ORIGINAL RESEARCH

Increased Left Ventricular Mass Index Is Associated With Compromised White Matter Microstructure Among Older Adults

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***Background*—**Left ventricular (LV) hypertrophy is associated with cerebrovascular disease and cognitive decline. Increased LV mass index is a subclinical imaging marker that precedes overt LV hypertrophy. This study relates LV mass index to white matter microstructure and cognition among older adults with normal cognition and mild cognitive impairment.

***Methods and Results*—**Vanderbilt Memory & Aging Project participants free of clinical stroke, dementia, and heart failure (n=318, 73±7 years, 58% male, 39% mild cognitive impairment) underwent brain magnetic resonance imaging, cardiac magnetic resonance, and neuropsychological assessment. Voxelwise analyses related LV mass index (g/m^2) to diffusion tensor imaging metrics. Models adjusted for age, sex, education, race/ethnicity, Framingham Stroke Risk Profile, cognitive diagnosis, and apolipoprotein E–ε4 status. Secondary analyses included a LV mass index×diagnosis interaction term with follow-up models stratified by diagnosis. With identical covariates, linear regression models related LV mass index to neuropsychological performances. Increased LV mass index related to altered white matter microstructure ($P<0.05$). In models stratified by diagnosis, associations between LV mass index and diffusion tensor imaging were present among mild cognitive impairment participants only ($P<0.05$). LV mass index was related only to worse visuospatial memory performance ($\beta=-0.003$, $P=0.036$), an observation that would not withstand correction for multiple testing.

***Conclusions*—**In the absence of prevalent heart failure and clinical stroke, increased LV mass index corresponds to altered white matter microstructure, particularly among older adults with clinical symptoms of prodromal dementia. Findings highlight the potential link between subclinical LV remodeling and cerebral white matter microstructure vulnerability. **(*J Am Heart Assoc.* 2018;7:e009041. DOI: 10.1161/JAHA.118.009041.)**

Key Words: cognitive impairment • diffusion-weighted imaging • left ventricular mass • white matter disease

Left ventricular (LV) hypertrophy (LVH), a pathologic increase in LV mass, is associated with cerebrovascular disease,[1] white matter hyperintensities,[2] and cognitive decline[3] in aging individuals, particularly elders with hypertension.[4,5] Increased LV mass index (LV mass/body surface area) is an imaging marker that precedes LVH[6] and reflects subclinical pathologic remodeling of the ventricular wall. Among older adults, LV mass index is associated with stroke,[1] white matter hyperintensities,[7] and global cognitive decline.[8,9] Despite these associations, it is unknown if subclinical changes in the ventricular wall correlate with more sensitive measures of white matter microstructure, such as diffusion tensor imaging (DTI), or specific cognitive domains among older adults.

The current study sought to examine the association between LV mass index obtained by cardiac magnetic resonance and DTI measures of white matter microstructure and neuropsychological performance among older individuals with normal cognition (NC) and mild cognitive impairment (MCI), a prodromal stage of dementia. Given prior research linking overt LVH to cognitive impairment[3] and white matter lesions,[2] we hypothesized that higher LV mass index would correlate with compromised white matter microstructure on DTI and worse neuropsychological performance (especially

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Accompanying Tables S1 through S4 are available at http://jaha.ahajournals.org/content/7/13/e009041/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- Our study results suggest that increased left ventricle mass index relates to compromised white matter microstructure, particularly among older adults with clinical symptoms of prodromal dementia, and these early cardiac structural changes may lead to silent cardioembolic ischemia affecting the cerebral microvasculature, causing white matter microstructural changes.

What Are the Clinical Implications?

- Understanding the association between subclinical cardiac structural changes and early alterations in white matter may allow for early detection and prevention of white matter damage, particularly among those with cognitive decline, in whom existing pathology may exacerbate these changes.

memory).[10] Secondarily, we tested whether associations differed by cognitive diagnosis.

Methods

Study Cohort

The Vanderbilt Memory & Aging Project[11] is a longitudinal observational study investigating vascular health and brain aging, enriched with older adults with MCI.[12] Inclusion required participants be ≥60 years, speak English, have adequate auditory and visual acuity, and have a reliable study partner. As part of a comprehensive screening, participants were excluded for a cognitive diagnosis other than NC, early MCI,[13] or MCI,[12] magnetic resonance imaging contraindication, history of neurological disease (eg, multiple sclerosis, stroke), heart failure, major psychiatric illness, head injury with loss of consciousness >5 minutes, or a systemic or terminal illness affecting follow-up participation. At enrollment, participants completed a comprehensive examination, including (but not limited to) fasting blood draw, physical examination, clinical interview, medication review, neuropsychological assessment, echocardiogram, cardiac magnetic resonance, and multimodal brain magnetic resonance imaging. Participants were excluded from this study for missing predictor, outcome, or covariate data. See Figure 1 for inclusion/exclusion details. The protocol was approved by the Vanderbilt University Medical Center Institutional Review Board. Written informed consent was obtained from participants before data collection. Due to participant consent restrictions in data sharing, a subset of data is available to others for purposes of reproducing the results or replicating procedures. These data, analytic methods, and study materials can be obtained by contacting the corresponding author.

Cardiac Magnetic Resonance

Cardiac magnetic resonance was acquired at Vanderbilt University Medical Center using a 1.5-T Siemens Avanto system (Siemens Medical Solutions USA, Inc, Malvern, PA) with a phased-array torso receiver coil. LV and right ventricular volume and function were assessed using a breath-hold, ECG-synchronized, cine steady-state free precession sequence with the following parameters: TR=180 milliseconds, TE=1.1 milliseconds, flip angle=80°, field of view=300 to 340 mm, and 156×192 matrix. Under the supervision of a board-certified radiologist (J.J.C.), trained analysts blinded to clinical information (J.G.T., S.N.) used QMass MR 7.6 Enterprise Solution (Medis, Leiden, the Netherlands) to define LV endocardial and epicardial contours at end systole and end diastole on short-axis images. LV end systole and end diastole volumes were calculated using Simpson's rule. Papillary muscles were considered part of the blood pool and excluded from LV mass calculation. LV mass was calculated at end diastole by summing the myocardial area for each slice, multiplying by slice thickness plus slice gap, and multiplying by 1.05 g/mL (the density of the myocardium). LV mass index was defined as LV mass/body surface area.

Neuropsychological Assessment

Participants completed a neuropsychological protocol assessing language, information-processing speed, executive functioning, visuospatial skills, and episodic memory. Measures were carefully selected to preclude floor or ceiling effects and were not used to screen or select participants into the study.

