Left Ventricular Hypertrophy and Remodeling and Risk of Cognitive Impairment and Dementia

MESA (Multi-Ethnic Study of Atherosclerosis)

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Abstract—Limited information exists on the longitudinal association between the left ventricular (LV) structure and function and future cognitive impairment and dementia in a large population without clinically recognized cardiovascular disease at baseline. The aim of the present study was to investigate the association between cardiac structure and function and risk of dementia and cognitive impairment in the MESA (Multi-Ethnic Study of Atherosclerosis) cohort. Measures of LV structure and function were determined using magnetic resonance imaging at baseline in 4999 participants free of clinically diagnosed cardiovascular disease and dementia. Probable incident clinical dementia was ascertained from hospitalization discharge records. Cognitive function was evaluated using tests addressing global cognitive function, processing speed, and memory. Associations of measures of LV structure and function with the incidence of clinically diagnosed dementia and cognitive performance were evaluated using Cox proportional hazard regression models adjusted for demographics, cardiovascular risk factors, and cardiovascular events. During a median follow-up of 12 years, 130 probable incident dementia cases were documented. Higher LV mass index (hazard ratio, 1.01; 95% confidence interval, 1.00–1.02) and LV mass-to-volume ratio (hazard ratio, 2.37; 95% confidence interval, 1.25–4.43) were independently associated with incident dementia and impaired cognitive function. Measures of LV function were not associated with risk of dementia or cognitive impairment. In conclusion, in a multiethnic cohort of participants without clinically detected cardiovascular disease and dementia at baseline, LV hypertrophy and concentric remodeling were independently associated with incident dementia and cognitive impairment. (***Hypertension*****. 2018;71:429-436. DOI: 10.1161/HYPERTENSIONAHA.117.10289.)** ● **Online Data Supplement**

Key Words: cognitive dysfunction ■ dementia ■ follow-up studies ■ heart ventricles ■ risk factors

Heart failure and dementia are 2 of the major geriatric public health problems worldwide. Heart failure affects >5 million adults in the United States and is responsible for 36% of cardiovascular deaths.[1] Dementia is a leading cause of morbidity and disability that substantially shortens life expectancy.[2] Heart failure and dementia often occur together, causing substantial financial burden on health and social network systems.[3,4] Both conditions share common risk factors, such as hypertension, obesity, and diabetes mellitus,[5,6] and population-based studies have shown that heart failure is independently associated with dementia.[7,8]

Although numerous studies have shown associations between clinical heart failure and dementia,[7,9,10] in the general population and in the absence of heart disease, the association

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between subclinical cardiac dysfunction and dementia has not been fully established. Findings from the Framingham Heart Study suggested that a nonlinear association exists between measures of systolic function and accelerated cognitive aging.[11] Recently, using echocardiography, it was shown that diastolic dysfunction (calculated using the Doppler peak E velocity divided by Doppler peak A velocity) was associated with dementia in the Rotterdam Study.[12] Left ventricular (LV) hypertrophy has also been associated with poor cognitive performance in older subjects.[13–15]

Cardiac magnetic resonance (CMR) imaging is a precise and reproducible tool for assessment of cardiac structure and function.[16] In this regard, there are no studies investigating the longitudinal association of systolic and diastolic function and structural measures of CMR imaging with incident dementia in a large population of men and women without clinically recognized cardiovascular disease at baseline. Therefore, in the present study, we aim to investigate the relationship between CMR-derived measures of cardiac structure and function at baseline MESA (Multi-Ethnic Study of Atherosclerosis) examination with cognitive impairment and incident dementia in a large multiethnic population of both sexes free of cardiovascular disease at baseline. We hypothesize that structural parameters, including LV mass index and mass-to-volume ratio but not functional (systolic or diastolic) parameters, are associated with future cognitive impairment/dementia.

Methods

Study Population

The data that support the findings of this study are available and can be accessed at https://www.mesa-nhlbi.org. The design of the MESA has been described previously.[17] Briefly, between July 2000 and August 2002, a total of 6814 men and women aged 45 to 84 years and free of clinically apparent cardiovascular disease were recruited from 6 US communities representing 4 racial/ethnic groups (white, black, Hispanic, and Chinese-American). Subjects with prior clinical diagnosis of cardiovascular disease at baseline were not included. To evaluate cardiac structure and function, a total of 4999 individuals underwent CMR at baseline, with 1502 participants agreeing to magnetic resonance imaging tagging as a part of the imaging protocol. The study protocol was approved by the institutional review board of each MESA field center, and all participants gave informed consent.

Magnetic Resonance Imaging

CMR imaging was performed using 1.5-T magnetic resonance imaging scanners (Avanto and Espree [Siemens Medical Systems] and Signa LX [GE Healthcare]) with a 6-channel anterior phased array torso coil and corresponding posterior coil elements.[18] The detailed MR protocol has been previously described in the online-only Data Supplement.[18]

Stroke volume was defined as the difference between LV end-diastolic volume and LV end-systolic volumes, and the LV ejection fraction was calculated as LV stroke volume divided by LV end-diastolic volume. LV mass was indexed to body surface area. LV mass-to-volume ratio was obtained with the papillary muscle mass being included in the LV cavity and excluded from the LV mass. LV shape indices were calculated both at end-diastole and end-systole as described previously.[19]

Tagged images were analyzed using harmonic phase imaging (Diagnosoft; Palo Alto, CA).[20] Regional myocardial systolic function was assessed using myocardial circumferential midwall shortening in tagged images as quantified by circumferential strain. Circumferential strain (Ecc) is a negative value, with lower values representing greater LV systolic function. Indices of diastolic function, including diastolic strain rate, torsion recoil rate, and strain relaxation index were also calculated from tagged images as described previously.[21] Lower diastolic strain rate and strain relaxation index and higher torsion recoil rate indicate greater diastolic function.

