The Relationship of Left Ventricular Mass and Geometry to Incident Cardiovascular Events

The MESA (Multi-Ethnic Study of Atherosclerosis) Study

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Objective

The purpose of this study was to evaluate the relationship of left ventricular (LV) mass and geometry measured with cardiac magnetic resonance imaging (MRI) to incident cardiovascular events in the MESA (Multi-Ethnic Study of Atherosclerosis) study.

Background

MRI is highly accurate for evaluation of heart size and structure and has not previously been used in a large epidemiologic study to predict cardiovascular events.

Methods

A total of 5,098 participants in the MESA study underwent cardiac MRI at the baseline examination and were followed up for a median of 4 years. Cox proportional hazard models were constructed to predict the end points of coronary heart disease (CHD), stroke, and heart failure (HF) after adjustment for cardiovascular risk factors.

Results

A total of 216 incident events were observed during the follow-up period. In adjusted models, the end points of incident CHD and stroke were positively associated with increased LV mass-to-volume ratio (CHD, hazard ratio [HR]: 2.1 per g/ml, p = 0.02; stroke, HR: 4.2 per g/ml, p = 0.005). In contrast, LV mass showed the strongest association with incident HF events (HR: 1.4 per 10% increment, p < 0.0001). The HF events occurred primarily in participants with LV hypertrophy, that is, ≥95th percentile of LV mass (HR: 8.6, 95% confidence interval: 3.7 to 19.9, reference group ≤50th percentile of LV mass).

Conclusions

The LV size was related to incident HF, stroke, and CHD in this multiethnic cohort. Whereas body size-adjusted LV mass alone predicted incident HF, concentric ventricular remodeling predicted incident stroke and CHD. (J Am Coll Cardiol 2008;52:2148–55) © 2008 by the American College of Cardiology Foundation

The Framingham Study (1–3) and other population-based studies (4–7) have shown that increased left ventricular (LV) mass, known as left ventricular hypertrophy (LVH), is an independent predictor of cardiovascular events in population-based studies using electrocardiograms (ECGs) or echocardiography to define LVH. The value of LVH to predict cardiovascular disease events holds for individuals without (1–3,7) as well as with prior known coronary heart disease (CHD) (5,8) and heart failure (HF) (9,10). Reduction of LV mass as a result of therapeutic intervention reduces cardiovascular events (11–14), indicating that LV mass is an important subclinical marker of cardiovascular disease (15).

LVH is associated with multiple factors, such as increased age, blood pressure, and diabetes (16–19), resulting in increased stiffness of the LV. Geometric changes of the ventricle, termed remodeling, have been investigated primarily by echocardiography in relationship to cardiovascular events (20–24). Echocardiographic estimates of LVH, defined by LV diameters and wall thickness normalized by body surface area >125 g/m² (25) and the ratio of posterior wall thickness to LV radius ≥0.45 (22), have been used to define concentric remodeling of the LV. The presence and pattern of ventricular remodeling has been noted to confer cardiovascular risk beyond LVH in some studies (22,24,26,27), but not in others (23,28).
Magnetic resonance imaging (MRI) is highly accurate and reproducible for assessing 3-dimensional ventricular size and shape (29–34), and thus may allow additional insight into the pathophysiology of myocardial remodeling. In this study, we report the relationship between LV mass and volume as determined by MRI to incident cardiovascular disease in a multiethnic cohort free from clinical cardiovascular disease at baseline.

**Methods**

**Subjects.** The MESA (Multi-Ethnic Study of Atherosclerosis) study has been previously described (35). In brief, between July 2000 and August 2002, 6,814 men and women who identified themselves as white, African-American, Hispanic, or Chinese and were 45 to 84 years old and free of clinically apparent cardiovascular disease were recruited from 6 U.S. communities: Baltimore City and Baltimore County, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; Northern Manhattan and the Bronx, New York; and St. Paul, Minnesota. Consenting participants underwent a cardiac MRI scan a median of 16 days after the baseline evaluation; 95% were completed by 11 weeks after the baseline examination. The institutional review boards at all participating centers approved the study, and all participants gave informed consent.

