁶ there is a need for further research to continue to elucidate the clinical meaning behind these findings in a cohort without clinical HF and to determine if there is a more direct causal relationship between cardiac dysfunction and these cerebrovascular lesions.

There are several limitations to our study. Our assessments of cardiac function were made using echocardiography. It is known that echocardiography has a limited accuracy, particularly for LV mass, but our large sample size helps mitigate the risk of a small systematic error and variability.^{27,28} Parameters that were felt to be the best indicators of LV structure, LV systolic function, and LV diastolic function, were included in the model, but the variables we considered were not comprehensive of all possible cardiac markers. Additionally, our models considered 1 cardiac predictor with the adjustment covariates of interest rather than all cardiac predictors together or with predictors from the other groups. This was a decision made based on concerns for collinearity among cardiac predictors, but such statistical considerations may influence results (Table S5). Our covariate model adjusted for a number of potential confounders, but residual confounding remains a possibility, particularly given the cross-sectional design of the study. Strengths of the study include the cohort (ARIC), a biracial prospective study in which all echocardiograms and MRI analyses were rigorously standardized and ascertained by an independent adjudication committee, with the analysis accounting for cohort sampling. The reasonably large sample size allows us to estimate interactions by race. In addition, we were able to look at a range of echocardiographic markers and tested hypotheses specific to likely mechanisms by which those cardiac changes might lead to brain vascular changes. Our data support other work evaluating cardiac markers in association with brain MRI findings,^{21,29,30} further emphasizing the importance of future studies of subtle cardiac dysfunction or structural abnormality in evaluating mechanisms not only of vascular disease in the brain but possibly also those of vascular cognitive impairment.

In conclusion, we have demonstrated that among participants in a large community-based cohort study, subclinical changes in LV mass were associated with greater odds of infarction and size of WMH even when controlling for hypertension. Such associations persisted in a cohort without prevalent heart failure or AF. These findings are likely at least partly due to end-organ sequelae from shared risk factors but may also represent a direct impact of cardiac disease on the brain. Further understanding of these changes may help to better delineate the link between other possible neurologic sequelae from subclinical cardiac changes, such as the potential for cognitive ramifications, and how this might relate to those individuals with clinical HF.

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Disclosures

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SUPPLEMENTAL MATERIAL

Table S1. Cardiac Predictors of Brain Structure with LV mass indexed to height (N=1829).

		WMH Beta Coefficients*	95% CI	P-values
LV Structure	End-diastolic left ventricular diameter (cm)	1.47	(-0.31,3.24)	0.11
	Mean LV wall thickness (mm)	0.66	(0.08,1.25)	0.03
	LV mass index (10g per m2.7)	1.25	(0.37,2.12)	0.01
LV Systolic Function	Ejection fraction (per 5%)	-0.25	(-0.80,0.30)	0.38
	Average Peak Longitudinal Strain (%)	0.31	(-0.04,0.65)	0.08
LV Diastolic Function	Lateral early diastolic myocardial velocity (cm per sec)	-0.08	(-0.39,0.23)	0.61
	E-Em lateral ratio (cm per sec)	0.15	(-0.07,0.36)	0.18
	LA volume index (5ml per m2)	0.18	(-0.25,0.61)	0.42
		Presence of Infarct Odds Ratios*	95% CI	P-values
LV Structure	End-diastolic left ventricular diameter (cm)	1.21	(0.88,1.68)	0.24
	Mean LV wall thickness (mm)	1.11	(1.01,1.23)	0.04
	LV mass index (10g per m2.7)	1.14	(0.98,1.33)	0.09
LV Systolic Function	Ejection fraction (per 5%)	0.85	(0.77,0.95)	0.00
	Average Peak Longitudinal Strain (%)	1.04	(0.98,1.10)	0.24
LV Diastolic Function	Lateral early diastolic myocardial velocity (cm per sec)	0.94	(0.87,1.01)	0.08
	E-Em lateral ratio (cm per sec)	1.00	(0.97,1.04)	0.82
	LA volume index (5ml per m2)	1.06	(0.97,1.16)	0.19

*Adjusted for age, sex, estimated total intracranial volume, education, hypertension, diabetes, smoking, alcohol, BMI, LDL, and history of myocardial infarction. Participants with heart failure or atrial fibrillation were excluded.