Follow-Up and End Points

A telephone interview was conducted every 9 to 12 months with each participant to identify interim hospitalizations, outpatient cardiovascular diagnoses, and deaths (Figure S1 in the online-only Data Supplement). For all events, medical records were obtained, including discharge diagnoses. Probable dementia cases included vascular dementia, Alzheimer, and Pick disease and were classified from the coded discharge diagnoses using the International Statistical Classification of Diseases Medical Diagnosis Codes, Ninth Revision. The candidate dementia cases were identified using the following diagnosis codes: *International Classification of Diseases—Ninth Revision* (*ICD-9*): 290, 294, 331.0, 331.1, 331.2, 331.82, 331.83, 331.9, 438.0, and 780.93; *ICD-10*: F00, F01, F03, F04, G30, G31 (excluding G31.2), I69.91, and R41 (Table S1). In addition, a physician ascertained all potential cases of dementia by reviewing the medical records of each case while blinded to *ICD* codes, looking for phrases that would indicate, or contradict, the diagnosis of dementia. For cases where medical records were indeterminate, the records were sent to the MESA adjudication committee. The use of hospital discharge *ICD* codes for probable dementia diagnosis has been used in prior publications from MESA.[22,23]

All cognitive measurements were examined during fifth MESA follow-up examination taking place between April 2010 and February 2012 (Table 1). The diagnoses of cardiovascular diseases were adjudicated and classified by 2 physicians from the MESA mortality and morbidity review committee.

Statistical Analysis

Categorical variables were presented as percent proportions and compared between groups using χ^2 tests. Continuous variables were presented as mean±SD and compared between groups using 2-sided *t* tests. Natural logarithmic transformation was applied to early diastolic strain rate and strain relaxation index given that these variables had skewed distributions.

Multivariable competing-risks Cox proportional hazard regression models were constructed to assess the association of LV structure and functional parameters with newly identified probable dementia.[24] Death before the diagnosis of dementia was considered as a competing event (Fine and Gray method[24]) because it hindered the observation of the dementia. Hazard ratios (HRs) were calculated along with the corresponding 95% confidence intervals to make statistical inference on the

Table 1. Cognitive Function Tests Used in the Present Study

Test	Cognitive Area Measured	Description
CASI	Global cognitive function	25 items testing attention, concentration, orientation, short-term memory, long-term memory, language, visual construction, verbal fluency, and abstraction/judgment
DSC	Processing speed	Measuring how quickly simple perceptual or mental operations can be performed
Digit span	Working memory	Administered in 2 parts requiring the participant to repeat gradually increasing spans of numbers (eg, 2–7–4) first forward and then backward

CASI indicates cognitive abilities screening instrument; and DSC, digit symbol coding.

covariate effects. The multivariable models used in the present study were based on prior literature[13–15] and were constructed as follows:

Model 1 was adjusted for demographics, educational level, and income level.

Model 2 included all variables in model 1 in addition to traditional cardiovascular disease risk factors at baseline MESA examination, including systolic blood pressure (BP), diastolic BP, pulse pressure, use of antihypertensives, resting heart rate, high-density lipoprotein, low-density lipoprotein, glucose level, body mass index, diabetes mellitus, CRP (C-reactive protein) levels, cigarette smoking, alcohol use, and coronary artery calcium score.

Model 3 was adjusted for all variables in model 2 and also interim cardiovascular events, including coronary events (myocardial infarction and resuscitated cardiac arrest), heart failure, coronary revascularization (percutaneous coronary intervention or coronary artery bypass surgery), and clinical stroke as time-varying covariates.

Model 4 included all variables in model 3 and also LV mass index.

Sensitivity analyses were performed with the exclusion of participants who had interim stroke, patients with suboptimal CMR imaging, and patients receiving medications that prevent cardiac remodeling. Cumulative event rate plots were calculated for tertiles of LV structure and functional parameters. General linear models were used to examine the associations between cognitive tests and the LV structure and functional indices adjusted for age, sex, race/ethnicity, level of education, income level, systolic BP, diastolic BP, pulse pressure, use of antihypertensives, resting heart rate, high-density lipoprotein, low-density lipoprotein, glucose level, body mass index, diabetes mellitus, CRP levels, cigarette smoking, alcohol use, coronary artery calcium score, cardiovascular events, including coronary events (myocardial infarction and resuscitated cardiac arrest), heart failure, coronary revascularization (percutaneous coronary intervention or coronary artery bypass surgery), and clinical stroke during the follow-up period. The cognitive abilities screening instrument variable was log-transformed to better approximate a normal distribution.

LV sphericity was measured and divided into quintiles as described previously.[19] Briefly, the LV shape was divided into quintiles of the SVI, with the first and last quintile representing low sphericity (or high conicity) and high sphericity, respectively. Quintiles 2 to 4 were combined to form the reference group.

Two-tailed *P* values <0.05 were used for significance testing. All statistical analysis was done using Stata 14.0 (StataCorp LP; College Station, TX).

Results

In total, 4999 MESA participants who underwent CMR at MESA baseline examination were included in this study. Data from tagged images were available for 1502 of the included participants. A total of 130 incident probable dementia cases were ascertained during a median of 12 years of follow-up, with 47 cases of probable dementia among individuals with available magnetic resonance imaging tagging data. Table 2 describes the baseline characteristics of those who developed dementia and those who did not. Participants with probable dementia were older and had lower income. They had higher systolic BP, pulse pressure, resting heart rate, and higher use of antihypertensive medications, and were more likely to have nonzero coronary artery calcium score. Furthermore, participants who developed probable dementia had higher unadjusted LV mass index, mass-to-volume ratio, and strain relaxation index, and lower unadjusted stroke volume and early diastolic strain rate.