Brain Magnetic Resonance Imaging

Participants were scanned at the Vanderbilt University Institute of Imaging Science on a 3-T Philips Achieva system (Best, the Netherlands) using an 8-channel SENSE reception coil array as part of a multimodal acquisition protocol. DTI data were acquired along 32 diffusion gradient vectors (repetition time/echo time=10 000/60 milliseconds, spatial resolution=2×2×2 mm^3, b-value=1000 s/mm^2) and post-processed through an established tract-based spatial statistics pipeline using the Functional Magnetic Resonance Imaging of the Brain Software Library version 4.1.4 (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL).[14]

Data were corrected for motion and eddy currents. A brain mask was created, the diffusion tensor model was fit using Functional Magnetic Resonance Imaging of the Brain's Diffusion Toolbox, and fractional anisotropy (FA), mean diffusivity, radial diffusivity, and axial diffusivity values were calculated. All FA images were nonlinearly registered and merged into a 4-dimensional image, and a mean image was

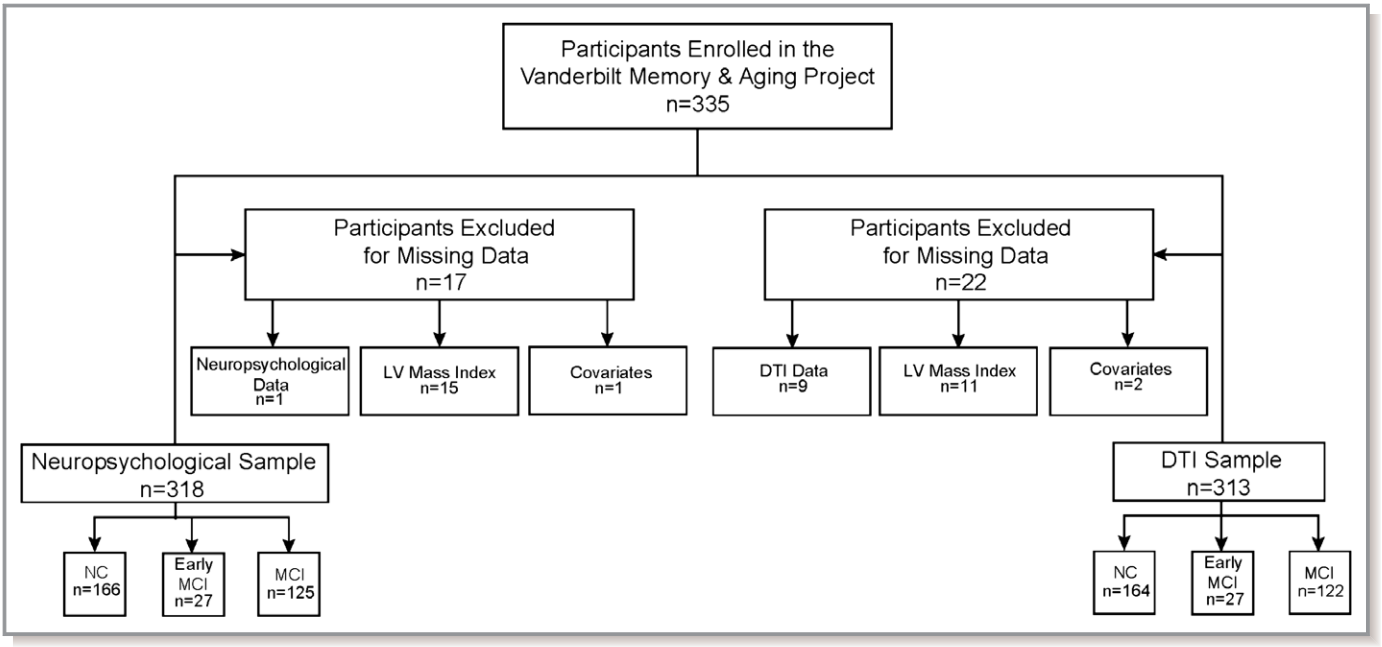

Figure 1. Participant inclusion/exclusion details. Missing data categories are mutually exclusive. Thirty-nine total participants with LVH, CVD, or atrial fibrillation were excluded for sensitivity analyses (LVH n=10; CVD n=10; atrial fibrillation n=15; LVH and atrial fibrillation n=3; CVD and atrial fibrillation n=1). CVD indicates cardiovascular disease; DTI, diffusion tensor imaging; LV, left ventricular; LVH, left ventricular hypertrophy; MCI, mild cognitive impairment; NC, normal cognition.

created. The mean image was used to generate a mean skeleton to which a threshold was applied to exclude voxels that did not overlap among ≥80% of participants. Each participant's FA image was projected onto the mean skeleton, and these skeleton projections were combined into a single 4-dimensional file containing skeletonized FA data from all participants. Nonlinear registration was also applied to the mean diffusivity, radial diffusivity, and axial diffusivity images for each participant. For each individual metric, all participant data were merged into a single 4-dimensional file that was projected onto the original mean FA skeleton.

Analytical Plan

Systolic blood pressure was the mean of 2 measurements. Diastolic blood pressure was the mean of 2 measurements. Medication review determined antihypertensive medication use. Hypertension was defined as antihypertensive medication usage, systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg. Diabetes mellitus was defined as fasting blood glucose ≥126 mg/dL, hemoglobin A_{1c} ≥6.5%, or oral hypoglycemic or insulin medication usage. Current cigarette smoking (yes/no within previous year) was ascertained by self-report. LVH was defined on echocardiogram as LV mass index >115 g/m^2 in men or >95 g/m^2 in women. Self-report atrial fibrillation was corroborated by any 1 of the following sources: echocardiogram, documentation of prior procedure/ablation for atrial fibrillation, or medication usage for atrial fibrillation. Self-report prevalent cardiovascular disease (CVD) with supporting evidence from available medical records included coronary heart disease, angina, or myocardial infarction (note, heart failure was a parent study exclusion). Framingham Stroke Risk Profile (FSRP) score applied points by sex for age, systolic blood pressure, antihypertensive medication usage, diabetes mellitus, current cigarette smoking, atrial fibrillation, LVH, and prevalent CVD.[15] For this study, age was included in the statistical models as a separate covariate, and LV mass index was the predictor, so points assigned to age and LVH were removed from the FSRP score. Apolipoprotein E (*APOE*) genotyping was quantified from DNA extracted from whole blood samples.[11] *APOE-ε4* carrier status was defined as positive (ε2/ε4, ε3/ε4, ε4/ε4) or negative (ε2/ε2, ε2/ε3, ε3/ε3).

Voxelwise analyses using general linear models and the Functional Magnetic Resonance Imaging of the Brain Software Library randomise with 5000 permutations related LV mass index (g/m^2) to FA, mean diffusivity, radial diffusivity, and axial diffusivity, adjusting for age, sex, education, race/ethnicity, FSRP (excluding points assigned to age and LVH), cognitive diagnosis, and *APOE-ε4* status. Excluding the small subset of participants with early MCI, models were repeated evaluating an *LV mass index×cognitive diagnosis* interaction term followed by stratification by cognitive diagnosis (NC, MCI). In post hoc analyses the effect of hypertension was examined by relating an *LV mass*

index×hypertension interaction to DTI metrics adjusting for age, sex, education, race/ethnicity, FSRP (excluding points assigned to age, LVH, and systolic blood pressure accounting for antihypertensive medication utilization), cognitive diagnosis, and *APOE-ε4* status. Models were repeated stratifying by hypertension status (yes, no). Multiple comparison correction was performed using the established cluster enhancement permutation procedure in the Functional Magnetic Resonance Imaging of the Brain Software Library.[16] The threshold for statistical significance was set a priori as corrected $P<0.05$, and sensitivity analyses, removing participants with LVH, prevalent CVD, or atrial fibrillation, were performed. Parametric estimates of statistically significant associations were calculated in R version 3.2.1 (www.r-project.org) using least-squares regression for illustration and interpretation.