†Abbreviations: WMH- White Matter Hyperintensities, LV-Left Ventricular, LA-Left Atrial

Table S2. Cardiac Predictors of Rates of Cortical and Lacunar Infarcts with LV mass indexed to height (N=1829).

		Cortical Infarcts Rate Ratios*	95% CI	P-values
LV Structure	End-diastolic left ventricular diameter (cm)	1.35	(0.83,2.21)	0.23
	Mean LV wall thickness (mm)	1.12	(0.97,1.28)	0.12
	LV mass index (10g per m ^{2.7})	1.11	(0.93,1.33)	0.25
LV Systolic Function	Ejection fraction (per 5%)	0.92	(0.78,1.08)	0.29
	Average Peak Longitudinal Strain (%)	1.00	(0.91,1.10)	0.97
LV Diastolic Function	Lateral early diastolic myocardial velocity (cm per sec)	0.99	(0.89,1.09)	0.77
	E-Em lateral ratio (cm per sec)	1.00	(0.94,1.05)	0.90
	LA volume index (5ml per m ²)	1.03	(0.91,1.17)	0.66
		Lacunar Infarcts Rate Ratios*	95% CI	P-values
LV Structure	End-diastolic left ventricular diameter (cm)	0.96	(0.68,1.36)	0.83
	Mean LV wall thickness (mm)	1.05	(0.94,1.17)	0.40
	LV mass index (10g per m ^{2.7})	1.02	(0.86,1.20)	0.82
LV Systolic Function	Ejection fraction (per 5%)	0.89	(0.80,1.00)	0.04
	Average Peak Longitudinal Strain (%)	1.03	(0.97,1.10)	0.27
LV Diastolic Function	Lateral early diastolic myocardial velocity (cm per sec)	0.96	(0.90,1.03)	0.28
	E-Em lateral ratio (cm per sec)	0.99	(0.95,1.03)	0.73
	LA volume index (5ml per m ²)	1.07	(0.99,1.16)	0.09

*Adjusted for age, sex, estimated total intracranial volume, education, hypertension, diabetes, smoking, alcohol, BMI, LDL, and history of myocardial infarction. Participants with heart failure or atrial fibrillation were excluded.

†Abbreviations: LV-Left Ventricular, LA-Left Atrial

Table S3. Sensitivity Analysis considering the association of Cardiac Predictors with Brain Structure when excluding participants with history of myocardial infarction (N=1673).

		WMH Beta Coefficients*	95% CI	P-values
LV Structure	End-diastolic left ventricular diameter (cm)	1.34	(-0.53,3.20)	0.16
	Mean LV wall thickness (mm)	0.69	(0.09,1.30)	0.02
	LV mass index (10g per m2)	0.64	(0.17,1.10)	0.01
LV Systolic Function	Ejection fraction (per 5%)	-0.15	(-0.71,0.42)	0.61
	Average Peak Longitudinal Strain (%)	0.29	(-0.06,0.65)	0.11
LV Diastolic Function	Lateral early diastolic myocardial velocity (cm per sec)	-0.06	(-0.37,0.25)	0.70
	E-Em lateral ratio (cm per sec)	0.14	(-0.08,0.36)	0.22
	LA volume index (5ml per m2)	0.19	(-0.25,0.63)	0.39
		Presence of Infarct Odds Ratios*	95% CI	P-values
LV Structure	End-diastolic left ventricular diameter (cm)	1.18	(0.85,1.64)	0.33
	Mean LV wall thickness (mm)	1.10	(0.99,1.23)	0.08
	LV mass index (10g per m2)	1.07	(0.99,1.16)	0.10
LV Systolic Function	Ejection fraction (per 5%)	0.87	(0.78,0.96)	0.01
	Average Peak Longitudinal Strain (%)	1.03	(0.97,1.10)	0.32
LV Diastolic Function	Lateral early diastolic myocardial velocity (cm per sec)	0.95	(0.88,1.02)	0.13
	E-Em lateral ratio (cm per sec)	1.00	(0.96,1.04)	0.93
	LA volume index (5ml per m2)	1.05	(0.96,1.15)	0.27

*Adjusted for age, sex, estimated total intracranial volume, education, hypertension, diabetes, smoking, alcohol, BMI, LDL. Participants with heart failure, atrial fibrillation and myocardial infarction were excluded.