Table 3 describes the adjusted HRs for probable dementia in relation to LV functional and structural parameters. All LV functional parameters showed linear associations with probable dementia. None of the indices of systolic function, including LV ejection fraction, stroke volume, or LV

Table 2. Baseline Characteristics of Study Participants Stratified by Dementia (n=4999)

Characteristics	No Dementia (4869)	Dementia (130)	*P* Value
Demographics			
Age, mean±SD	61±9	73±7	<0.001*
Men, n (%)	2.308 (47.4)	71 (54.6)	0.11
Race, n (%)			0.58
White	1893 (39)	62 (47.6)	
Chinese	644 (13.2)	9 (7.1)	
Black	1247 (25.6)	36 (27.7)	
Hispanic	1085 (22.2)	23 (17.6)	
Income, US$			<0.001*
<20 000	1052 (22.3)	46 (37.4)	
20 000–49 999	1708 (36.2)	56 (45.5)	
≥50 000	1954 (41.5)	21 (17.1)	
Cardiovascular risk factors			
Systolic blood pressure, mm Hg; mean±SD	125±21	135±23	<0.001*
Diastolic blood pressure, mm Hg; mean±SD	71±10	72±10	0.41
Pulse pressure, mm Hg; mean±SD	53±16	62±18	<0.001*
Hypertension medication use, n (%)	1697 (34.8)	66 (50.7)	<0.001*
β-Blocker use, n (%)	580 (11.9)	29 (22.3)	0.01*
Angiotensin-converting enzyme inhibitor, n (%)	770 (15.8)	36 (27.6)	0.003*
Angiotensin receptor blocker use, n (%)	223 (4.5)	9 (6.9)	0.23*
Heart rate, mean±SD	62±9	64±10	0.030*
Body mass index, kg/m^2; mean±SD	27±4	27±4	0.175
HDL cholesterol, mg/dL; mean±SD	51±14	51±14	0.68
Total cholesterol, mg/dL; mean±SD	194±35	193±33	0.87
Diabetes mellitus, n (%)	558 (11.49)	20 (15.38)	0.37
Smoking status, n (%)			0.81
Former	1738 (35.8)	46 (35.38)	
Current	620 (12.77)	14 (10.77)	
Alcohol use, n (%)	2723 (69.34)	69 (70.41)	0.92
Coronary artery calcium score, n (%)			<0.001*
0	2538 (52.1)	34 (26.2)	
1–99	1296 (26.6)	27 (20.7)	
100–399	616 (12.6)	40 (30.7)	
>399	420 (8.7)	29 (22.4)	

(*Continued*)

Table 2. Continued

Characteristics	No Dementia (4869)	Dementia (130)	*P* Value
CMR indexes (n=4999)			
LV mass index, g/m^2; mean±SD	77±16	81±15	0.007*
Mass-to-volume ratio, g/mL; mean±SD	1.16±0.24	1.30±0.28	<0.001*
LV ejection fraction, %; mean±SD	69±7	68±8	0.81
Stroke volume, mL; mean±SD	46±8	43±8	<0.001*
CMR indexes (n=1502)			
LV circumferential strain, % mean±SD	−15.07±2.86	−14.79±2.87	0.51
LV torsion recoil, (deg/cm/ms), mean±SD	−19.39±11.24	−22.13±14.38	0.15
Strain relaxation index, (ms/%) ± SD	0.74±0.01	0.97±0.07	0.017*
Early diastolic strain rate, (%/ms) mean±SD	−2.22±0.012	−2.38±0.05	0.019*

CMR indicates cardiac magnetic resonance; HDL, high-density lipoprotein; and LV, left ventricular.

*Statistical significance (P<0.05).

circumferential strain index were associated with dementia in multivariable analysis (Table 3). In contrast, the markers of diastolic dysfunction and LV remodeling were associated with the risk of probable dementia, including LV mass index, mass-to-volume ratio, LV global function index, strain relaxation index, and early diastolic strain rate. The HR remained significant after adjustment for sociodemographics, cardiovascular risk factors, and cardiovascular events during follow-up (Table 3). However, inclusion of the LV mass index into the regression model abolished the significant association between diastolic measures of strain relaxation index and early diastolic strain rate with risk of probable dementia (Model 4, Table 3). Nevertheless, adjustment for LV mass index did not attenuate the significant relationship between structural parameters of mass-to-volume ratio with risk of dementia (Table 3). The relationship remained significant even after a sensitivity analysis was performed, including only patients receiving medications, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or β-blockers that prevent LV remodeling (HR, 5.50; 95% CI, 1.30–23.22; P=0.020). The findings were similar when participants who developed clinically recognized stroke during follow-up were excluded. Excluding patients who had suboptimal CMR images (22 patients) did not alter any of the observed associations. The Figure shows the cumulative incidence curves for probable dementia.

Table 4 demonstrates the HRs for the prediction of dementia using sphericity volume index. Low sphericity at end-diastole was a predictor of dementia independent of conventional risk factors. This relationship remained significant even after adjustment for LV mass index (Table 4).

The association between cognitive test scores and LV functional and structural parameters is shown in Table 4. Increases in LV mass index and mass-to-volume ratio (all of which are indicative of increased cardiac remodeling) were associated with decreased cognitive performance (Table 5). None of the LV systolic or diastolic function parameters were associated with measures of cognitive performance.

Table 3. HR for Association Between LV Functional Parameters and Risk of Dementia

	HR (95% CI)			
	Model 1	Model 2	Model 3	Model 4
Systolic function				
LV ejection fraction, %	0.98 (0.96–1.00)	0.98 (0.95–1.02)	0.99 (0.96–1.01)	0.99 (0.96–1.00)
Stroke volume, mL	0.99 (0.97–1.00)	0.99 (0.96–1.00)	0.98 (0.96–1.01)	0.98 (0.96–1.01)
LV circumferential strain, %	1.00 (0.90–1.12)	1.05 (0.93–1.16)	1.05 (0.92–1.18)	1.05 (0.93–1.18)
Diastolic function				
LV torsion recoil, degree/cm per ms	0.98 (0.95–1.01)	0.98 (0.96–1.01)	0.98 (0.95–1.01)	0.98 (0.95–1.01)
Log (strain relaxation index), ms/%	1.51 (1.01–2.24)*	1.61 (1.05–2.45)*	1.60 (1.05–2.42)*	1.53 (0.99–2.33)
Log (early diastolic strain rate), %/ms	0.60 (0.37–0.94)*	0.57 (0.35–0.95)*	0.58 (0.34–0.95)*	0.60 (0.36–1.01)
LV structural indices				
LV mass index, g/m^2	1.01 (1.00–1.02)*	1.01 (1.00–1.03)*	1.01 (1.00–1.02)*	
LV mass-to-volume ratio, g/mL	2.20 (1.21–3.99)*	2.28 (1.23–4.25)*	2.31 (1.23–4.29)*	2.37 (1.25–4.43)*