Linear regression models with ordinary least-squares estimates related LV mass index to neuropsychological performance (1 variable per model), adjusting for identical covariates. Excluding the small subset of participants with early MCI, models were repeated evaluating an LV mass index×cognitive diagnosis interaction term followed by stratification by cognitive diagnosis (NC, MCI). In post hoc analyses, the effect of hypertension was examined by relating an LV mass index×hypertension interaction to neuropsychological performance (1 variable per model) adjusting for age, sex, education, race/ethnicity, FSRP (excluding points assigned to age, LVH, and systolic blood pressure accounting for antihypertensive medication utilization), cognitive diagnosis, and *APOE-ε4* status. Models were repeated stratified by hypertension status (yes, no). For significant models, follow-up sensitivity analyses excluded participants with LVH, prevalent CVD, or atrial fibrillation to test if these conditions accounted for the results. Significance was set a priori at $P<0.05$, and analyses were conducted using R.

Results

Participant Characteristics

For participants in the neuropsychological (n=318, 73±7 years, 58% male, 87% non-Hispanic white) and the DTI samples (n=313, 73±7 years, 57% male, 87% non-Hispanic white), LV mass index ranged 29.5 to 91.1 g/m^2. See Table 1 for participant characteristics of the neuropsychological sample and DTI sample, stratified by NC, early MCI, and MCI.

LV Mass Index and DTI Metrics

LV mass index was negatively correlated with FA primarily in the superior frontal gyrus (corrected $P<0.049$). LV mass index was positively associated with mean diffusivity primarily in the anterior corona radiata (corrected $P=0.003$). LV mass index was also positively associated with radial diffusivity, primarily in the medial orbital gyrus (corrected $P=0.004$). Finally, LV mass index was positively associated with axial diffusivity in the superior corona radiata (corrected $P=0.002$; see Figure 2 and Table 2 for details). Associations with mean, radial, and axial diffusivity persisted after exclusion for LVH, CVD, and atrial fibrillation (corrected $P<0.05$; Table S1).

LV mass index did not interact with cognitive diagnosis on any DTI metric (corrected $P>0.3$). However, diagnostic stratification revealed that LV mass index was associated with DTI metrics among MCI participants. Specifically, LV mass index positively related to mean diffusivity (corrected $P=0.015$) and axial diffusivity (corrected $P<0.05$) primarily in the superior corona radiata, and radial diffusivity (corrected $P=0.016$) in the striatum (Figure 2, Table S2). The association with mean diffusivity persisted after exclusion for LVH, CVD, and atrial fibrillation (corrected $P<0.049$; Table S1), whereas the associations with radial diffusivity (corrected $P=0.073$) and axial diffusivity (corrected $P=0.068$) were modestly attenuated. LV mass index was unrelated to FA (corrected $P>0.066$) among MCI participants. LV mass index was unrelated to any DTI metric among NC participants (corrected $P>0.15$; Figure 2).

LV mass index did not interact with hypertension on any DTI metric (corrected $P>0.13$). However, stratification by hypertension status revealed that LV mass index was associated with DTI metrics among hypertensive participants. LV mass index was negatively associated with FA primarily in the superior frontal gyrus (corrected $P<0.05$). LV mass index was positively associated with mean diffusivity (corrected $P=0.002$) in the superior corona radiata, radial diffusivity (corrected $P=0.004$) in the inferior temporal gyrus, and axial diffusivity (corrected $P<0.001$) in the straight gyrus (see Table S3 for details). The associations with mean, radial, and axial diffusivity persisted after exclusion for LVH, CVD, and atrial fibrillation (corrected $P<0.041$; Table S1). LV mass index was unrelated to any DTI metric among normotensive participants (corrected $P>0.17$).

LV Mass Index and Neuropsychological Performances

Among all participants, LV mass index only related to Biber Figure Learning Test Recognition performance ($\beta=-0.003$, $P=0.036$), an association that remained significant after exclusion for LVH, CVD, and atrial fibrillation ($\beta=-0.003$, $P=0.045$). LV mass index did not interact with cognitive diagnosis on neuropsychological performance, and diagnostic stratification results were null (see Table 3 for details). LV mass index did not interact with hypertension on neuropsychological performance ($P>0.13$). However, stratification revealed LV mass index associations with Biber

Table 1. Participant Characteristics

	Neuropsychological Sample					DTI Sample				
	Total (n=318)	NC (n=166)	Early MCI (n=27)	MCI (n=125)	*P* Value	Total (n=313)	NC (n=164)	Early MCI (n=27)	MCI (n=122)	*P* Value
Demographic and health characteristics										
Age, y	73±7	72±7	73±6	73±8	0.69	73±7	72±7	73±6	73±7	0.73
Sex, % male	58	58	74	55	0.20	58	58	74	56	0.21
Race, % Non-Hispanic white	87	88	85	86	0.81	87	88	85	87	0.92
Education, y	16±3	16±2	16±3	15±3	<0.001*†	16±3	16±2	16±3	15±3	<0.001*†
APOE-ε4, % positive	34	29	22	44	0.01†	35	29	22	45	<0.006*†
FSRP, total score‡	12±4	12±4	13±3	13±4	0.02†§	12±4	12±4	13±3	13±4	0.03†§
Systolic blood pressure, mm Hg	142±18	140±17	150±18	145±19	0.003†§	142±18	140±17	150±18	145±19	0.005†§
Antihypertensive medication usage, %	53	52	56	54	0.88	53	52	56	53	0.95
Diabetes mellitus, %	18	14	22	22	0.18	17	14	22	20	0.34
Current smoking, %	2	1	4	3	0.44	2	1	4	3	0.44
Atrial fibrillation, %	6	5	11	6	0.43	6	5	11	7	0.44
Prevalent CVD, %	3	4	0	3	0.53	4	4	0	3	0.53
Left ventricular hypertrophy, %	4	2	4	6	0.23	4	2	4	7	0.22
Left ventricular mass index, g/m^2	51.0±9.9	50.6±10.2	53.3±8.0	51.0±9.9	0.35	51.0±10.0	50.7±10.3	53.3±8.0	51.0±10.0	0.38
Neuropsychological performance‖										
Montreal Cognitive Assessment	25.4±3.2	27.0±2.2	25.4±2.4	23.2±3.3	<0.001*†§	25.4±3.2	27.0±2.2	25.4±2.4	23.3±3.3	<0.001*†§
Boston Naming Test	26.8±3.1	27.9±2.0	26.6±2.4	25.3±3.8	<0.001†§	26.8±3.1	27.9±2.0	26.6±2.4	25.4±3.7	<0.001†§
Animal Naming	18.9±5.4	20.9±4.8	19.4±3.4	16.2±5.2	<0.001*†	19.0±5.4	21.0±4.8	19.4±3.4	16.2±5.3	<0.001*†
WAIS-IV Digit-Symbol Coding	52.7±12.8	57.5±11.5	53.4±11.2	46.3±12.1	<0.001*†	52.9±12.7	57.4±11.6	53.4±11.2	46.7±11.9	<0.001*†
DKEFS Number Sequencing, s	42.0±18.9	35.9±12.6	42.0±13.2	50.3±23.4	<0.001†§	42.1±19.1	35.9±12.7	42.0±13.2	50.5±23.6	<0.001†§
Executive Function Composite	0.0±0.9	0.4±0.6	0.2±0.4	−0.6±1.0	<0.001*†§	0.0±0.9	0.4±0.6	0.2±0.4	−0.6±1.0	<0.001*†§
DKEFS Letter Number Switching, s	107±48	87±34	93±22	138±52	<0.001*†§	107±48	87±34	93±22	138±53	<0.001*†§
DKEFS Tower Test	15.0±4.7	16.1±4.3	16.2±3.5	13.2±4.7	<0.001*†	15.0±4.7	16.2±4.3	16.2±3.5	13.2±4.8	<0.001*†
DKEFS Color-Word Inhibition, s	69.2±23.5	60.0±13.5	74.6±15.5	80.0±29.6	<0.001†§	69.1±23.6	60.0±13.6	74.6±15.5	79.8±29.9	<0.001†§
Letter Fluency (FAS) Test	38.7±11.6	42.9±11.4	37.9±11.1	33.3±9.7	<0.001†§	38.8±11.6	42.8±11.5	37.8±11.1	33.5±9.7	<0.001†§
Hooper Visual Organization Test	24.5±3.1	25.4±2.5	24.7±2.2	23.3±3.6	<0.001†	24.5±3.1	25.4±2.5	24.7±2.2	23.3±3.7	<0.001†
Memory Composite	0.0±1.0	0.6±0.7	−0.1±0.8	−0.7±0.8	<0.001*†§	0.0±1.0	0.6±0.7	−0.1±0.8	−0.7±0.7	<0.001*†§
CVLT-II Trials 1 to 5 Total Learning	40.6±11.8	47.1±9.3	40.1±9.7	32.1±9.6	<0.001*†§	40.6±11.8	47.0±9.3	40.1±9.7	32.1±9.7	<0.001*†§
CVLT-II Long Delay Free Recall	8.1±4.2	10.5±3.3	7.6±3.5	5.1±3.4	<0.001*†§	8.1±4.2	10.5±3.3	7.6±3.5	5.0±3.5	<0.001*†§
CVLT-II Recognition	2.4±1.0	3.0±0.7	2.3±0.8	1.7±0.9	<0.001*†§	2.4±1.0	3.0±0.7	2.3±0.8	1.8±0.9	<0.001*†§