†Abbreviations: WMH-White Matter Hyperintensities, LV-Left Ventricular, LA-Left Atrial

Table S4. Sensitivity Analysis considering Cardiac Predictors of rates of Cortical and Lacunar Infarcts when excluding participants with history of myocardial infarction (N=1673).

		Cortical Infarcts Rate Ratios*	95% CI	P-values
LV Structure	End-diastolic left ventricular diameter (cm)	1.39	(0.84,2.32)	0.20
	Mean LV wall thickness (mm)	1.12	(0.95,1.30)	0.17
	LV mass index (10g per m2)	1.08	(0.98,1.19)	0.12
LV Systolic Function	Ejection fraction (per 5%)	0.90	(0.76,1.06)	0.20
	Average Peak Longitudinal Strain (%)	0.99	(0.89,1.10)	0.85
LV Diastolic Function	Lateral early diastolic myocardial velocity (cm per sec)	0.99	(0.90,1.10)	0.90
	E-Em lateral ratio (cm per sec)	0.99	(0.94,1.05)	0.74
	LA volume index (5ml per m2)	1.00	(0.87,1.14)	1.00
		Lacunar Infarcts Rate Ratios*	95% CI	P-values
LV Structure	End-diastolic left ventricular diameter (cm)	0.88	(0.62,1.25)	0.47
	Mean LV wall thickness (mm)	1.05	(0.93,1.18)	0.43
	LV mass index (10g per m2)	1.00	(0.92,1.09)	0.92
LV Systolic Function	Ejection fraction (per 5%)	0.92	(0.82,1.03)	0.16
	Average Peak Longitudinal Strain (%)	1.03	(0.97,1.09)	0.38
LV Diastolic Function	Lateral early diastolic myocardial velocity (cm per sec)	0.98	(0.91,1.05)	0.50
	E-Em lateral ratio (cm per sec)	0.99	(0.95,1.03)	0.56
	LA volume index (5ml per m2)	1.07	(0.98,1.16)	0.13

*Adjusted for age, sex, estimated total intracranial volume, education, hypertension, diabetes, smoking, alcohol, body mass index, low density lipoprotein. Participants with heart failure, atrial fibrillation and myocardial infarction were excluded.

†Abbreviations: LV-Left Ventricular, LA-Left Atrial

Table S5. Sensitivity Analysis considering the impact of modeling approaches on the association of Cardiac Predictors with Brain Structure.

