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## Relation of the Myocardial Contraction Fraction, as Calculated from M-Mode Echocardiography, with Incident Heart Failure, Atherosclerotic Cardiovascular Disease and Mortality (Results from the Cardiovascular Health Study)

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### Abstract

We evaluated the association between two-dimensional (2D) echocardiography (echo) determined myocardial contraction fraction (MCF) and adverse cardiovascular outcomes including incident heart failure (HF), atherosclerotic cardiovascular disease (ASCVD) and mortality. The MCF, the ratio of left ventricular (LV) stroke volume (SV) to myocardial volume (MV), is a volumetric measure of myocardial shortening that can distinguish pathologic from physiologic hypertrophy. Using 2D-echo-guided M-mode data from the Cardiovascular Health Study, we calculated MCF among individuals with LV ejection fraction (EF)  $\geq 55\%$ , and used Cox models to evaluate its association with incident HF, ASCVD, and all-cause mortality after adjusting for clinical and echo parameters. We assessed whether  $\log_2(SV)$  and  $\log_2(MV)$  were consistent with the expected 1:–1

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ratio used in the definition of MCF. Among 2147 participants (age  $72\pm 5$ ), average MCF was  $59\pm 13\%$ . After controlling for clinical and echo variables, each 10% absolute increment in MCF was associated with lower risk of HF (HR=0.88; 95% CI=0.82, 0.94), ASCVD (HR=0.90; 95% CI=0.85, 0.95) and death (HR=0.93; 95% CI=0.89, 0.97). Moreover, the MCF was still significantly associated with ASCVD and mortality, but not HF, after adjustment for percent predicted LV mass. Significant departure from the 1:–1 ratio was not observed for ASCVD or death, but did occur for HF, driven by a stronger association for MV than SV. In conclusion, among older adults without CVD or low LVEF, 2D-echo-guided M-mode-derived MCF was independently associated with lower risk of adverse cardiovascular outcomes, but this ratiometric index may not capture the full relationship that is apparent when its components are modeled separately in the case of HF.

## Keywords

myocardial contraction fraction; ejection fraction; aging; heart failure; cardiovascular disease

Left ventricular ejection fraction (LVEF) is the most commonly used measure of LV systolic function, but this measure has well-recognized disadvantages, including dependency on loading conditions<sup>1</sup> and heart rate<sup>2</sup>. LVEF is also normal or preserved in many patients with heart failure regardless of the presence of LV hypertrophy.<sup>3</sup> We previously defined a novel volumetric index, the myocardial contraction fraction (MCF), as the ratio of LV stroke volume (SV) to myocardial volume (MV), and demonstrated that measurement of the MCF by three-dimensional (3D) echocardiography (echo) could successfully distinguish patients with heart failure (HF) with preserved EF (HFpEF) from healthy athletes with LV hypertrophy and normal controls.<sup>4</sup> More recently, MCF was determined by magnetic resonance imaging (MRI) in the Framingham study, where it was linked to higher incidence of a composite of atherosclerotic cardiovascular disease (ASCVD) and HF events.<sup>5</sup> We leveraged a community-based older cohort, the Cardiovascular Health Study (CHS), who underwent standardized 2D echo, to further evaluate the association of MCF determined using this modality individually with HF, ASCVD, and death. We hypothesized that among older people with normal LVEF and no prevalent CVD, lower MCF would be independently associated with higher risk for these outcomes. We also tested the premise that this ratiometric measure adequately captures the predictive information contained by its individual components, SV and MV, modeled separately, a requirement for ratiometric measures that in the case of MCF has not to date been formally examined.

## Methods

The overall design, objectives, and recruitment strategy of CHS have been reported in detail.<sup>6</sup> Community-dwelling individuals 65 years of age or older were recruited from 4 geographically dispersed U.S. field centers. People were excluded from CHS if they were receiving active treatment for cancer, were wheelchair bound or institutionalized, or were unable to participate in the examination. The original cohort (recruited in 1989 to 1990; n=5,201) and a supplemental cohort of African Americans (recruited in 1992 to 1993; n=687) formed a total of 5,888 study participants. The present analyses focused on

echocardiograms obtained at the baseline visit for the original cohort (1989–90) and at 2 years after the baseline visit (1994–95) for the supplemental cohort. Among the 5,888 total CHS participants, the current study excluded 754 with reduced LVEF (<55%); 1,251 with normal LVEF having prevalent CVD; 1,237 with missing echo measures necessary to calculate MCF; and 504 with one or more missing covariates included in multivariable models. This left 2,147 participants eligible for analysis.