Model 1 included covariates for demographics, including age, sex, race/ethnicity, level of education, and income level. Model 2 included all variables in model 1 in addition to risk factors, including systolic blood pressure, diastolic blood pressure, pulse pressure, use of antihypertensives, resting heart rate, high-density lipoprotein, low-density lipoprotein, fasting glucose level, body mass index, diabetes mellitus, CRP (C-reactive protein) levels, cigarette smoking, alcohol use, and coronary artery calcium score. Model 3 included all model 2 variables, with the addition of cardiovascular events, including coronary events (myocardial infarction and resuscitated cardiac arrest), heart failure, coronary revascularization (percutaneous coronary intervention or coronary artery bypass surgery), and clinical stroke during the follow-up period. Model 4 included all variables in model 3, with the addition of LV mass index. CI indicates confidence interval; HR, hazard ratio; and LV, left ventricular.

*Significant HR and their CIs.

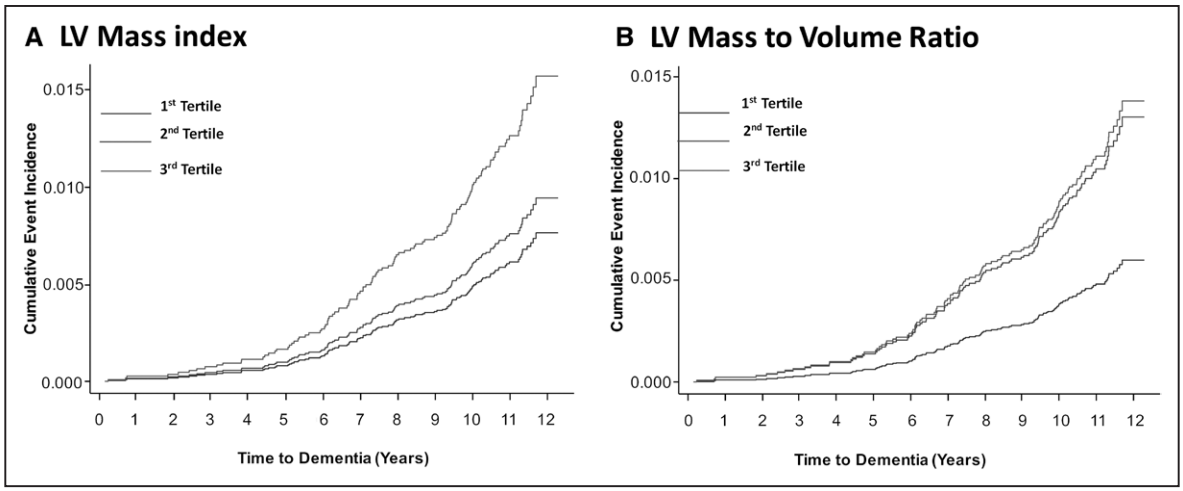

Figure. Cumulative event rates for probable dementia events by tertiles for left ventricular (LV) mass index (**A**), LV mass-to-volume ratio (**B**), controlled for age, sex, race/ethnicity, level of education and income, systolic blood pressure, diastolic blood pressure, pulse pressure, use of antihypertensives, resting heart rate, high-density lipoprotein, low-density lipoprotein, fasting glucose level, body mass index, diabetes mellitus, CRP (C-reactive protein) levels, cigarette smoking, alcohol use, coronary artery calcium score, and cardiovascular events, including coronary events (myocardial infarction and resuscitated cardiac arrest), heart failure, coronary revascularization (percutaneous coronary intervention or coronary artery bypass surgery), and clinical stroke during the follow-up period (model 3).

Discussion

The findings of the present study indicate that in a large multiethnic cohort, free of clinically recognized cardiovascular disease at enrollment, measures of LV hypertrophy and concentric remodeling were strongly associated with a higher risk of cognitive impairment and probable dementia. These findings were independent of demographic confounders, cardiovascular risk factors, and cardiovascular events. Diastolic dysfunction was originally associated with probable dementia and cognitive impairment, but this relationship was eliminated after adjusting for LV mass index, suggesting that LV hypertrophy mediates the association of diastolic dysfunction and dementia. There was no association between systolic function and either probable dementia or cognitive impairment.

In the present study, greater LV mass index and concentric remodeling (defined by elevated LV mass-to-volume ratio) were inversely associated with measures of cognitive function. Additionally, both parameters were also associated with increased risk of probable dementia. These associations remained significant after adjustments for multiple covariates, including BP and use of antihypertensive medications. Previous studies have also shown the association between LV mass and cognitive performance, after adjusting for age and sex.[13–15] Although the association was found to be attenuated with adjustment for mean systolic BP in earlier studies,[14,15] in a more recent study performed on 400 elderly subjects, similar associations were found between increased LV mass index and worse cognitive performance, regardless of adjustment for BP values.[13] Although the study population was older (mean

Table 4. HR for Association Between Sphericity Indices at End-Diastole and End-Systole and Risk of Dementia