Continued

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Table 1. Continued

	Neuropsychological Sample					DTI Sample				
	Total (n=318)	NC (n=166)	Early MCI (n=27)	MCI (n=125)	*P* Value	Total (n=313)	NC (n=164)	Early MCI (n=27)	MCI (n=122)	*P* Value
BFLT Trials 1 to 5 Total Learning	113±41	136±30	110±28	82±35	<0.001*†§	113±41	136±30	110±28	82±35	<0.001*†§
BFLT Long Delay Recall	27.0±10.4	32.6±7.5	28.0±6.6	19.4±9.7	<0.001*†§	27.0±10.4	32.5±7.5	28.0±6.6	19.5±9.8	<0.001*†§
BFLT Recognition	0.7±0.2	0.8±0.2	0.7±0.2	0.6±0.2	<0.001*†§	0.7±0.2	0.8±0.2	0.7±0.2	0.6±0.2	<0.001*†§

Values are displayed as mean±SD or frequency. Participant characteristics were compared across cognitive diagnosis using Kruskal-Wallis test for continuous variables and chi-squared test for categorical variables. *APOE* indicates apolipoprotein E; BFLT, Biber Figure Learning Test; Boston Naming Test, Boston Naming Test-30 Item Odd Version; CVD, cardiovascular disease; CVLT-II, California Verbal Learning Test, 2nd Edition; DKEFS, Delis-Kaplan Executive Function System; DTI, diffusion tensor imaging; FSRP, Framingham Stroke Risk Profile; MCI, mild cognitive impairment; NC, normal cognition; WAIS-IV, Wechsler Adult Intelligence Scale, 4th Edition.

*Early MCI different than MCI.

†NC different from MCI.

‡A modified FSRP score was included in statistical models excluding points assigned to age and LVH (Total=6±3, NC=6±3, Early MCI=7±3, MCI=7±3).

§NC different from Early MCI.

‖All neuropsychological performance values are shown as total correct excluding timed tasks, which are represented by s=seconds.

Figure Learning Test Recognition performance (β=−0.005, *P*=0.03) and Biber Figure Learning Test Total Trials (β=−0.949, *P*=0.045) among normotensive participants. The association with Biber Figure Learning Test Recognition remained significant after exclusion for LVH, CVD, and atrial fibrillation (β=−0.007, *P*=0.03). LV mass index was unrelated to neuropsychological performance among hypertensive participants (*P*>0.18; see Table S4 for details).

Discussion

Among our community-dwelling cohort of older adults without a clinical history of stroke, dementia, or heart failure, higher LV mass index was associated with compromised white matter microstructure measured with DTI. Specifically, LV mass index was negatively associated with FA and positively associated with mean, radial, and axial diffusivity. Follow-up stratified analyses revealed that these findings were present in MCI and hypertensive participants only. Together, these results suggest that higher LV mass index, a subclinical marker of cardiovascular structure, is associated with declining white matter microstructure in cognitively symptomatic individuals, independent of LVH, CVD, or atrial fibrillation.

This study is among the first to report an association between LV mass index and white matter microstructure as measured by DTI. Several pathways may account for this connection. First, increased LV mass index and compromised white matter microstructure may be explained by a common etiology, such as hypertension. As the left ventricle pumps against a high-pressure arterial system over time, the myocardium hypertrophies[17] to provide enough force for adequate perfusion. Thus, hypertension directly contributes to LV remodeling and has been shown to directly lead to changes in the cerebral vasculature, damaging the white matter.[18] Alternatively, the increase in LV mass index could directly contribute to diminished white matter microstructure by reducing cardiac functional efficiency. For example, when the left ventricle hypertrophies, the electrical tracts in the myocardium lengthen, increasing the risk for cardiac arrhythmias.[17] As the synchronized conduction of the heart becomes compromised, risk for blood stasis increases,[19] potentially leading to thrombus formation.[17] Therefore, those older adults with increased LV mass index could experience silent cardioembolic ischemia, leading to subclinical brain microvascular changes. This hypothesis is consistent with research showing that LV remodeling is associated with asymptomatic changes in cerebral white matter.[20] Such pathologic cerebral vasculature changes may contribute to axonal damage[21] or incite inflammatory processes,[22] both of which have been associated with white matter microstructure changes.[23] Thus, early changes in the ventricle wall, preceding an LVH diagnosis, may