**Risk factor measures.** Standardized questionnaires were used to obtain information about smoking history and medication usage for high blood pressure, high cholesterol, and diabetes. Smoking was defined as current, former, or never. Subjects had their height and weight measured. Resting blood pressure was measured 3 times with participants in the seated position with a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, GE Healthcare, Waukesha, Wisconsin). The average of the last 2 measurements was used in analysis. Total and high-density lipoprotein cholesterol and glucose levels were measured from blood samples obtained after a 12-h fast. Low-density lipoprotein cholesterol was calculated with the Friedewald equation (36).

Diabetes was defined as fasting glucose ≥126 mg/dl or use of hypoglycemic medication. Impaired fasting glucose was defined as fasting glucose 100 to 125 mg/dl. Hypertension status was classified according to the Seventh Report of the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure (37). Body mass index (kg/m²) was calculated from weight measured to the nearest 0.5 kg and height to the nearest 0.1 cm.

**Cardiac MRI.** Cardiac MRI was performed with 1.5-T magnets with determination of LV mass and volumes as previously described (38). Briefly, a stack of short-axis images covering the entire LV was acquired with time to repetition/time to echo 8 to 10 ms/3 to 5 ms, flip angle 20°, 6-mm slice thickness, 4-mm gap, flow compensation, in-plane resolution 1.4 to 1.6 mm (frequency) × 2.2 to 2.5 mm. The endocardial and epicardial myocardial borders were contoured using a semiautomated method (MASS 4.2, Medis, Leiden, the Netherlands). The difference between the epicardial and endocardial areas for all slices 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. Papillary muscle mass was included in the LV cavity and excluded from the LV mass. This approach showed better reproducibility than contouring of individual papillary muscles in preliminary data analyses. A study of repeat measurements of LV mass on 79 MESA study subjects performed between 3 and 6 months after the initial measurement showed the technical error of measurement percent of the mean was 6% and 4% for LV mass and end-diastolic volume, respectively, and the intraclass correlation coefficients were 0.98 and 0.98, respectively (38).

Preliminary evaluation showed that MRI measured LV mass and volume indexed by body surface area, height²/², or height¹.⁰ did not fully remove the correlation of these measures with weight and/or height. Using an allometric approach (39), regression models for body size were derived from a sample of 1,746 MESA study participants without obesity, hypertension, antihypertensive medication use, diabetes, impaired fasting glucose, or hypoglycemic medication use using a multiplicative model estimated by regressing log(LV mass) on log(height), log(weight), and sex. The LV mass was adjusted for body size by dividing 100 × LV mass by the predicted LV mass based on height, weight, and sex, as: 100 × LV mass / (a × height⁰.⁵₅ × weight¹.₆₁), where a = 6.82 for women and 8.25 = men with mass in grams, height in meters, weight in kilograms. Similarly, the body size-adjusted LV end-diastolic volume was computed as: 100 × LV × volume/(b × height¹.₂₅ × weight⁰.⁴₃), where b = 10.0 for women and 10.5 for men and LV end-diastolic volume is in milliliters.

**Adjudication of events.** Participants were followed up for incident cardiovascular events up to 5.2 years from their baseline examinations. In addition to 3 follow-up MESA study examinations, a telephone interviewer contacted each participant every 9 to 12 months to inquire about all interim hospital admissions, cardiovascular outpatient diagnoses, and deaths. To verify self-reported diagnoses, copies were requested of all death certificates and medical records for all hospitalizations and outpatient cardiovascular diagnoses. Next-of-kin interviews for out-of-hospital cardiovascular deaths were obtained. We were successful in getting medical records on an estimated 98% of hospitalized cardiovascular events and information on 95% of outpatient cardiovascular
diagnostic encounters. Follow-up telephone interviews were completed in 92% of living participants.