	HR (95% CI)			
	Model 1	Model 2	Model 3	Model 4
SVIED				
Low sphericity/high conicity	7.31 (1.67–52.66)*	8.15 (1.92–60.46)*	8.19 (2.1–59.60)*	8.07 (1.11–58.73)*
High sphericity	1.37 (0.59–3.20)	1.34 (0.59–3.05)	1.42 (0.62–3.26)	1.46 (0.62–3.43)
SVIES				
Low sphericity/high conicity	1.62 (0.74–3.55)	1.49 (0.58–3.78)	1.48 (0.58–3.73)	1.40 (0.55–3.54)
High sphericity	1.33 (0.48–3.69)	1.71 (0.57–5.05)	1.71 (0.58–5.03)	1.57 (0.52–4.71)

Model 1 included covariates for demographics, including age, sex, race/ethnicity, level of education, and income level. Model 2 included all variables in model 1 in addition to risk factors, including systolic blood pressure, diastolic blood pressure, pulse pressure, use of antihypertensives, resting heart rate, high-density lipoprotein, low-density lipoprotein, fasting glucose level, body mass index, diabetes mellitus, CRP (C-reactive protein) levels, cigarette smoking, alcohol use, and coronary artery calcium score. Model 3 included all model 2 variables, with the addition of cardiovascular events, including coronary events (myocardial infarction and resuscitated cardiac arrest), heart failure, coronary revascularization (percutaneous coronary intervention or coronary artery bypass surgery), and clinical stroke during the follow-up period. Model 4 included all variables in model 3, with the addition of LV mass index. CI indicates confidence interval; HR, hazard ratio; LV, left ventricle; SVIED, sphericity volume index at end-diastole; and SVIES, sphericity volume index at end-systole.

*Significant HR and their CIs.

Table 5. Coefficients for Multivariable Linear Regression of the Associations Between Cognitive Test Scores and LV Functional Parameters

	CASI		DSC		Digit Span			
					Forward		Backward	
Systolic function								
LV ejection fraction, %	−0.099 (−2.345 to 1.751)	0.79	0.009 (−1.281 to 0.127)	0.24	0.039 (−0.172 to 0.251)	0.49	0.012 (−0.151 to 0.014)	0.81
Stroke volume, mL	−0.064 (−0.121 to 0.672)	0.89	0.010 (−0.721 to 1.281)	0.33	0.044 (−0.172 to 0.239)	0.46	−0.014 (−0.412 to 0.011)	0.82
LV circumferential strain, %	−0.027 (−1.231 to 1.145)	0.92	−0.015 (−0.192 to 0.123)	0.12	0.08 (−0.152 to 0.381)	0.61	0.023 (−0.126 to 0.131)	0.56
Diastolic function								
LV torsion recoil, degree/cm per ms	−1.839 (−4.261 to 1.189)	0.23	−0.006 (−0.716 to 0.912)	0.82	−0.09 (−0.712 to 0.012)	0.54	−0.130 (−0.812 to 0.182)	0.44
Log (strain relaxation index), ms/%	0.046 (−0.1.124 to 0.812)	0.71	0.046 (−0.012 to 0.329)	0.48	−0.007 (−0.192 to 0.015)	0.34	−0.008 (−0.182 to 0.081)	0.35
Log (early diastolic strain rate), %/ms	−0.010 (−1.241 to 0.871)	0.22	0.001 (−0.012 to 0.001)	0.21	−0.001 (−0.193 to 0.028)	0.34	0.009 (−0.124 to 0.301)	0.19
LV structural indices								
LV mass index, g/m^2	−2.367 (−4.110 to −1.231)*	0.002*	−0.105 (−0.691 to −0.012)*	0.001*	−0.23 (−1.231 to −0.001)*	0.01*	−0.449 (−1.192 to −0.012)*	0.001*
LV mass-to-volume ratio, g/mL	−0.030 (−0.078 to −0.001)*	0.013*	−0.001 (−0612 to −0.000)*	0.001*	−0.003 (−0.191 to −0.000)*	0.009*	−0.005 (−0.017 to −0.000)*	0.001*

Coefficients and 95% CIs (in brackets) for multivariable linear regression model to assess the associations between CMR variables with different cognitive performance domains. Models adjusted for demographics, including age, sex, race/ethnicity, level of education and income, risk factors, including systolic blood pressure, diastolic blood pressure, pulse pressure, use of antihypertensives, resting heart rate, high-density lipoprotein, low-density lipoprotein, fasting glucose level, body mass index, diabetes mellitus, CRP (C-reactive protein) levels, cigarette smoking, alcohol use, coronary artery calcium score, and cardiovascular events, including coronary events (myocardial infarction and resuscitated cardiac arrest), heart failure, coronary revascularization (percutaneous coronary intervention or coronary artery bypass surgery) and clinical stroke during the follow-up period. CASI indicates cognitive abilities screening instrument; CI, confidence intervals; CMR, cardiac magnetic resonance; DSC, digit symbol coding; and LV, left ventricle.

*Statistical significance ($P<0.05$).

age, 79 years) with a higher prevalence of hypertension (70%) compared with the present study, the results showed that the association between increased LV mass index and higher likelihood of having dementia was independent of BP levels or large artery stiffness.

Although high BP is a key risk factor in the development of increased LV mass and LV hypertrophy and remodeling,[25] one possible explanation for the observed association between measures of LV structure and cognition, independent of BP levels, could be ascribed to the fact that both markers represent sensitive indicators of lifelong exposure to higher BP levels.[26] Results from the British birth cohort study showed that elevated BP from early midlife predicted higher LV mass index and LV remodeling in later life, even after accounting for current BP levels.[27] The authors also found that subjects receiving antihypertensive medications had higher LV mass index and prevalence of LV hypertrophy, suggesting that effective treatment of hypertension may not achieve complete reversal of cardiac target organ damage.[27]

The results of the present study showed that low sphericity or increased conicity at end-diastole was associated with increased risk of probable future dementia. The relationship was independent of sociodemographics, cardiovascular risk factors, cardiovascular events during follow-up, and LV mass index. It has previously been shown that patients exhibiting low sphericity on CMR imaging have greater concentric remodeling and ventricular hypertrophy, leading to increased cardiomyocyte stress as evidenced by higher levels of NT-proBNP (N-terminal pro-B-type natriuretic peptide) found in this group of patients.[19] Low sphericity has been indicative of a stiffer and more fibrotic ventricle and has been shown to be a predictor of incident cardiovascular disease.[28] These findings suggest that the LV geometry is a predictor of future dementia independent of LV size or conventional risk factors.