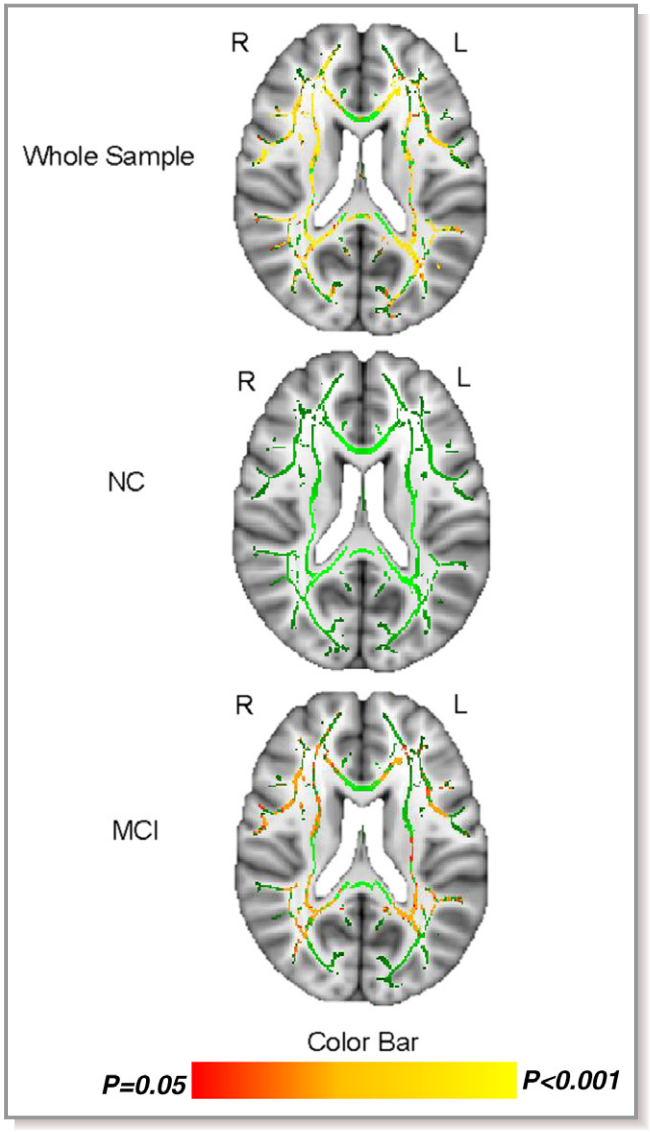

Figure 2. LV mass index and mean diffusivity. Association between LV mass index and mean diffusivity. Skeletons show regions where LV mass index is positively associated with mean diffusivity in the whole sample (n=313), NC participants only (n=164), and MCI participants only (n=122). No significance was seen in the NC group. Images taken at Z=91. L indicates left; LV, left ventricular; MCI, mild cognitive impairment; NC, normal cognition; R, right.

correspond with pathologic changes in white matter microstructure captured by DTI.

Among the entire sample, LV mass index was associated with all 4 DTI metrics in both anterior and posterior regions of the brain, suggesting a global effect on white matter microstructure, not specific to 1 degenerative process or region. Although anatomic regions where the associations are most prominent can be identified, the associations are not restricted to these regions and likely represent a global process, as illustrated by the skeleton image in Figure 2.

The findings presented here also suggest that the association between LV mass index and DTI is modified by cognitive diagnosis and hypertension. Although there was not an interaction with cognitive diagnosis, and stratified results must be interpreted with caution, LV mass index was globally associated with diminished white matter microstructure among MCI participants, whereas results were null among NC participants. One explanation is that a higher degree of white matter microstructural damage, as seen in MCI,[24] may be necessary before LV mass index relates to DTI measurements. MCI participants are more likely to have amyloid and tau pathology,[25] which have been associated with white matter damage.[26] It is possible that in the presence of pathology and more susceptible white matter, as seen in MCI, small changes in LV structure lead to greater changes in white matter microstructure. Additionally, although the interaction between LV mass index and hypertension was not statistically significant, stratified results suggest that LV mass index was associated with diminished white matter microstructure among hypertensive, but not normotensive, participants. This association, which should be interpreted with caution, is consistent with prior work showing the associations among hypertension, LV mass index,[17] and white matter disease.[18] Those with longstanding hypertension may have some underlying structural brain changes present,[27] making the white matter more vulnerable to small changes in LV structure. Future research is needed to understand these group differences.

Our results show a very limited association between LV mass index and cognition, implicating only visuospatial memory. Although this observation is consistent with some prior work,[9,10] the remaining null cognitive results contrast with literature reporting cognitive associations with LVH[8] or increased LV mass index[3,28] in aging cohorts that include dementia cases. Although increased LV mass index is an early marker of pathologic LV remodeling, it may not strongly correspond with subtle cognitive changes in cognitively normal individuals or elders with only mild prodromal symptoms of dementia, such as those participants studied here. Furthermore, prior work has shown that the association between increased LV mass index and cognition is attenuated when other cardiovascular risk factors are adjusted for,[3,8-10] as was done here with the inclusion of a vascular risk score.

The current study has several strengths, including a clinically well characterized cohort emphasizing participants free of clinical dementia along with excellent methods for quantifying white matter microstructure, LV mass index, and neuropsychological performance. Additional strengths include comprehensive ascertainment of potential confounders and the application of a cluster enhancement permutation procedure in the DTI analyses to correct for multiple comparisons, thereby reducing the possibility of a false-positive finding. Finally, core laboratories using quality control procedures

Table 2. Region-Specific LV Mass Index Associations With DTI Metrics

	Anatomical Region	Hemisphere	Volume (mm^3)	Cluster Statistics		Corrected *P* Value‡	MNI Coordinate§		
				β*	*P* Value†				
Fractional anisotropy	Superior frontal gyrus	Right	12 111	−0.296	9.60×10^{-7}	0.016	17	−12	52
	Precentral gyrus	Left	269	−0.309	1.75×10^{-6}	0.047	−18	−16	49
	Precuneus	Left	216	−0.267	2.15×10^{-5}	0.047	−20	−51	44
	Posterior thalamic radiation	Left	89	−0.198	1.54×10^{-3}	0.048	−29	−71	10
	Inferior frontal gyrus	Right	63	−0.198	1.39×10^{-3}	0.048	28	33	6
	Posterior thalamic radiation	Left	22	−0.205	1.18×10^{-3}	0.049	−33	−64	0
Mean diffusivity	Anterior corona radiata	Right	50 234	0.264	7.69×10^{-6}	0.003	17	33	−12
Radial diffusivity	Medial orbital gyrus	Left	49 411	0.259	1.04×10^{-5}	0.004	−19	16	−18
Axial diffusivity	Superior corona radiata	Right	33 798	0.325	1.20×10^{-8}	0.002	19	7	34

DTI indicates diffusion tensor imaging; LV, left ventricular; MNI, Montreal Neurological Institute.
*β is standardized.
†Parametric *P*-values were calculated using least-squares regression to relate raw DTI values extracted from each participant skeleton and LV mass index.
‡*P*-value has been corrected for multiple comparisons.
§Coordinates represent the voxel with the minimum *P*-value in each cluster.

analyzed all magnetic resonance imaging measurements in batch, and technicians were blinded to clinical information. Despite these strengths, the study is cross-sectional and cannot address causality. Longitudinal studies are needed to understand the temporal nature of associations reported here. Also, the cohort was predominantly non-Hispanic white with participants 60 to 92 years of age, thus limiting generalizability to other races, ethnicities, and age groups.