Trained personnel abstracted any medical records suggesting possible cardiovascular events. Two physicians from the MESA study events committee independently reviewed all medical records for end point classification and assignment of incidence dates. The reviewers were blinded to the MESA study MRI results and used pre-specified criteria (see Online Appendix for detailed criteria for all events). If the reviewing physicians disagreed on the event classification, they adjudicated differences. If disagreements persisted, the full events committee made the final classification.

Reviewers classified myocardial infarction as definite, probable, or absent, based primarily on combinations of symptoms (e.g., chest pain), ECG abnormalities, and cardiac biomarker levels (Online Appendix). Coronary heart disease death was classified as present or absent based on hospital records and interviews with families. Definite fatal CHD required a myocardial infarction within 28 days of death, chest pain within the 72 h before death, or a history of CHD and the absence of a known nonatherosclerotic or noncardiac cause of death. Adjudicators graded angina based on their clinical judgment as definite, probable, or absent. Definite and probable angina required clear documentation of chest pain or anginal equivalent. Definite angina also required objective evidence of reversible myocardial ischemia or obstructive coronary artery disease (e.g., ≥70% coronary artery obstruction or a positive stress test). Stroke required documented focal neurological deficit lasting 24 h or until death, or if <24 h, there was a clinically relevant lesion on brain imaging. Patients with focal neurological deficits secondary to brain trauma, tumor, infection, or other nonvascular cause were excluded. Definite and probable HF required clinical symptoms (e.g., shortness of breath) or signs (e.g., edema), because asymptomatic disease was not an end point. Probable HF further required a physician diagnosis of HF and medical treatment for HF. Definite HF also required: 1) pulmonary edema/congestion by chest radiograph; and/or 2) dilated ventricle or poor LV function by echocardiography or ventriculography, or evidence of LV diastolic dysfunction.

Statistical methods. Unadjusted Cox proportional hazards models were first calculated for each end point (CHD events, stroke, HF) for LV mass and end-diastolic volume separately as continuous variables (per 10% increment) and then for LV mass and end-diastolic volume jointly in the same model to assess the role of LV geometry. Probable and definite HF and CHD events were considered in the analysis. All stroke events were definite. In additional models, the ratio of LV mass/volume was included both with and without adjustment for body size. In all instances, there were only minor differences in the fit between these models, and for simplicity we only show the results for the ratio of unadjusted LV mass/volume. Then age, sex, ethnicity, diabetes (diabetic, impaired fasting glucose, normal), cigarette smoking (present, former, never), total cholesterol, high-density lipoprotein cholesterol, use of antihypertensive or lipid-lowering medication, and systolic and diastolic blood pressure were added to the models.

These analyses were repeated for incident CHD and stroke using quartiles of LV mass/volume. For incident HF, in which body size-adjusted LV mass was the best predictor of risk, instead of quartiles, the intervals were constructed to display the nonlinearity in risk that was evident from nonlinear modeling (results not shown) of the risk in the Cox models. Kaplan-Meier cumulative event rate plots were calculated for the above discrete intervals of the LV measures. Rates in 100 person-years are shown for descriptive purposes for the quartiles of each LV measure.

All analyses were performed using Stata 10.0 for Windows (Stata Corp., College Station, Texas). Values of p < 0.05 are considered statistically significant and presented for descriptive purposes. Confidence intervals (CIs) are expressed as 95% CIs.

Results

Subject characteristics. Of the 6,814 MESA study participants, 5,098 underwent cardiac MRI (75%) and 5,004 (73%) had technically adequate data. Thirty-six participants had no follow-up information, leaving 4,968 participants in the analysis. Compared with those not included in the analysis (n = 1,846), those included were slightly younger (2.3 years younger), had lower systolic blood pressure (4.3 mm Hg lower) and body mass index (2.2 U lower), were less likely to be African American (7.7% less), were more likely to be Asian (4.8% more), and were less likely to have treated hypertension (7.0% less) or diabetes (3.0% less). The mean age of the participants was 62 years (range 45 to 85 years); 52% of participants were female, 13% were Chinese-American, 26% were African American, 22% were Hispanic, and 39% were white.