Previous reports have indicated an increased risk of dementia among patients with overt cardiac disease, including heart failure,[7,29] atrial fibrillation,[30–32] and coronary heart disease.[33,34] However, limited information exists among asymptomatic populations on systolic and diastolic function related to dementia. Recently, findings from the Rotterdam Study showed that worse diastolic function is related to an increased risk of dementia through echocardiography measures in people without clinical cardiac disease.[12] In the present study, measures of impaired diastolic function were associated with increased risk of probable dementia after adjusting for patients' demographics, cardiovascular risk factors, and cardiovascular events. However, when LV mass index was added to the covariate set, the relation between diastolic function and

probable dementia was rendered nonsignificant. These findings suggest that LV hypertrophy plays an important role in the relation between diastolic function and probable dementia.

The association between systolic function and dementia in the general population without cardiovascular disease has not been consistent among all studies. Although the Rotterdam Study did not find any association between measures of systolic function and risk of dementia,[12] findings from the Framingham Heart Study demonstrated a U-shaped association between LV systolic function and cognitive performance.[11] Similarly, other studies have shown that diminished systolic function is related to lower brain volume[35] and silent brain infarcts,[36] both of which are important markers of brain aging. However, these studies used echocardiography for systolic function measurement[12,36] or were cross-sectional by design.[11,35] In the present study, both global and regional systolic function was assessed using CMR, which has proven to be the most accurate method to assess cardiac systolic function.[16] Our results indicate that measures of systolic function at baseline are not related to impaired cognitive function or dementia in individuals without overt cardiovascular disease.

The present study has several limitations. Probable incident dementia cases were ascertained from hospitalization records using *ICD-9* codes. This method of dementia diagnosis likely underestimates the incidence of disease because it only identifies subjects who were hospitalized and dementia was included among their discharge diagnoses. In addition, the presence of multiple diagnosis in hospitalized patients creates a downward bias in the association by decreasing the probability of the dementia diagnosis being recorded among the discharge codes. However, this method of identifying dementia cases has been shown to have adequate positive predictive value in a recent validation study on MESA participants with the diagnosis of dementia.[22] In addition, the strong association between both poor cognitive scores and probable dementia cases and LV structural measures suggests that the present study is identifying true dementia cases. Another limitation of the present study is the notion that while many known risk factors for cardiovascular and brain disease were adjusted for in the multivariable analyses, the possibility that unmeasured confounders might be involved in the observed associations cannot be excluded. Therefore, the results of the present study should be interpreted in the context of its limitations.

Perspectives

The results of the present study indicate that in a large diverse population-based study with long follow-up periods among individuals free of symptomatic cardiovascular disease at enrollment, measures of increased LV mass and LV remodeling and lower sphericity but not LV function were associated with the risk of cognitive impairment and probable clinical dementia. These findings highlight the possibility of early involvement of the heart in patients with dementia and may be useful in identification of individuals at risk of cognitive impairment. Whether normalization of LV mass and reversal of LV remodeling through improved BP control and other measures could prevent future cognitive impairment and dementia remains to be established.

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Disclosures

None.

References

1. Mozaffarian D, Benjamin EJ, Go AS, et al; Writing Group Members; American Heart Association Statistics Committee; Stroke Statistics Subcommittee. Executive summary: heart disease and stroke statistics–2016 update: a report from the American Heart Association. *Circulation*. 2016;133:447–454. doi: 10.1161/CIR.0000000000000366.
2. Todd S, Barr S, Roberts M, Passmore AP. Survival in dementia and predictors of mortality: a review. *Int J Geriatr Psychiatry*. 2013;28:1109–1124. doi: 10.1002/gps.3946.
3. Dayer M, Cowie MR. Heart failure: diagnosis and healthcare burden. *Clin Med (Lond)*. 2004;4:13–18.
4. Rizzi L, Rosset I, Roriz-Cruz M. Global epidemiology of dementia: Alzheimer's and vascular types. *Biomed Res Int*. 2014;2014:908915. doi: 10.1155/2014/908915.
5. Rosengren A, Skoog I, Gustafson D, Wilhelmsen L. Body mass index, other cardiovascular risk factors, and hospitalization for dementia. *Arch Intern Med*. 2005;165:321–326. doi: 10.1001/archinte.165.3.321.
6. Xu WL, Qiu CX, Wahlin A, Winblad B, Fratiglioni L. Diabetes mellitus and risk of dementia in the Kungsholmen project: a 6-year follow-up study. *Neurology*. 2004;63:1181–1186.
7. Qiu C, Winblad B, Marengoni A, Klarin I, Fastbom J, Fratiglioni L. Heart failure and risk of dementia and Alzheimer disease: a population-based cohort study. *Arch Intern Med*. 2006;166:1003–1008. doi: 10.1001/archinte.166.9.1003.
8. Vogels RL, Scheltens P, Schroeder-Tanka JM, Weinstein HC. Cognitive impairment in heart failure: a systematic review of the literature. *Eur J Heart Fail*. 2007;9:440–449. doi: 10.1016/j.ejheart.2006.11.001.
9. Ampadu J, Morley JE. Heart failure and cognitive dysfunction. *Int J Cardiol*. 2015;178:12–23. doi: 10.1016/j.ijcard.2014.10.087.
10. Alagiakrishnan K, Mah D, Ahmed A, Ezekowitz J. Cognitive decline in heart failure. *Heart Fail Rev*. 2016;21:661–673. doi: 10.1007/s10741-016-9568-1.
11. Jefferson AL, Himali JJ, Au R, Seshadri S, Decarli C, O'Donnell CJ, Wolf PA, Manning WJ, Beiser AS, Benjamin EJ. Relation of left ventricular ejection fraction to cognitive aging (from the Framingham Heart Study). *Am J Cardiol*. 2011;108:1346–1351. doi: 10.1016/j.amjcard.2011.06.056.
12. de Bruijn RF, Portegies ML, Leening MJ, Bos MJ, Hofman A, van der Lugt A, Niessen WJ, Vernooij MW, Franco OH, Koudstaal PJ, Ikram MA. Subclinical cardiac dysfunction increases the risk of stroke and dementia: the Rotterdam Study. *Neurology*. 2015;84:833–840. doi: 10.1212/WNL.0000000000001289.
13. 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. doi: 10.1093/eurheartj/ehp133.
14. 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. doi: 10.1161/01.HYP.0000256361.68158.24.
15. Kähönen-Väre 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.
16. Sechtem U, Mahrholdt H, Vogelsberg H. Cardiac magnetic resonance in myocardial disease. *Heart*. 2007;93:1520–1527. doi: 10.1136/hrt.2005.067355.