Echocardiographic methods in CHS have been published previously.<sup>7</sup> In brief, standardized M-mode, 2-D, color Doppler, and spectral Doppler examinations with pre-specified sequence, technique and priorities were performed at each field site with a Toshiba SSH-160A ultrasound machine (Tustin, California) fitted with standard 2.5-MHz transducers. Studies were recorded onto super-VHS videotapes and batch-mailed to the echo reading center at the University of California Irvine, where images from each study were selected and digitized. Measurements were obtained using a digital image analysis system (Nova Microsonics). Two-dimensionally guided M-mode measurements of systolic and diastolic LV dimensions and wall thicknesses were obtained, and LV mass determined using a validated formula.<sup>8</sup> LV mass was indexed to sex, height, and weight using a regression equation developed in a subset of healthy CHS participants, and the indexed value multiplied by 100 to yield percent predicted LV mass, as detailed previously.<sup>9</sup> Determinations of LVEF, LV fractional shortening (FS), left atrial anteroposterior diameter and relative wall thickness (RWT) have been previously described, as have Doppler assessments of aortic and mitral valvular regurgitation and stenosis, and transmitral diastolic filling indices.<sup>7,10, 11</sup>

Using echocardiographic data (1989–90 for the original cohort, 1994–95 for the supplemental cohort), MCF was calculated as the ratio of LV stroke volume to myocardial volume. LV end-diastolic and -systolic volumes (EDV and ESV, respectively) were calculated from 2D-guided M-mode echo dimensions by a previously validated technique<sup>12, 13</sup>:

$$EDV=4.5*(LV \text{ diastolic dimension})^2$$

$$ESV=3.72*(LV \text{ systolic dimension})^2$$

Because this technique has been shown to be reliable only in symmetrically contracting ventricles with normal LVEF, participants with reduced LVEF were excluded from this analysis. From EDV and ESV, LV SV was calculated as EDV – ESV. Myocardial volume was estimated from the measurement of LV myocardial mass, as determined by the ASE formula<sup>8</sup>, divided by the density of myocardial tissue (1.04 g/ml). As previously reported<sup>14</sup>, the inter-reader mean percent measure differences for LV mass, septal thickness and posterior wall thickness were 17%, whereas for LV internal diastolic dimension, the value was no higher than 6%.

Information on clinical covariates was obtained at each CHS examination through standardized questionnaires, anthropometric assessment, physical examination, blood

collection, and electrocardiography, as reported previously.<sup>6</sup> Laboratory methods and procedures have been detailed elsewhere.<sup>15,16</sup> Diabetes was defined as fasting blood glucose  $\geq 126$  mg/dl, non-fasting blood glucose  $\geq 200$  mg/dl or use of anti-diabetes medication. Cystatin C was used to derive estimated glomerular filtration rate (eGFR).<sup>17</sup> FEV1 was measured during pulmonary function testing.<sup>18</sup> For the supplemental cohort, FEV1 was obtained in the year prior to echo and LDL cholesterol (LDL<sub>c</sub>), and HDL cholesterol (HDL<sub>c</sub>) and cystatin C from two years prior to echo. Missing values for income were imputed.

The primary outcomes were HF, ASCVD and all-cause mortality. Prevalent CVD was an exclusion criterion, comprising coronary heart disease (CHD), stroke, transient ischemic attack, peripheral arterial disease, HF, and atrial fibrillation; methods for ascertainment have been reported.<sup>19</sup> Surveillance for incident CVD events, hospitalizations and mortality entailed semi-annual participant contacts through in-person visits or telephone calls. Incident CVD events, including HF and ASCVD, and deaths were investigated by review of medical records and adjudicated by CHS events committees.<sup>20,21</sup> ASCVD was defined as nonfatal myocardial infarction, nonfatal stroke, and death due to CHD, stroke, or other atherosclerotic disease during follow up. HF was based on diagnosis by a physician and treatment for HF plus a constellation of symptoms, signs, and radiographic findings. Ascertainment of events was through June 30, 2013.