Cardiovascular events. There were 216 total events through 5.2 years of follow-up (median 4 years). Angina was most frequent (71 events), followed by HF (48 events), myocardial infarction (45 events), stroke (39 events), and CHD death (13 events). Baseline characteristics of participants with and without cardiovascular events are shown in Table 1. Of CHD events, 100 were definite and 15 were probable. Of HF events, 33 were definite and 15 were probable. The participants who had cardiovascular events versus no events were more likely to be older at baseline (by 8 years), men (59% vs. 47%), diabetic (24% vs. 12%), and current smokers (except for stroke events), and to use lipid lowering medication (28% vs. 15%) and hypertension medication (57% vs. 35%), respectively. Participants in whom HF events developed versus no events were additionally more likely to be African American (35% vs. 26%), whereas stroke events versus no events were more likely in Hispanics (31% vs. 22%) and those with systolic hypertension (29% vs. 21%), respectively.
Relationship of LV mass and geometry to incident CHD. The results of the unadjusted and adjusted Cox proportional hazard models are shown in Table 2 for incident CHD events. After adjustment for risk factors, body size-adjusted LV mass, and end-diastolic volume considered separately were not significant predictors of CHD events. In combination, a greater LV mass/volume ratio was positively associated with incident CHD (hazard ratio (HR) for incident CHD: 2.1 per g/ml, p = 0.02). The LV mass/volume ratio model had a similar fit to the model that included both body size-adjusted LV mass and end-diastolic volume (not shown). A similar conclusion was
reached for a model based on quartiles of LV mass/volume (HR: 2.3 per g/ml for the upper quartile compared with the first quartile, p = 0.01) (Fig. 1).

Relationship of LV mass and geometry size to incident stroke. After adjustment for risk factors and in separate models, body size-adjusted LV mass but not LV end-diastolic volume was positively associated with incident stroke (LV mass, HR: 1.2 per 10% increment, p = 0.01) (Table 3). In the adjusted model, a greater LV mass/volume ratio was positively associated with stroke events (HR: 4.2 per g/ml, p = 0.005). The LV mass/volume ratio model had a similar fit to a model that included both body size-adjusted LV mass and end-diastolic volume (not shown). With increasing LV mass/volume ratio, the number of stroke events increased in the adjusted model (highest quartile vs. lowest quartile, HR: 11.1, p = 0.02) (Fig. 2).

Relationship of LV mass and geometry to incident HF. As shown in Table 4, in separate models both body size-adjusted LV mass and end-diastolic volume were positively associated with incident HF before and after adjustment for risk factors (after adjustment, LV mass, HR: 1.4 per 10% increment, p < 0.0001; LV volume, HR: 1.3 per 10% increment, p < 0.0001). However, unlike incident CHD or stoke, incident HF in the fully adjusted models was not significantly associated with LV mass/volume ratio (Table 4) (p = 0.11). Thus, body size-adjusted LV mass alone was the best measure of heart size to predict incident HF. Inclusion of LV ejection fraction in a model with LV mass showed little change in the adjusted HRs or model fit.

Because only 1 HF event occurred in the reference group (1st quartile of LV mass), the HR ratio estimates with this reference group were unstable. Most events occurred in participants with body size-adjusted LV mass ≥90% of predicted based on height and weight. To examine the gradient of relative risk, 4 categories of LV mass index were compared: below the median (50th) percentile of LV mass index (reference category), the 50th to 89th percentile, the 90th to 94th percentile, and 95th percentile of LV mass index (as previously taken to be the definition of LVH (3,4,10,24)). The HR for participants with LVH (95th