17. Bild DE, Bluemke DA, Burke GL, et al. Multi-Ethnic Study of Atherosclerosis: objectives and design. *Am J Epidemiol*. 2002;156:871–881.
18. Natori S, Lai S, Finn JP, Gomes AS, Hundley WG, Jerosch-Herold M, Pearson G, Sinha S, Arai A, Lima JA, Bluemke DA. Cardiovascular function in Multi-Ethnic Study of Atherosclerosis: normal values by age, sex, and ethnicity. *AJR Am J Roentgenol*. 2006;186(6 suppl 2):S357–S365. doi: 10.2214/AJR.04.1868.
19. Ambale-Venkatesh B, Yoneyama K, Sharma RK, Ohyama Y, Wu CO, Burke GL, Shea S, Gomes AS, Young AA, Bluemke DA, Lima JA. Left ventricular shape predicts different types of cardiovascular events in the general population. *Heart*. 2017;103:499–507. doi: 10.1136/heartjnl-2016-310052.
20. Garot J, Bluemke DA, Osman NF, Rochitte CE, McVeigh ER, Zerhouni EA, Prince JL, Lima JA. Fast determination of regional myocardial strain fields from tagged cardiac images using harmonic phase MRI. *Circulation*. 2000;101:981–988.
21. Ambale-Venkatesh B, Armstrong AC, Liu CY, Donekal S, Yoneyama K, Wu CO, Gomes AS, Hundley GW, Bluemke DA, Lima JA. Diastolic function assessed from tagged MRI predicts heart failure and atrial fibrillation over an 8-year follow-up period: the Multi-Ethnic Study of Atherosclerosis. *Eur Heart J Cardiovasc Imaging*. 2014;15:442–449. doi: 10.1093/ehjci/jet189.
22. Fujiyoshi A, Jacobs DR Jr, Alonso A, Luchsinger JA, Rapp SR, Duprez DA. Validity of death certificate and hospital discharge ICD codes for dementia diagnosis: the Multi-Ethnic Study of Atherosclerosis. *Alzheimer Dis Assoc Disord*. 2017;31:168–172. doi: 10.1097/WAD.0000000000000164.
23. Fujiyoshi A, Jacobs DR Jr, Fitzpatrick AL, Alonso A, Duprez DA, Sharrett AR, Seeman T, Blaha MJ, Luchsinger JA, Rapp SR. Coronary artery calcium and risk of dementia in MESA (Multi-Ethnic Study of Atherosclerosis). *Circ Cardiovasc Imaging*. 2017;10:e005349. doi: 10.1161/CIRCIMAGING.116.005349.
24. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496–509.
25. Hammond IW, Devereux RB, Alderman MH, Laragh JH. Relation of blood pressure and body build to left ventricular mass in normotensive and hypertensive employed adults. *J Am Coll Cardiol*. 1988;12:996–1004.
26. Verdecchia P, Carini G, Circo A, Dovellini E, Giovannini E, Lombardo M, Solinas P, Gorini M, Maggioni AP; MAVI (MAssa Ventricolare sinistra nell'Ipertensione) Study Group. Left ventricular mass and cardiovascular morbidity in essential hypertension: the MAVI study. *J Am Coll Cardiol*. 2001;38:1829–1835. doi: 10.1016/S0735-1097(01)01663-1.
27. Ghosh AK, Hardy RJ, Francis DP, Chaturvedi N, Pellerin D, Deanfield J, Kuh D, Mayet J, Hughes AD; Medical Research Council National Survey of Health and Development (NHSD) Scientific and Data Collection Team. Midlife blood pressure change and left ventricular mass and remodelling in older age in the 1946 British Birth Cohort Study. *Eur Heart J*. 2014;35:3287–3295. doi: 10.1093/eurheartj/ehu389.
28. Ohyama Y, Ambale-Venkatesh B, Noda C, et al. Association of aortic stiffness with left ventricular remodeling and reduced left ventricular function measured by magnetic resonance imaging: the Multi-Ethnic Study of Atherosclerosis. *Circ Cardiovasc Imaging*. 2016;9:e004426. doi: 10.1161/CIRCIMAGING.115.004426.
29. Haeusler KG, Laufs U, Endres M. Chronic heart failure and ischemic stroke. *Stroke*. 2011;42:2977–2982. doi: 10.1161/STROKEAHA.111.628479.
30. Medi C, Hankey GJ, Freedman SB. Stroke risk and antithrombotic strategies in atrial fibrillation. *Stroke*. 2010;41:2705–2713. doi: 10.1161/STROKEAHA.110.589218.
31. Ott A, Breteler MM, de Bruyne MC, van Harskamp F, Grobbee DE, Hofman A. Atrial fibrillation and dementia in a population-based study. The Rotterdam Study. *Stroke*. 1997;28:316–321.
32. Thacker EL, McKnight B, Psaty BM, Longstreth WT Jr, Sitlani CM, Dublin S, Arnold AM, Fitzpatrick AL, Gottesman RF, Heckbert SR. Atrial fibrillation and cognitive decline: a longitudinal cohort study. *Neurology*. 2013;81:119–125. doi: 10.1212/WNL.0b013e31829a33d1.
33. Dutta M, Hanna E, Das P, Steinhubl SR. Incidence and prevention of ischemic stroke following myocardial infarction: review of current literature. *Cerebrovasc Dis*. 2006;22:331–339. doi: 10.1159/000094847.
34. Newman AB, Fitzpatrick AL, Lopez O, Jackson S, Lyketsos C, Jagust W, Ives D, Dekosky ST, Kuller LH. Dementia and Alzheimer's disease incidence in relationship to cardiovascular disease in the Cardiovascular Health Study cohort. *J Am Geriatr Soc*. 2005;53:1101–1107. doi: 10.1111/j.1532-5415.2005.53360.x.
35. Jefferson AL, Himali JJ, Beiser AS, Au R, Massaro JM, Seshadri S, Gona P, Salton CJ, DeCarli C, O'Donnell CJ, Benjamin EJ, Wolf PA, Manning WJ. Cardiac index is associated with brain aging: the Framingham Heart Study. *Circulation*. 2010;122:690–697. doi: 10.1161/CIRCULATIONAHA.109.905091.
36. Russo C, Jin Z, Homma S, Elkind MS, Rundek T, Yoshita M, DeCarli C, Wright CB, Sacco RL, Di Tullio MR. Subclinical left ventricular dysfunction and silent cerebrovascular disease: the Cardiovascular Abnormalities and Brain Lesions (CABL) study. *Circulation*. 2013;128:1105–1111. doi: 10.1161/CIRCULATIONAHA.113.001984.