We detailed the levels of baseline covariates across quartiles of MCF using standard descriptive statistics and assessed for linear trends using linear regression or a chi-square test, as appropriate. Cox regression was used to analyze the association of MCF (for every 10% unit increment) with incident HF, ASCVD and mortality, accounting for clinical and echo covariates in a sequential manner. We first adjusted for age, sex, and race (Model 1); then additionally for income, body mass index, systolic blood pressure, anti-hypertensive medications, diabetes, LDL<sub>c</sub>, HDL<sub>c</sub>, smoking, alcohol intake, eGFR, self-reported health status, FEV1, and lipid-lowering therapy (Model 2); next also for echo covariates including LA diameter and transmitral E/A ratio<sup>10</sup> (Model 3); and subsequently also for percent predicted LV mass (Model 4). An exploratory analysis of Model 3 with RWT was performed. Finally, since NT-proBNP is not obtained as part of routine care in community-dwelling individuals but is an important CVD predictor, we evaluated in an exploratory model whether the associations of MCF with primary outcomes persisted after further adjustment for the logarithm of NT-proBNP (Model 5). We further assessed the functional form of the associations of MCF with our outcomes of interest in Model 3 using penalized smoothing splines. These were consistent with a linear trend even after allowing for up to a fourth order polynomial. The proportional hazards assumption was assessed using Schoenfeld's residuals, which revealed no meaningful violations.

We also investigated the associations of MCF components, SV and MV, with outcomes, and evaluated the premise that MCF adequately captures the predictive information of these components modeled separately. To this end, we logarithmically transformed (base 2) SV and MV to assess their associations with outcomes of interest in Models 1–3 using a multiplicative model<sup>22</sup> to allow for potential heteroskedasticity of each individual component. We then evaluated whether the regression coefficients of  $\log_2$ SV and  $\log_2$ MV

are consistent with the hypothesized 1:–1 by constructing a 95% CI on the linear sum of the regression coefficients of  $\log_2SV$  and  $\log_2MV$ . Significant departure from a linear sum of 0 would indicate departure of the expected ratio used in the computation of MCF. All statistical analyses were performed with STATA 11 and R 3.1.1 and two-sided  $p < 0.05$  was considered statistically significant.

## Results

As compared with the 1737 participants missing clinical and echo measures, the 2147 participants having such information were younger and tended to have fewer cardiovascular risk factors. The average MCF in the study sample was  $59 \pm 13\%$  (range: 13–107%). The demographic, clinical, and echo characteristics of the study cohort, both overall and stratified by quartiles of MCF, are shown in Table 1. Participants were similar in age across quartiles of MCF. A higher proportion of male participants and African Americans were in the lower quartiles of MCF relative to the higher quartiles of MCF. At the lower quartiles of MCF, average eGFR measurements were lower and average systolic blood pressure was higher relative to other quartiles of MCF. There was a higher prevalence of diabetes, higher alcohol consumption, higher HDLc and higher use of antihypertensive medication across decreasing MCF quartiles. Lower MCF quartiles were associated with lower SV and higher MV, percent predicted LV mass, and RWT. Lower quartiles of MCF were also associated with lower FS, higher left atrial diameter and NT-proBNP, and higher proportions of transmitral E/A  $< 0.7$ .

Over a median follow-up of 14.6 years, there were 638 incident cases of HF, 832 incident cases of ASCVD, and 1658 deaths in the study population. Table 2 presents the risk estimates associated with higher MCF for each of these outcomes for each model. Higher MCF was associated with significantly lower risk of HF, ASCVD and all-cause mortality after adjustment for demographic factors (Model 1). These associations were attenuated after further adjustment for clinical (Model 2), as well as echo covariates (Model 3), but remained statistically significant ( $p < 0.001$  for each outcome), such that every 10% absolute increase in MCF imparted 12% (95% CI: 18%, 6%), 10% (95% CI: 15%, 5%) and 7% (95% CI: 11%, 3%) lower risks of HF, ASCVD, and death, respectively. In exploratory analyses, MCF remained significantly associated with all three outcomes after adjustment for RWT, and with ASCVD and death, but not HF, after further adjustment for percent predicted LV mass (Model 4). MCF was significantly associated with all outcomes upon adjustment for NT-proBNP in addition to Model 3 covariates (Model 5).