Cardiac Predictor	Model 1S: Primary Significant Predictor from each Group*		Model 2S: Significant Cardiac Predictors within Group*		Model 3S: All Cardiac Predictors*				
	Effect estimate, P-value	95% CI	Effect estimate, P-value	95% CI	Effect estimate, P-value	95% CI			
LV Structure	End-diastolic left ventricular diameter (cm)	n/a	n/a	n/a	n/a	n/a	n/a	White Matter Hyperintensities Beta Coefficients	
	Mean LV wall thickness (mm)	n/a	n/a	0.03, 0.95	n/a	0.05, 0.90	n/a		
	LV mass index (10g per m2)	0.70, 0.003	(0.23, 1.17)	0.62, 0.05	(0.01,1.23)	0.52, 0.11	(-0.11,1.15)		
LV Systolic Function	Ejection fraction (per 5%)	0.003, 0.99	(-0.52, 0.53)	n/a	n/a	n/a	n/a		
	Average Peak Longitudinal Strain (%)	n/a	n/a	0.31, 0.08	n/a	0.27, 0.09	n/a		
LV Diastolic Function	Lateral early diastolic myocardial velocity (cm per sec)	-0.088, 0.54	n/a	n/a	n/a	n/a	n/a		
	E-Em lateral ratio (cm per sec)	n/a	n/a	n/a	n/a	n/a	n/a		
	LA volume index (5ml per m2)	n/a	n/a	n/a	n/a	n/a	n/a		
LV Structure	End-diastolic left ventricular diameter (cm)	n/a	n/a	n/a	n/a	n/a	n/a		Presence of Infarcts Odds Ratios
	Mean LV wall thickness (mm)	n/a	n/a	1.04, 0.54	(0.91,1.20)	1.08, 0.33	(0.93,1.25)		
	LV mass index (10g per m2)	1.07, 0.13	(0.98, 1.16)	1.06, 0.26	(0.96,1.18)	1.03, 0.62	(0.92,1.15)		
LV Systolic Function	Ejection fraction (per 5%)	0.88, 0.02	(0.79, 0.98)	0.85, 0.001	(0.77,0.95)	0.87, 0.01	(0.78,0.97)		
	Average Peak Longitudinal Strain (%)	n/a	n/a	n/a	n/a	n/a	n/a		
LV Diastolic Function	Lateral early diastolic myocardial velocity (cm per sec)	0.96, 0.24	n/a	0.94, 0.08	n/a	0.96, 0.28	n/a		
	E-Em lateral ratio (cm per sec)	n/a	n/a	n/a	n/a	n/a	n/a		
	LA volume index (5ml per m2)	n/a	n/a	n/a	n/a	n/a	n/a		

*All models (1S, 2S and 3S) adjusted for age, sex, estimated total intracranial volume, education, hypertension, diabetes, smoking, alcohol, BMI, LDL, and history of myocardial infarction

Model 1S: Outcome of interest (white matter hyperintensities; infarcts) modeled as a function of three predictors: LV mass index, Ejection fraction and Lateral early diastolic myocardial velocity. These predictors represent the primary statistically significant (p -value <0.05) predictor in univariate analysis from each of the three groups: LV structure, LV systolic function and LV diastolic function.

Model 2S: Outcome of interest (white matter hyperintensities; infarcts) modeled as a function of the cardiac predictors statistically significant in univariate analysis (p -value <0.05) within each of the three group (LV structure, LV systolic function or LV diastolic function)

Model 3S: Outcome of interest (white matter hyperintensities; infarcts) modeled as a function of all cardiac predictors statistically significant in univariate analysis (p -value <0.05) regardless of the group in which the predictor was contained (LV structure, LV systolic function or LV diastolic function predictors all considered together)

Table S6. Cardiac predictors of Brain Structures by Race.

		Whites		Blacks		Interaction p-value
		WMH Beta Coefficients*	95% CI	WMH Beta Coefficients*	95% CI	
LV Structure	End-diastolic left ventricular diameter (cm)	1.25	(-0.71,3.22)	2.75	(-0.32,5.83)	0.40
	Mean LV wall thickness (mm)	0.57	(-0.06,1.20)	1.06	(0.07,2.04)	0.38
	LV mass index (per 10g/m ²)	0.58	(0.10,1.05)	0.98	(0.18,1.79)	0.38
LV Systolic Function	Ejection fraction (per 5%)	-0.31	(-0.91,0.28)	0.03	(-1.06,1.12)	0.58
	Average Peak Longitudinal Strain (%)	0.34	(-0.06,0.75)	0.15	(-0.43,0.73)	0.59
LV Diastolic Function	Lateral early diastolic myocardial velocity (cm per sec)	-0.13	(-0.49,0.22)	0.04	(-0.50,0.59)	0.58
	E-Em lateral ratio (cm per sec)	0.13	(-0.11,0.36)	0.31	(-0.18,0.79)	0.50
	LA volume index (per 5ml/m ²)	0.01	(-0.49,0.47)	0.85	(0.05,1.65)	0.07
		Presence of Infarct Odds ratio*	95% CI	Presence of Infarct Odds ratio*	95% CI	
LV Structure	End-diastolic left ventricular diameter (cm)	1.22	(0.82,1.81)	1.20	(0.78,1.86)	0.96
	Mean LV wall thickness (mm)	1.11	(0.98,1.26)	1.12	(0.97,1.29)	0.95
	LV mass index (per 10g/m ²)	1.09	(0.99,1.19)	1.07	(0.96,1.21)	0.86
LV Systolic Function	Ejection fraction (per 5%)	0.83	(0.73,0.94)	0.92	(0.78,1.09)	0.33
	Average Peak Longitudinal Strain (%)	1.04	(0.96,1.13)	1.03	(0.94,1.12)	0.82
LV Diastolic Function	Lateral early diastolic myocardial velocity (cm per sec)	0.97	(0.88,1.06)	0.88	(0.79,0.98)	0.17
	E-Em lateral ratio (cm per sec)	0.99	(0.95,1.04)	1.05	(0.99,1.11)	0.11
	LA volume index (per 5ml/m ²)	1.06	(0.94,1.18)	1.08	(0.95,1.22)	0.83