### Table 3: The Relationship of LV End-Diastolic Volume and Mass to Stroke Events

<table>
<thead>
<tr>
<th>Model</th>
<th>Cox Models for Incident Stroke</th>
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<tbody>
<tr>
<td></td>
<td>Unadjusted HR (95% CI) p Value</td>
<td>Adjusted* HR (95% CI) p Value</td>
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<tr>
<td>LV mass† (per 10%)</td>
<td>1.2 (1.1–1.4) &lt;0.0001</td>
<td>1.2 (1.0–1.4) 0.01</td>
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<tr>
<td>LV volume† (per 10%)</td>
<td>0.9 (0.7–1.1) 0.16</td>
<td>0.9 (0.8–1.1) 0.51</td>
<td></td>
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<tr>
<td>LV mass/LV volume (g/ml)</td>
<td>7.8 (3.6–17.3) &lt;0.0001</td>
<td>4.2 (1.5–11.2) 0.005</td>
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<tr>
<td>LV mass/LV volume in quartiles</td>
<td></td>
<td></td>
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<tr>
<td>1st quartile (0.51–1.0)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
<td></td>
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<tr>
<td>2nd quartile (1.0–1.13)</td>
<td>6.0 (0.7–50.2) 0.10</td>
<td>4.1 (0.5–50.2) 0.20</td>
<td></td>
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<tr>
<td>3rd quartile (1.13–1.29)</td>
<td>10.2 (1.3–80.1) 0.03</td>
<td>6.8 (0.9–54.0) 0.07</td>
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<tr>
<td>4th quartile (1.29–2.89)</td>
<td>23.0 (3.1–170.5) 0.003</td>
<td>11.1 (1.4–84.8) 0.02</td>
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*Adjusted for the following risk factors: age, sex, race, cigarette smoking, total cholesterol, high-density lipoprotein cholesterol, use of lipid-lowering medication, systolic blood pressure, diastolic blood pressure, use of antihypertensive drugs, and diabetes. †Adjusted for body size.

Abbreviations as in Table 2.
percentile) versus those below the median for LV mass was 8.6 (95% CI: 3.7 to 19.9, p < 0.0001) (Fig. 3).

**Discussion**

The pathophysiologic changes in the size and function of the heart in response to cardiovascular risk factors are complex, and increasingly accurate tools are now available to explore these relationships. The MESA study is the first epidemiologic study that has used cardiac MRI in a large cohort to evaluate incident cardiovascular events. There are several conclusions from this study: 1) In a diverse, multi-ethnic cohort, LVH confers a substantially elevated risk for incident HF, consistent with prior reports from predominantly white or African-American cohorts. 2) Elevated LV mass in most individuals was accommodated over the 4-year period of follow-up, with only the top 5% of the cohort showing increased risk for incident HF in adjusted models. 3) Concentric remodeling (defined by elevated LV mass/volume ratio), rather than elevated ventricular mass, was predictive of incident non-HF cardiovascular events, specifically stroke and CHD.

Data from the Framingham study has previously linked LVH detected by ECG to CHD (myocardial infarction, angina, sudden death) (1). Electrocardiogram-defined LVH had a 3-fold risk of developing clinically apparent CHD (including HF) compared with the group without LVH. In other observational studies, the relative risk of ECG-defined LVH for incident HF only was 1.4 to 2.9 (3,5,6). An ECG is a relatively low-cost method of detecting LVH (3,4,40,41), but the sensitivity of ECG for LVH is only 6% to 20% (3,41). Using echocardiography, the reported relative risk of LVH for incident HF in previous observational studies was 1.6 to 3.4 (3,4,7).

For LV mass ≥95th percentile compared with the reference group of <50th percentile, the adjusted HR for HF in the MESA study population was 8.6 (95% CI: 3.7 to 19.9) using MRI to measure heart size. The greater risk conferred by LVH in this study compared with other cohorts is notable. This greater risk may be explained by demographic differences between the cohorts, different approaches to statistical assessment, and/or different methods of heart size assessment (MRI vs. echocardiography or ECG). The high accuracy and reproducibility of cardiac MRI (standard errors of about 5% [32,42,43] compared with 20% for echocardiography [44] in single-center studies) should facilitate risk estimates for short-term studies that by nature will entail fewer events. It is notable that LV mass <95th percentile did not predict incident HF events over the 4-year period of follow-up in a cohort that was asymptomatic at baseline.