Both MV and SV were associated with the outcomes of interest after mutual adjustment. Specifically, in our final model (Model 3),  $\log_2(SV)$  was inversely associated with HF (HR=0.73; 95% CI=0.54, 0.98;  $p=0.036$ ), ASCVD (HR=0.69; 95% CI=0.54, 0.89;  $p=0.005$ ) and mortality (HR=0.75; 95% CI: 0.63 - 0.90;  $p=0.002$ ). In contrast,  $\log_2(MV)$  in Model 3 was directly associated with HF (HR=2.07; 95% CI=1.56, 2.74;  $p < 0.001$ ), ASCVD (HR=1.67; 95% CI=1.31, 2.14;  $p < 0.001$ ) and mortality (HR=1.43; 95% CI=1.20, 1.70;  $p < 0.001$ ) (see Figure 1). We next assessed whether the coefficients of  $\log_2SV$  and  $\log_2MV$  departed from the 1:–1 ratio inherent in the computation of MCF. In the case of HF, the sum of the coefficients was significantly different from 0 (0.41 [95% CI: 0.14, 0.68];  $p=0.003$ ),

indicating deviation from the 1:–1 ratio. For ASCVD and death, the sums of the observed estimates of 0.15 (95% CI: –0.09, 0.39) and 0.07 (95% CI: –0.10, 0.24), respectively, are consistent with the hypothesis that the coefficients for the individual components of MCF occur in the expected 1:–1 ratio.

## Discussion

The present study shows that among participants without prevalent CVD or reduced LVEF from a population-based cohort of older adults, higher MCF was significantly associated with lower risk of HF, ASCVD and death after adjustment for clinical risk factors and echo measures, which persisted even after additional adjustment for NT-proBNP. Moreover, in additional exploratory analyses, the MCF was still significantly associated with ASCVD and mortality but not HF after adjustment for percent predicted LV mass. Corresponding regression coefficients did not deviate from the expected 1:–1 ratio inherent in MCF for ASCVD or all-cause mortality, but there was evidence of such a departure for the HF outcome.

Measures of LV chamber performance are based on the premise that the myocardium is nearly incompressible and does not change volume significantly from end-diastole to end-systole. Evidence for the incompressibility of the myocardium comes from tomographic imaging,<sup>23,24</sup> and eliminates the need to account for myocardial deformations in measuring ventricular performance, making governing equations much less complicated.<sup>25,26</sup> Capitalizing on this fundamental principle by indexing SV to MV, the MCF is an index of the volumetric shortening of the myocardium that is independent of chamber size and geometry. As a measure of myocardial shortening, SV is most appropriately assessed relative to the myocardium, and specifically to MV, because it is the myocardium that shortens. Thus, MCF is a measure of the amount by which the myocardium contracts during systole relative to total MV, although the myocardium itself has not undergone a reduction in volume. MCF, though operationalized prior to the widespread use of strain in echo,<sup>4</sup> is highly correlated with global longitudinal strain.

To our knowledge, MCF has only been evaluated in relation to outcomes by a single prospective, population-based study. Using cardiac MRI to quantify MCF in a subset of participants (n=318) with normal EF, the Framingham study<sup>5</sup> demonstrated that the lowest quartile of MCF was associated with a ~7-fold increased relative risk of a composite CVD endpoint as compared with the remaining quartiles, whereas EF was not. The number of incident composite CVD events was modest (n=31), but the association persisted after adjustment for Framingham risk score and even LV mass. Our findings extend these observations to a large subset of participants from a population-based study of older adults having normal EF and no clinically overt CVD at baseline. The present analyses demonstrate that MCF estimated from 2D-guided M-mode echo measures routinely obtained in clinical practice is associated with HF, ASCVD and death independent of clinical risk factors and other echo variables in this population. Notably, the associations of MCF with ASCVD and death persisted after additional adjustment for percent predicted LV mass, as it did for composite CVD events in Framingham, but not with HF individually. Moreover, the larger number of incident events in the current study allowed us to test whether combining



the individual components of the MCF into a ratio compromises the predictive information obtained when these components are modeled separately. Such potential loss of predictive information is a well-described pitfall of ratiometric measures, which carry widespread appeal in clinical practice.<sup>27</sup>