Novelty and Significance

What Is New?

- Studies investigating the longitudinal association of systolic and diastolic function and structural measures with cognitive performance and incident dementia in a large population of men and women without clinically recognized cardiovascular disease at baseline are sparse.

What Is Relevant?

- Cardiac magnetic resonance measures of increased left ventricular remodeling were independently associated with increased risk of cognitive impairment and probable dementia. This association remained significant after controlling for sociodemographics, cardiovascular risk factors, and cardiovascular events during follow-up.

Summary

In a large multiethnic cohort, free of clinically recognized cardiovascular disease at enrollment, cardiac magnetic resonance measures of left ventricular hypertrophy and concentric remodeling were strongly associated with a higher risk of future cognitive impairment and dementia.

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ONLINE SUPPLEMENT

Left Ventricular Hypertrophy and Remodeling and Risk of Cognitive Impairment and Dementia: MESA (Multi-Ethnic Study of Atherosclerosis)

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MRI protocol:

Cine images for assessment of LV structure and function included 4-chamber and 2-chamber views and stack of short axis images covering the entire left ventricle from above the mitral valve plane to the LV apex with retrospective gating using cine fast gradient recalled echo (FGRE) sequence. The MRI parameters were: repetition time 8-10 msec, echo train length 3-5 msec, flip angle 20 degrees, slice thickness 6 mm, slice gap 4 mm, field of view 360-400 mm, with a temporal resolution of cine images obtained approximately 50 msec or less. The imaging protocol also included tagged images in 3 short axis slices at the LV base, mid-ventricle and apex by nonselective radiofrequency pulses separated by a spatial modulation of magnetization-encoding gradients as previously described[17]. Parallel striped tags were prescribed in two orthogonal orientations (0° and 90°).

The epicardial and endocardial borders in cine images were contoured using a semi-automated method (MASS 4.2, Medis, Leiden, the Netherlands) to determine the LV volumes. The difference between the

epicardial and endocardial areas for all slices at end-diastolic phase was multiplied by the slice thickness and section gap, and then multiplied by the specific gravity of myocardium (1.04 g/ml) to determine the ventricular mass [17].

Table S1. Description of ICD codes used to identify probable dementia cases.

ICD codes	Description
ICD 9 codes	
290	Dementias, including Presenile dementia, Senile dementia with delusional or depressive features, Vascular dementia,
294	Persistent mental disorders due to conditions classified elsewhere, including Dementia in conditions classified elsewhere, Dementia, unspecified,
331.0	Alzheimer's disease
331.1	Frontotemporal dementia
331.82	Dementia with Lewy bodies
331.9	Cerebral degeneration
438.0	Late effects of cerebrovascular disease, cognitive deficits
780.93	Memory loss
ICD 10 codes	
F00	Dementia in Alzheimer's disease
F01	Vascular dementia
F03	Unspecified dementia
F04	Organic amnesic syndrome, not induced by alcohol and other psychoactive substances, excluding amnesia and Korsakov's syndrome
G30	Alzheimer's disease with early onset
G31	Degenerative disease of nervous system, unspecified
169.91	Cognitive deficits following unspecified cerebrovascular disease
R41	Other symptoms and signs involving cognitive functions and awareness

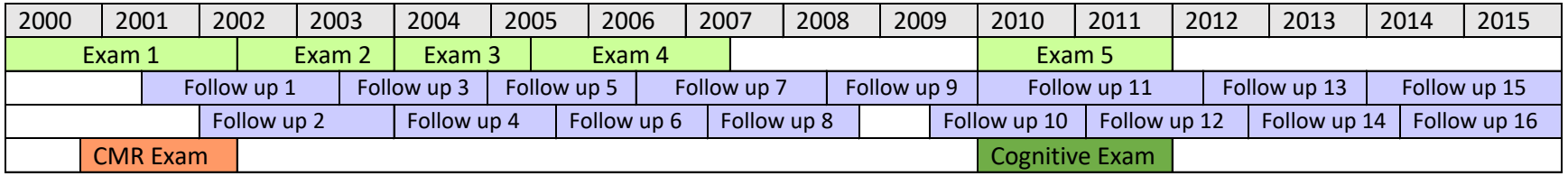

Figure S1. Time table of MESA follow up and examinations.