The current study demonstrates a novel association between LV mass index and white matter microstructure. Results suggest a connection between early pathologic LV remodeling and compromised white matter microstructure, an

Table 3. LV Mass Index Associations With Neuropsychological Performance

	β	95% Confidence Interval	*P* Value
Boston Naming Test	0.007	−0.030, 0.043	0.72
Animal Naming	−0.026	−0.088, 0.035	0.39
WAIS-IV Coding	−0.031	−0.178, 0.115	0.67
DKEFS Number Sequencing, s	−0.079	−0.303, 0.145	0.49
Executive Function Composite	0.003	−0.006, 0.012	0.52
DKEFS Letter Number Switching, s	−0.166	−0.674, 0.341	0.52
DKEFS Tower Test	0.035	−0.022, 0.093	0.23
DKEFS Color-Word Inhibition, s	−0.008	−0.290, 0.274	0.95
Letter Fluency (FAS) Test	−0.032	−0.170, 0.106	0.65
Hooper Visual Organization Test	−0.011	−0.049, 0.027	0.56
Memory Composite	−0.001	−0.010, 0.009	0.91
CVLT-II Trials 1 to 5 Total Learning	0.008	−0.111, 0.127	0.90
CVLT-II Long Delay Free Recall	0.007	−0.036, 0.050	0.75
CVLT-II Recognition	0.002	−0.008, 0.013	0.66
BFLT Trials 1 to 5 Total Learning	−0.262	−0.665, 0.141	0.20
BFLT Long Delay Recall	−0.092	−0.200, 0.016	0.09
BFLT Recognition	−0.003	−0.005, −0.0002	0.04

Analyses performed on n=318 participants. Participants missing a subset of neuropsychological test performances were excluded in a pairwise fashion to maximize data available for analyses. Models were adjusted for age, sex, education, race/ethnicity, Framingham stroke risk profile (excluding points assigned for age and LVH), cognitive diagnosis, and *APOE-ε4* status. *APOE* indicates apolipoprotein E; BFLT, Biber Figure Learning Test; Boston Naming Test, Boston Naming Test-30 Item Odd Version; CVLT-II, California Verbal Learning Test, 2nd Edition; DKEFS, Delis-Kaplan Executive Function System; LV, left ventricular; LVH, LV hypertrophy; WAIS-IV, Wechsler Adult Intelligence Scale, 4th Edition.

observation that is more pronounced in cognitively symptomatic older adults. Additional research is needed to further assess the mechanisms and longitudinal changes related to the associations reported here.

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Disclosures

None.

References

1. Bikkina M, Levy D, Evans JC, Larson MG, Benjamin EJ, Wolf PA, Castelli WP. Left ventricular mass and risk of stroke in an elderly cohort. The Framingham Heart Study. *J Am Med Assoc*. 1994;272:33–36.
2. Buchman AS, Schneider JA, Leurgans S, Bennett DA. Physical frailty in older persons is associated with Alzheimer disease pathology. *Neurology*. 2008;71:499–504.
3. Kahonen-Vare M, Brunni-Hakala S, Lindroos M, Pitkala K, Strandberg T, Tilvis R. Left ventricular hypertrophy and blood pressure as predictors of cognitive decline in old age. *Aging Clin Exp Res*. 2004;16:147–152.
4. Lee S, Park J, Kwon S, Kim Y, Roh J, Yoon B. Left ventricular hypertrophy is associated with cerebral microbleeds in hypertension patients. *Neurology*. 2004;63:16–21.
5. Kohara K, Zhao B, Jiang Y, Takata Y, Fukuoka T, Igase M, Miki T, Hiwada K. Relation of left ventricular hypertrophy and geometry to asymptomatic cerebrovascular damage in essential hypertension. *Am J Cardiol*. 1999;83:367–370.
6. Savage DD, Garrison RJ, Kannel WB, Levy D, Anderson SJ, Stokes J III, Feinleib M, Castelli WP. The spectrum of left ventricular hypertrophy in a general population sample: the Framingham Study. *Circulation*. 1987;75:I26–I33.
7. Fox ER, Taylor HA Jr, Benjamin EJ, Ding J, Liebson PR, Arnett D, Quin EM, Skelton TN. Left ventricular mass indexed to height and prevalent MRI cerebrovascular disease in an African American cohort: the Atherosclerotic Risk in Communities study. *Stroke*. 2005;36:546–550.
8. Scuteri A, Coluccia R, Castello L, Nevola E, Brancati AM, Volpe M. Left ventricular mass increase is associated with cognitive decline and dementia in the elderly independently of blood pressure. *Eur Heart J*. 2009;30:1525–1529.
9. Haring B, Omidpanah A, Suchy-Dicey AM, Best LG, Verney SP, Shibata DK, Cole SA, Ali T, Howard BV, Buchwald D, Devereux RB. Left ventricular mass, brain magnetic resonance imaging, and cognitive performance: results from the Strong Heart Study. *Hypertension*. 2017;70:964–971.
10. Elias MF, Sullivan LM, Elias PK, D'Agostino RB Sr, Wolf PA, Seshadri S, Au R, Benjamin EJ, Vasan RS. Left ventricular mass, blood pressure, and lowered cognitive performance in the Framingham offspring. *Hypertension*. 2007;49:439–445.
11. Jefferson AL, Gifford KA, Acosta LM, Bell SP, Donahue MJ, Davis LT, Gottlieb J, Gupta DK, Hohman TJ, Lane EM, Libon DJ, Mendes LA, Niswender K, Pechman KR, Rane S, Ruberg FL, Su YR, Zetterberg H, Liu D. The Vanderbilt Memory & Aging Project: study design and baseline cohort overview. *J Alzheimers Dis*. 2016;52:539–559.
12. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, Gamst A, Holtzman DM, Jagust WJ, Petersen RC, Snyder PJ, Carrillo MC, Thies B, Phelps CH. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7:270–279.
13. Aisen PS, Petersen RC, Donohue MC, Gamst A, Raman R, Thomas RG, Walter S, Trojanowski JQ, Shaw LM, Beckett LA, Jack CR Jr, Jagust W, Toga AW, Saykin AJ, Morris JC, Green RC, Weiner MW; Alzheimer's Disease Neuroimaging Initiative. Clinical core of the Alzheimer's Disease Neuroimaging Initiative: progress and plans. *Alzheimers Dement*. 2010;6:239–246.
14. Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM, Behrens TE. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage*. 2006;31:1487–1505.
15. D'Agostino RB, Wolf PA, Belanger AJ, Kannel WB. Stroke risk profile: adjustment for antihypertensive medication. The Framingham Study. *Stroke*. 1994;25:40–43.
16. Smith SM, Nichols TE. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. *Neuroimage*. 2009;44:83–98.
17. Henry WL, Morganroth J, Pearlman AS, Clark CE, Redwood DR, Itscoitz SB, Epstein SE. Relation between echocardiographically determined left atrial size and atrial fibrillation. *Circulation*. 1976;53:273–279.
18. de Leeuw FE, de Groot JC, Oudkerk M, Witteman JC, Hofman A, van Gijn J, Breteler MM. Hypertension and cerebral white matter lesions in a prospective cohort study. *Brain*. 2002;125:765–772.
19. Fatkin D, Kelly RP, Feneley MP. Relations between left atrial appendage blood flow velocity, spontaneous echocardiographic contrast and thromboembolic risk in vivo. *J Am Coll Cardiol*. 1994;23:961–969.
20. Selvetella G, Notte A, Maffei A, Calistri V, Scamardella V, Frati G, Trimarco B, Colonnese C, Lembo G. Left ventricular hypertrophy is associated with asymptomatic cerebral damage in hypertensive patients. *Stroke*. 2003;34:1766–1770.
21. Scheltens P, Barkhof F, Leys D, Wolters EC, Ravid R, Kamphorst W. Histopathologic correlates of white matter changes on MRI in Alzheimer's disease and normal aging. *Neurology*. 1995;45:883–888.
22. van Dijk EJ, Prins ND, Vermeer SE, Vrooman HA, Hofman A, Koudstaal PJ, Breteler MM. C-reactive protein and cerebral small-vessel disease: the Rotterdam Scan Study. *Circulation*. 2005;112:900–905.
23. Marchi N, Bazarian JJ, Puvenna V, Janigro M, Ghosh C, Zhong J, Zhu T, Blackman E, Stewart D, Ellis J, Butler R, Janigro D. Consequences of repeated blood-brain barrier disruption in football players. *PLoS One*. 2013;8:e56805.
24. Medina D, DeToledo-Morrell L, Urresta F, Gabrieli JD, Moseley M, Fleischman D, Bennett DA, Leurgans S, Turner DA, Stebbins GT. White matter changes in mild cognitive impairment and AD: a diffusion tensor imaging study. *Neurobiol Aging*. 2006;27:663–672.
25. Small GW, Kepe V, Ercoli LM, Siddarth P, Bookheimer SY, Miller KJ, Lavretsky H, Burggren AC, Cole GM, Vinters HV, Thompson PM, Huang SC, Satyamurthy N, Phelps ME, Barrio JR. PET of brain amyloid and tau in mild cognitive impairment. *N Engl J Med*. 2006;355:2652–2663.
26. Bendlin BB, Carlsson CM, Johnson SC, Zetterberg H, Blennow K, Willette AA, Okonkwo OC, Sodhi A, Ries ML, Birdsill AC, Alexander AL, Rowley HA, Puglielli L, Asthana S, Sager MA. CSF T-Tau/Aβ(42) predicts white matter microstructure in healthy adults at risk for Alzheimer's disease. *PLoS One*. 2012;7:e37720.
27. Debette S, Seshadri S, Beiser A, Au R, Himali JJ, Palumbo C, Wolf PA, DeCarli C. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. *Neurology*. 2011;77:461–468.
28. Moazzami K, Ostovaneh MR, Ambale Venkatesh B, Habibi M, Yoneyama K, Wu C, Liu K, Pimenta I, Fitzpatrick A, Shea S, McClelland RL, Heckbert S, Gottesman RF, Bluemke DA, Hughes TM, Lima JAC. Left ventricular hypertrophy and remodeling and risk of cognitive impairment and dementia: MESA (Multi-Ethnic Study of Atherosclerosis). *Hypertension*. 2018;71:429–436.