Our analyses suggest that in the case of incident HF, though not for ASCVD and mortality, MCF performed less well than its individual components modeled separately. Specifically, MV was more strongly associated with HF than SV, with regression coefficients of SV to MV approximating a 1:–2 ratio on the logarithmic scale. This dominant relationship for MV relative to SV for HF, but not ASCVD or death, is consistent with the greater importance of adverse LV remodeling as a determinant of HF risk as compared with these other major outcomes. The observed relationship of  $\log_2$ SV and  $\log_2$ MV with HF, however, would translate to a ratiometric variable of  $SV/MV^2$  on the original scale, having units of  $ml^{-1}$ , which would lose the appeal of the unitless MCF index. Hence, our findings support an approach that considers SV and MV individually, rather than as a ratiometric variable, in relation to incident HF. Future studies will need to examine how MCF, SV and MV individually, and  $SV/MV^2$  compare to LV mass index in formal analyses of risk prediction of HF and other major cardiovascular outcomes.

Several limitations to our work should be noted. The MCF could not be calculated in 21% of the entire CHS cohort, but was available in the healthier subset of participants with available echo measurements. Moreover, we focused the current analysis on participants having no baseline CVD, and particularly normal EF, given that the techniques employed to estimate ventricular volumes are accurate only in symmetrically contracting ventricles. Hence, these findings are not generalizable to elders with poorer health status, prevalent CVD or low EF. Our estimates of LV chamber and myocardial volumes, contrary to the original description of MCF which used 3D echo,<sup>4</sup> were derived from linear dimensions obtained by 2D-guided M-mode, which may have introduced random misclassification from oblique LV orientations. Moreover, the corresponding derivations of chamber volumes are influenced by chamber dilation and sphericity, producing overestimation of LV and particularly myocardial volumes.<sup>28</sup> The resulting bias, however, would be to underestimate the true association of higher MV's with outcomes, suggesting that more accurate imaging modalities would yield stronger relationships for MCF, but perhaps also compound the loss of information associated with this ratiometric index by further strengthening the association for MV relative to SV with outcomes. Further study of this question by various imaging approaches, in different populations, and with statistical techniques for evaluating prediction will provide insights into the usefulness of MCF and its components for improving prediction of the outcomes of interest.