*Adjusted for age, sex, estimated total intracranial volume, education, hypertension, diabetes, smoking, alcohol, body mass index, low density lipoprotein, and history of myocardial infarction

†Abbreviations: WMH-White Matter Hyperintensities, LV-Left Ventricular, LA-Left Atrial

Table S7. Cardiac predictors of rates of Cortical and Lacunar Infarcts by Race .

		Whites		Blacks		Interaction p-value	
		Rate ratios*	95%CI	Rate ratios*	95%CI		
LV Structure	End-diastolic left ventricular diameter (cm)	1.63	(0.88,2.99)	0.80	(0.43,1.47)	0.10	Cortical Infarcts
	Mean LV wall thickness (mm)	1.07	(0.90,1.27)	1.21	(0.98,1.49)	0.33	
	LV mass index (10g per m2)	1.07	(0.96,1.18)	1.10	(0.96,1.27)	0.70	
LV Systolic Function	Ejection fraction (per 5%)	0.89	(0.73,1.09)	0.97	(0.75,1.26)	0.59	
	Average Peak Longitudinal Strain (%)	0.93	(0.82,1.05)	1.18	(1.03,1.35)	0.01	
LV Diastolic Function	Lateral early diastolic myocardial velocity (cm per sec)	1.05	(0.93,1.19)	0.83	(0.71,0.98)	0.02	
	E-Em lateral ratio (cm per sec)	0.98	(0.91,1.04)	1.05	(0.96,1.14)	0.17	
	LA volume index (5ml per m2)	0.97	(0.83,1.15)	1.14	(0.95,1.37)	0.23	
LV Structure	End-diastolic left ventricular diameter (cm)	0.89	(0.58,1.37)	1.16	(0.71,1.89)	0.40	
	Mean LV wall thickness (mm)	1.03	(0.90,1.18)	1.08	(0.94,1.25)	0.59	
	LV mass index (10g per m2)	1.00	(0.90,1.11)	1.07	(0.94,1.22)	0.37	
LV Systolic Function	Ejection fraction (per 5%)	0.86	(0.74,0.99)	0.97	(0.81,1.14)	0.30	
	Average Peak Longitudinal Strain (%)	1.06	(0.99,1.14)	0.98	(0.89,1.07)	0.18	
LV Diastolic Function	Lateral early diastolic myocardial velocity (cm per sec)	0.98	(0.90,1.06)	0.93	(0.84,1.04)	0.49	
	E-Em lateral ratio (cm per sec)	0.99	(0.94,1.04)	1.00	(0.94,1.07)	0.69	
	LA volume index (5ml per m2)	1.04	(0.94,1.15)	1.14	(0.99,1.30)	0.31	

*Adjusted for age, sex, estimated total intracranial volume, education, hypertension, diabetes, smoking, alcohol, body mass index, low density lipoprotein, and history of myocardial infarction

†Abbreviations: LV-Left Ventricular, LA-Left Atrial