SUPPLEMENTAL MATERIAL

Table S1. Region Specific LV Mass Index Associations with DTI Metrics, excluding LVH, CVD, and Atrial Fibrillation Participants.

	Anatomical Region	Hemisphere	Volume (mm^3)	Cluster Statistics		Corrected p-value‡	MNI Coordinate§		
				β*	p-value†				
Main Effect (n=274)									
Fractional Anisotropy	--	--	--	--	--	--	--	--	--
Mean Diffusivity	Splenium of the Corpus Callosum	Right	36870	0.283	$7.02x10^{-6}$	0.006	8	-29	23
Radial Diffusivity	Body of the Corpus Callosum	Left	35492	0.275	$1.17x10^{-5}$	0.01	-12	-2	31
Axial Diffusivity	Middle Frontal Gyrus	Right	18706	0.319	$7.95x10^{-8}$	0.003	22	15	35
	External Capsule	Left	102	0.290	$2.10x10^{-5}$	0.044	-21	22	-6
	Putamen	Left	11	0.229	$9.20x10^{-4}$	0.05	-19	21	-6
MCI Participants (n=104)									
Fractional Anisotropy	--	--	--	--	--	--	--	--	--
Mean Diffusivity	Splenium of the Corpus Callosum	Right	1337	0.412	$3.88x10^{-5}$	0.042	5	-25	23
	Superior Frontal Gyrus	Left	92	0.541	$2.49x10^{-6}$	0.049	-18	-9	47
	Superior Corona Radiata	Right	86	0.393	$1.54x10^{-4}$	0.049	20	0	40
Radial Diffusivity	--	--	--	--	--	--	--	--	--
Axial Diffusivity	--	--	--	--	--	--	--	--	--
Hypertensive Participants (n=201)									
Fractional Anisotropy	--	--	--	--	--	--	--	--	--
Mean Diffusivity	Superior Corona Radiata	Right	35463	0.311	$6.89x10^{-6}$	0.009	17	-2	35
Radial Diffusivity	Lingual Gyrus	Right	35199	0.312	$5.28x10^{-6}$	0.014	23	-55	-2
Axial Diffusivity	Superior Corona Radiata	Right	16262	0.339	$4.59x10^{-7}$	0.007	24	-1	35

Angular Gyrus	Left	1184	0.374	7.06×10^{-7}	0.041	-51	-49	26

Empty rows indicate no significance. No significant regions were observed for NC or normotensive participants. *β is standardized; †parametric p-values were calculated using least squares regression to relate raw DTI values extracted from each participant skeleton and LV mass index; ‡p-value has been corrected for multiple comparisons; §coordinates represent the voxel with the minimum p-value in each cluster; LV= left ventricular; DTI=diffusion tensor imaging; LVH= left ventricular hypertrophy; CVD=cardiovascular disease; MCI=mild cognitive impairment; NC=normal cognition.

Table S2. Region Specific LV Mass Index Associations with DTI Metrics in MCI Participants.

	Anatomical Region	Hemisphere	Volume (mm^3)	Cluster Statistics		Corrected p-value‡	MNI Coordinat	
				β*	p-value†			
Fractional Anisotropy	--	--	--	--	--	--	--	--
Mean Diffusivity	Superior Corona Radiata	Right	37432	0.379	$6.79x10^{-5}$	0.015	19	-3
Radial Diffusivity	Striatum	Right	35605	0.377	$6.38x10^{-5}$	0.016	39	-22
Axial Diffusivity	Superior Corona Radiata	Right	7054	0.478	$3.97x10^{-7}$	0.01	24	-1
	Splenium of the Corpus Callosum	Left	5935	0.434	$3.02x10^{-6}$	0.026	-22	-50
	Superior Parietal Lobule	Right	4838	0.411	$1.58x10^{-5}$	0.017	26	-51
	Envelope	Right	910	0.352	$2.33x10^{-4}$	0.043	10	-19
	Supramarginal Gyrus	Right	55	0.330	$1.49x10^{-3}$	0.048	43	-32
	Fornix	--	33	0.241	$1.01x10^{-2}$	0.049	0	-10
	Angular Gyrus	Right	10	0.386	$3.46x10^{-4}$	0.05	41	-54
	Fornix	Right	4	0.208	$4.19x10^{-2}$	0.05	1	-13
	Fornix	Left	3	0.277	$5.27x10^{-3}$	0.05	-3	-2

Empty rows indicate no significance. No significant regions were observed for NC participants. *β is standardized; †parametric p-values were calculated using least squares regression to relate raw DTI values extracted from each participant skeleton and LV mass index; ‡p-value ha been corrected for multiple comparisons; §coordinates represent the voxel with the minimum p-value in each cluster; LV=left ventricular; MC mild cognitive impairment; DTI=diffusion tensor imaging.