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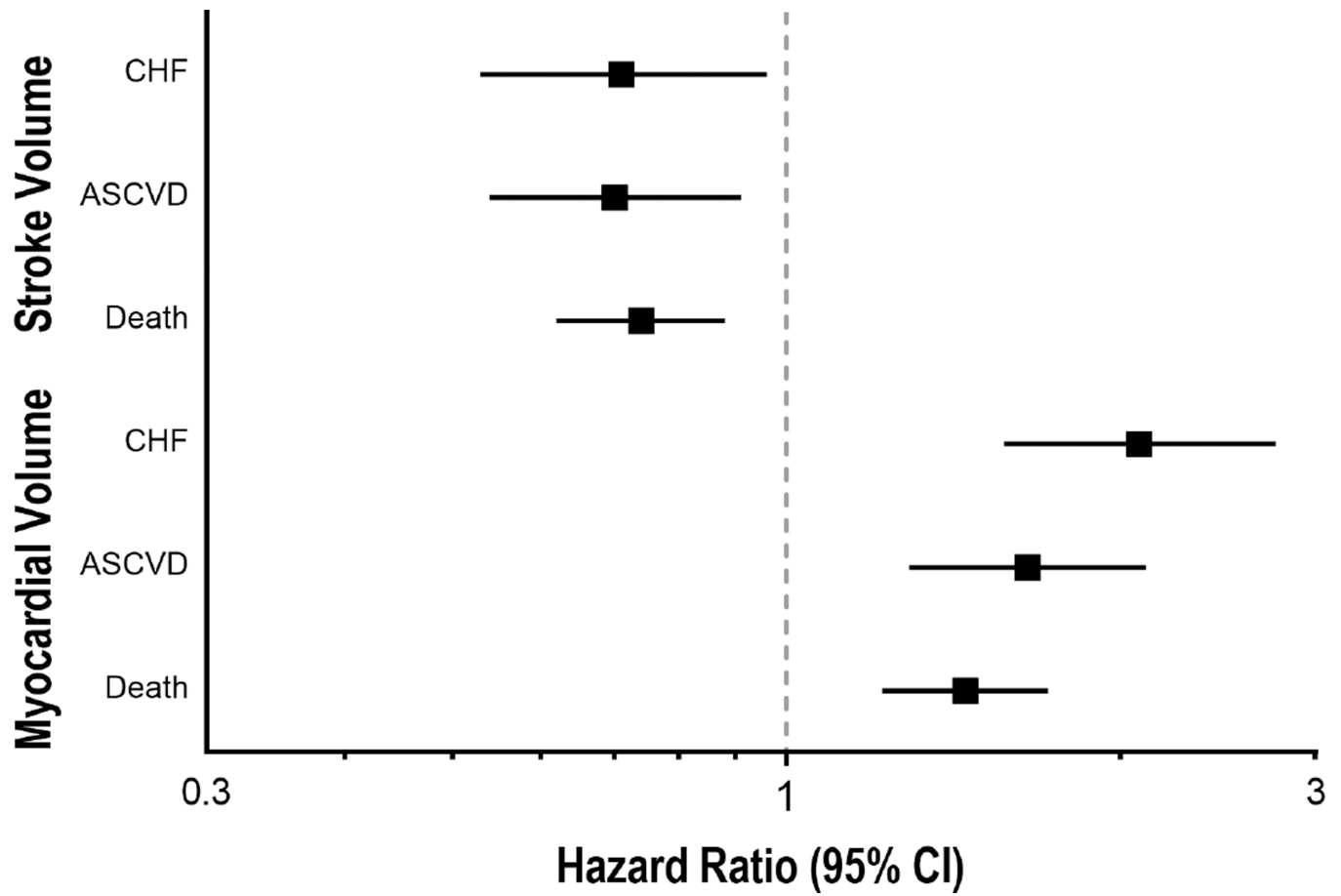
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**Figure 1.** Hazard ratios and 95% CI's for associations of components of MCF, specifically  $\log_2$  (stroke volume) and  $\log_2$ (Myocardial Volume), with HF, ASCVD and death in a model controlling for demographic, clinical and echocardiographic variables (Model 3 in Table 2).

**Table 1**  
Demographic, Clinical and Echocardiographic Parameters by Quartile of Myocardial Contraction Fraction

	All (N=2147)	Quartile 1 (13.3 – 50.1%) (n=536)	Quartile 2 (50.1 – 57.8%) (n=537)	Quartile 3 (57.8 – 66.8%) (n=537)	Quartile 4 (66.8 – 106.8%) (n=537)	P value
Age (years)	72.2±4.8	73.1±5.0	72.2±4.8	71.9±4.7	71.5±4.5±	<0.001
Men	663 (31%)	253 (47%)	177 (33%)	128 (24%)	105 (20%)	<0.001
Black	286 (13%)	99 (18%)	68 (13%)	67 (12%)	52 (10%)	<0.001
BMI (kg/m <sup>2</sup> )	26.3 ±4.3	27.3±4.5	26.5±4.2	26.2±4.3	25.1±4.1	<0.001
Systolic BP (mm Hg)	135±21	140±23	134±21	133±19	131±21	<0.001
Prevalent Diabetes	230 (11%)	86 (16%)	60 (11%)	46 (9%)	38 (7%)	<0.001
Alcohol use (drinks/week)	2.5 (6.2%)	3.1 (7.1%)	2.5 (6.4%)	2.2 (5.3%)	2.4 (5.8%)	0.03
Smoker						0.11
Never	1051 (49.0%)	235 (43.8%)	272 (50.7%)	273 (50.8%)	271 (50.5%)	
Former	839 (39.1%)	227 (42.4%)	209 (38.9%)	194 (36.1%)	209 (38.9%)	
Current	257 (12.0%)	74 (13.8%)	56 (10.4%)	70 (13.0%)	57 (10.6%)	
Good/Excellent Health	1829 (85.2%)	446 (83.2%)	463 (86.2%)	456 (84.9%)	464 (86.4%)	0.43
Income > \$25,000	972 (45%)	237 (44%)	245 (46%)	242 (45%)	248 (46%)	0.93
Anti-hypertensive	785 (37%)	246 (46%)	197 (37%)	190 (35%)	152 (28%)	<0.001
Any lipid medication	101 (5%)	24 (4%)	19 (4%)	25 (5%)	33 (6%)	0.24
LDL <sub>c</sub> (mg/dl)	131±35	131±33	134±37	130±36	130±34	0.22
HDL <sub>c</sub> (mg/dl)	57±16	54±15	56±16	59±15	61±16	<0.001
eGFR (ml/min/1.73 m <sup>2</sup> )	82±19	77±19	83±18	83±17	84±19	<0.001
FEV1 (liters)	2.1±0.6	2.1±0.7	2.1±0.6	2.0±0.6	2.1±0.6	0.07
Transmitral E/A ratio						<0.001
<0.7	301 (14%)	107 (20%)	82 (15.3%)	65 (12.1%)	47 (8.8%)	