The relative role of LVH versus concentric remodeling associated with cardiovascular events has been unclear. Koren et al. (22) originally reported a cardiovascular event rate of 4.2 per 100 patient-years when concentric remodeling was present, versus 1.8 per 100 patient years when there was normal LV geometry. Similar results were identified in other studies (21,24,26,27), but no additional predictive value for concentric hypertrophy beyond LV mass was

<table>
<thead>
<tr>
<th>Model</th>
<th>Unadjusted</th>
<th>Adjusted*</th>
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<td></td>
<td>HR (95% CI)</td>
<td>p Value</td>
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<td>LV mass† (per 10%)</td>
<td>1.4 (1.3–1.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV volume† (per 10%)</td>
<td>1.3 (1.2–1.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV mass/LV volume (g/ml)</td>
<td>7.4 (3.6–15.4)</td>
<td>&lt;0.0001</td>
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<tr>
<td>LV mass† in intervals</td>
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<tr>
<td>&lt;50th percentile</td>
<td>1.0 (reference)</td>
<td></td>
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<tr>
<td>50th to 90th percentile</td>
<td>1.7 (0.8–3.7)</td>
<td>0.21</td>
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<tr>
<td>90th to 95th percentile</td>
<td>2.7 (0.6–12.3)</td>
<td>0.20</td>
</tr>
<tr>
<td>≥95th percentile</td>
<td>13.0 (6.1–27.7)</td>
<td>&lt;0.0001</td>
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</table>

*Adjusted for the following risk factors: age, sex, race, cigarette smoking, total cholesterol, high-density lipoprotein cholesterol, use of lipid-lowering medication, systolic blood pressure, diastolic blood pressure, use of antihypertensive drugs, and diabetes. †Adjusted for body size.

Abbreviations as in Table 2.

**Figure 3** Cumulative Event Rates for HF Events by Intervals of Left Ventricular Mass (Body Size-Adjusted)

HF = heart failure.
found in the Framingham study (23) or in hypertensive subjects studied by Verdecchia et al. (28). In general, prior studies have combined types of cardiovascular events to examine the relationship to LV mass or geometry. The results of this study show that stroke and CHD events were better predicted by elevated LV geometry, whereas HF events were driven primarily by LV mass alone. Although our results do not indicate causality, potential mechanisms relating LV remodeling to abnormal arterial structure and function (45) and to stroke and CHD (46) have been previously described.

Reliable evaluation of the relationship of ethnicity in relationship to LV mass and cardiovascular events will require additional follow-up and/or larger sample sizes. The general applicability of our results may be limited by selection and survivor biases. Because MESA study participants had no known cardiovascular disease at baseline, the older individuals undergoing MRI in this cohort represent a particularly healthy sample of the population at large. The mechanisms by which cardiovascular events result from changes in heart size are not elucidated by these observational data. At the time of data collection, only the fast-gradient echocardiographic MRI pulse sequence was available at all of the field centers; the steady-state free-precession sequence has since been developed for cardiac MRI, and this sequence shows better reproducibility for cardiac mass and volume measurement. As indicated in the Methods section, we did not include the papillary muscle mass as part of the LV mass. The papillary muscle mass is directly related to LV mass over a wide range of values. The LV mass methods that include papillary muscles would thus be somewhat larger and mass/volume ratios smaller than we have reported. The diagnosis of HF is not as definitive as other cardiovascular events such as stroke or myocardial infarction. Therefore, we required that participants be symptomatic with physician-diagnosed HF documented in medical records that were adjudicated by physician reviewers.

**Conclusions**

In an ethnically diverse population free of symptomatic cardiovascular disease at baseline, the end-diastolic volume and mass of the LV determined by MRI were strongly associated with cardiovascular events. The association between stroke and CHD may be mediated through concentric ventricular remodeling, whereas incident HF was most closely associated with very high levels of LV mass.

**Acknowledgement**

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