Table S3. Region Specific LV Mass Index Associations with DTI Metrics in Hypertensive Participants.

	Anatomical Region	Hemisphere	Volume (mm^3)	Cluster Statistics		Corrected p-value‡	MNI Coordinate§		
				β*	p-value†				
Fractional Anisotropy	Superior Frontal Gyrus	Right	3640	-0.395	$1.03x10^{-8}$	0.028	17	-12	53
	Superior Parietal Lobule	Left	521	-0.336	$6.34x10^{-7}$	0.04	-19	-51	45
	Striatum	Right	369	-0.328	$3.91x10^{-6}$	0.042	38	-17	-9
	Superior Corona Radiata	Left	87	-0.238	$9.14x10^{-4}$	0.048	-20	-15	41
	Precentral Gyrus	Left	26	-0.343	$2.14x10^{-6}$	0.048	-25	-19	56
	Posterior Limb of the Internal Capsule	Left	21	-0.324	$2.19x10^{-5}$	0.049	-18	-10	4
	Precentral Gyrus	Left	20	-0.269	$3.97x10^{-4}$	0.05	-22	-20	61
	Precentral Gyrus	Right	15	-0.246	$1.07x10^{-3}$	0.05	48	-16	37
	Precentral Gyrus	Left	12	-0.245	$1.18x10^{-3}$	0.05	-15	-26	58
	Precentral Gyrus	Left	6	-0.298	$8.28x10^{-5}$	0.05	-29	-19	61
Mean Diffusivity	Superior Corona Radiata	Right	51875	0.293	$9.86x10^{-6}$	0.002	27	-17	19
Radial Diffusivity	Inferior Temporal Gyrus	Right	50038	0.289	$9.24x10^{-6}$	0.004	43	-14	-20
Axial Diffusivity	Straight Gyrus	Right	37728	0.363	$1.70x10^{-8}$	<0.001	8	36	-19

No significant regions were observed for normotensive participants. *β is standardized; †parametric p-values were calculated using least squares regression to relate raw DTI values extracted from each participant skeleton and LV mass index; ‡p-value has been corrected for multiple comparisons; §coordinates represent the voxel with the minimum p-value in each cluster; LV=left ventricular; DTI=diffusion tensor imaging.

Table S4. LV Mass Index x Hypertension Interaction Associations with Neuropsychological Performance and Stratification by Hypertension.

	LV Mass Index x Hypertension Interaction (n=318)*			Hypertensive Participants (n=234)†			Normotensive Participants (n=84)†		
	β	95% Confidence Interval	*p*-value	β	95% Confidence Interval	*p*-value	β	95% Confidence Interval	*p*-value
Boston Naming Test	-0.040	-0.111, 0.031	0.26	0.017	-0.027, 0.061	0.44	-0.010	-0.070, 0.049	0.73
Animal Naming	-0.087	-0.206, 0.032	0.15	-0.008	-0.079, 0.064	0.84	-0.087	-0.207, 0.033	0.15
WAIS-IV Coding	0.049	-0.235, 0.334	0.73	-0.031	-0.201, 0.139	0.72	0.140	-0.164, 0.443	0.36
DKEFS Number Sequencing, s	0.122	-0.313, 0.557	0.58	-0.096	-0.364, 0.172	0.48	-0.118	-0.501, 0.265	0.54
Executive Function Composite	-0.006	-0.024, 0.012	0.51	0.004	-0.007, 0.015	0.44	-0.001	-0.018, 0.016	0.91
DKEFS Letter Number Switching, s	0.498	-0.489, 1.485	0.32	-0.263	-0.874, 0.349	0.40	0.214	-0.670, 1.098	0.63
DKEFS Tower Test	0.026	-0.086, 0.138	0.65	0.035	-0.029, 0.010	0.28	0.040	-0.093, 0.173	0.55
DKEFS Color-Word Inhibition, s	-0.164	-0.713, 0.385	0.56	0.022	-0.308, 0.353	0.90	-0.188	-0.735, 0.359	0.50
Letter Fluency (FAS) Test	-0.206	-0.473, 0.062	0.13	0.004	-0.146, 0.155	0.96	-0.198	-0.524, 0.128	0.23
Hooper Visual Organization Test	-0.020	-0.093, 0.054	0.59	-0.004	-0.047, 0.039	0.84	-0.044	-0.127, 0.039	0.30
Memory Composite	-0.005	-0.023, 0.013	0.57	0.004	-0.007, 0.015	0.46	-0.014	-0.034, 0.006	0.16
CVLT-II Trials 1-5 Total Learning	-0.027	-0.259, 0.205	0.82	0.059	-0.074, 0.192	0.39	-0.177	-0.443, 0.089	0.19
CVLT-II Long Delay Free Recall	-0.012	-0.097, 0.072	0.78	0.026	-0.024, 0.076	0.31	-0.036	-0.128, 0.056	0.43
CVLT-II Recognition	-0.002	-0.023, 0.018	0.83	0.004	-0.009, 0.016	0.57	-0.002	-0.024, 0.020	0.85
BFLT Trials 1-5 Total Learning	-0.363	-1.155, 0.429	0.37	-0.047	-0.493, 0.398	0.83	-0.949	-1.875, -0.023	0.045
BFLT Long Delay Recall	-0.037	-0.248, 0.175	0.74	-0.048	-0.169, 0.072	0.43	-0.232	-0.476, 0.013	0.06
BFLT Recognition	-0.002	-0.007, 0.003	0.41	-0.002	-0.005, 0.001	0.18	-0.005	-0.011, -0.0004	0.03

Participants missing a subset of neuropsychological test performances were excluded in a pairwise fashion to maximize data available for analyses. *Models were adjusted for age, sex, education, race/ethnicity, Framingham stroke risk profile (excluding points assigned for age, LVH, and systolic blood pressure accounting for anti-hypertensive medication utilization), hypertension (defined as anti-hypertensive medication usage, systolic blood pressure ≥140mmHg, or diastolic blood pressure ≥90mmHg), cognitive diagnosis, and *APOE-ε4* status. †Models were adjusted for age, sex, education, race/ethnicity, Framingham stroke risk profile (excluding points assigned for age, LVH, and systolic blood pressure accounting for anti-hypertensive medication utilization), cognitive diagnosis, and *APOE-ε4* status. Boston Naming Test=Boston Naming Test-30 Item Odd Version; WAIS-IV=Wechsler Adult Intelligence Scale, 4th Edition; DKEFS=Delis-Kaplan Executive Function System; CVLT-II=California Verbal Learning Test, 2nd Edition; BFLT=Biber Figure Learning Test.