	All (N=2147)	Quartile 1 (13.3 – 50.1%) (n=536)	Quartile 2 (50.1 – 57.8%) (n=537)	Quartile 3 (57.8 – 66.8%) (n=537)	Quartile 4 (66.8 – 106.8%) (n=537)	P value
0.7 – 1.5	1772 (82.5%)	413 (77.1%)	440 (81.9%)	458 (85.3%)	461 (85.8%)	
>1.5	74 (3.5%)	16 (2.9%)	15 (2.8%)	14 (2.6%)	29 (5.4%)	
Fractional Shortening, % †	43.0±7.5	39.3±8.0	42.5±7.1	43.9±6.6	46.1±6.7	<0.001
LA diameter (cm)	3.8±0.6	3.9±0.6	3.8±0.6	3.8±0.6	3.7±0.6	<0.001
Percent predicted LV mass,	109±30	128±30	112±20	104±20	92±20	<0.001
Stroke volume (ml)	77.0±19.0	70.9±19.1	76.4±18.8	78.8±17.3	82.2±18.9	<0.001
Myocardial volume (ml)	136.0±42.0	168.8±50.6	141.4±34.7	127.1±28.0	108.7±26.0	<0.001
Valvular disease	188 (8.8%)	47 (8.8%)	55 (10.2%)	46 (8.6%)	40 (7.4%)	0.45
Relative wall thickness	0.35 (0.08)	0.42 (0.09)	0.36 (0.05)	0.33 (0.05)	0.29 (0.05)	<0.001
NT-proBNP (pg/ml) ‡	93.2 (49.3 – 176)	107.4 (50.6 – 199.7)	85.8 (40.8 – 175.1)	88.19 (52.1 – 146.9)	95.2 (53.8 – 168.8)	0.004

\* Data were available in 2,143 subjects.

‡ Data was available in 1,683 subjects and data is median (IQR).

**Table 2**

Association between Myocardial Contraction Fraction and incident Heart Failure, Atherosclerotic Coronary Vascular Disease and Death

Outcome (Cumulative incidence)	HF (n=638)	ASCVD (n=823)	Death (n=1658)
	HR* (95% CI)	HR* (95% CI)	HR* (95% CI)
<b>Models</b>			
Unadjusted	0.79 (0.74, 0.84)	0.83 (0.78, 0.87)	0.86 (0.82, 0.89)
Model 1	0.82 (0.76, 0.87)	0.86 (0.81, 0.91)	0.91 (0.87, 0.94)
Model 2	0.87 (0.82, 0.93)	0.89 (0.84, 0.95)	0.92 (0.89, 0.96)
Model 3	0.88 (0.82, 0.94)	0.90 (0.85, 0.95)	0.93 (0.89, 0.97)
Model 4	0.93 (0.86, 1.01)	0.92 (0.86, 0.99)	0.94 (0.90, 0.99)
Model 5	0.88 (0.82, 0.95)	0.90 (0.84, 0.96)	0.92 (0.88, 0.97)

\* per 10% absolute increase in MCF

Model 1: adjusted for age, sex, and race

Model 2: adjusted for Model 1 + income, BMI, SBP, diabetes, LDLc, HDLc, eGFR, smoking, alcohol use, anti-hypertensive medications, self-reported health status, FEV1, and lipid-lowering therapy

Model 3: adjusted for Model 2+ valve disease, transmitral E/A ratio, left atrial dimension

Model 4 (exploratory): adjusted for Model 3+ percent predicted left ventricular mass index

Model 5 (exploratory): adjusted for Model 3+ log NT-proBNP