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Left Ventricular Dysfunction as a Risk Factor for Cardiovascular and Non-Cardiovascular Hospitalizations in African-Americans

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Abstract

Background—A substantial portion of the public health burden of heart failure is due to hospitalizations, many of which are for causes other than cardiovascular disease. We assessed whether left ventricular (LV) systolic dysfunction was associated with increased risk of both cardiovascular and non-cardiovascular hospitalizations in a community sample of African-Americans.

Methods—African-American participants from the Jackson, MS site of the Atherosclerosis Risk in Communities (ARIC) study who underwent echocardiography were followed for twelve years. Hospitalization rates among individuals with and without LV systolic dysfunction were compared using negative binomial regression.

Results—Among 2416 participants with echocardiograms, LV systolic dysfunction was found in 61 (2.5%). Participants with LV dysfunction experienced 366 hospitalizations, a rate of 1.27 per person-year, compared to 0.25 per person-year among individuals without LV dysfunction. The incidence rate ratio adjusted for demographics, comorbidities, and other risk factors was 3.11 (95% CI 2.22–4.35). The adjusted rate ratios were 4.76 (95% CI 2.90–7.20) for cardiovascular and 2.67 (95% CI 1.82–3.90) for non-cardiovascular diagnoses, with similar findings in the subset of individuals with asymptomatic LV dysfunction. The percent attributable risks for hospitalizations were 87% and 74% for cardiovascular and non-cardiovascular causes (79% and 63% after adjustment).

Conclusions—African-American individuals with LV dysfunction are at an increased risk of hospitalization due to a wide range of causes with non-cardiovascular hospitalizations accounting for nearly half the increased risk. To the extent that estimates of risk focus on cardiovascular morbidity, they may underestimate the true health burden of LV dysfunction.

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BACKGROUND

A substantial portion of the public health and financial burden of heart failure (HF) is due to hospitalizations. ^{1, 2} Annually, HF is listed as the primary diagnosis for 1.1 million hospitalizations per year. ³ This figure represents only a fraction of admissions of HF patients, who are frequently hospitalized for causes other than HF and cardiovascular disease, including pneumonia, chronic obstructive pulmonary disease (COPD), and renal failure. ^{4–7} The frequency of non-cardiac admissions implies that HF, and specifically left ventricular (LV) dysfunction, may contribute to the morbidity of non-cardiovascular disease. Prior studies of hospitalization risk related to LV dysfunction have been limited by non-representative samples, ^{8–13} lack of data on asymptomatic LV systolic dysfunction, ^{8–11, 14} and a narrow focus on cardiovascular-specific hospitalizations. ^{13–17} To test our hypothesis that LV dysfunction predicts an increased risk of both cardiovascular and non-cardiovascular hospitalizations, we examined this relationship in a population-based cohort, the Atherosclerosis Risk in Communities (ARIC) study. We paid particular attention to the risk of hospitalization among individuals with asymptomatic LV systolic dysfunction and evaluated their risk of cardiovascular and non-cardiovascular hospitalizations in the community.

METHODS

Study Design and Population

The ARIC study is a prospective cohort study of the etiology and outcomes of cardiovascular disease in four communities. Details of study design have previously been published. ¹⁸ Briefly, individuals aged 45 to 64 were recruited between 1987 and 1989 from four communities (Forsyth County, NC; Jackson, MS; suburbs of Minneapolis, MN; and Washington County, MD). A total of 15,792 individuals participated in the initial examination. Three additional study examinations were performed approximately every three years. During the third study visit (1993–1995), participants at the Jackson, MS site underwent echocardiographic examination. The Jackson, MS field center recruited only African-Americans.

Echocardiography Assessment

Echocardiography was performed using an Acuson XP 128/10c machine with both M-mode and pulsed Doppler evaluation following a standard protocol. ¹⁹ Two cardiologists interpreted the images offline using a Freeland system. Details of echocardiography, including quality control, have previously been reported. ²⁰ Ejection fraction was determined semi-quantitatively using visual assessment and a modified Quinones formula. ^{21, 22} Left ventricular systolic dysfunction was defined as an ejection fraction less than 50%. ^{23, 24}

Covariates

Covariate information was obtained at the time of the third ARIC visit, with the two exceptions of education attainment (obtained at visit 1) and eGFR (obtained at visit 2). Education level was categorized as basic (≤ 11 years), intermediate (12–16 years), advanced (≥ 17 years). Smoking was categorized as current smoker, previous smoker, and never smoker. Body mass index (BMI) was determined by dividing weight in kilograms by height in meters squared. Blood pressure was calculated as the average of the second and third measurements taken by certified technician using a random-zero sphygmomanometer. Hypertension was defined as blood pressure greater than 140/90 or use of antihypertensive medication. Laboratory measurements were obtained through standard ARIC protocol. ¹⁹ eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) equation. ²⁵ History of diabetes was defined as a fasting blood glucose of ≥ 126 mg/dl, a nonfasting glucose ≥ 200 mg/dl, report of a physician diagnosis of diabetes, or current use of diabetes medication. Diagnoses of lung disease, asthma, and cancer were self reported. Coronary heart disease (CHD) was defined as

a history of myocardial infarction, silent myocardial infarction, fatal CHD event, coronary artery bypass surgery, or angioplasty.

Prevalent heart failure was defined by one of the following methods: reported HF medication use during study visits 1, 2, or 3; manifest heart failure defined by Gothenberg criteria stage 3 26-27 during study visits 1 or 2; self-reported history of heart failure; or previous hospitalization with a discharge diagnosis of heart failure (ICD-9 code of 428.28). Self-reported heart failure medication use was determined if a participant responded affirmatively to the question: "were any of the medications you took during the past two weeks for heart failure." Manifest heart failure stage 3 by Gothenberg criteria was defined by the presence of three criteria: history of dyspnea, treatment with loop diuretic or digitalis, and positive cardiac score, as defined by history of heart disease, angina, lower extremity edema, orthopnea, pulmonary rales, or atrial fibrillation; Gothenberg stage 3 was shown to include cases as heart failure defined by Framingham criteria.²⁷ We were unable to assess Gothenberg score at visit 3 as the medical history did not contain questions related to dyspnea at this examination. In lieu of this missing information, we relied on self-reported HF diagnosis at visit 3.

Hospitalization Assessment

Our primary outcome was number of hospitalizations. Hospitalizations were identified from annual questionnaires of cohort participants and through community-wide surveillance of hospital discharge indexes. Discharge diagnoses were obtained using International Classifications of Diseases-Ninth Revision (ICD-9) codes. We classified hospitalizations according to first (primary) discharge diagnosis as due to either cardiovascular disease (390–449) or non-cardiovascular disease (all admissions with an ICD-9 code other than 390–449). Non-cardiovascular disease was further classified as pulmonary disease (460–519), COPD (490–491, 492–496), pneumonia (480–486), cancer (140–239), infectious (1–139), mental disorders (290–319), gastrointestinal disease (520–579), kidney disease (580–589), diabetes mellitus (250), and musculoskeletal disease (710–739).²⁹ Follow-up information was obtained from time of echocardiography through January 1, 2006.

Statistical analysis

Baseline characteristics of participants with and without left ventricular dysfunction were compared using the chi-squared test for binary and categorical variables. Continuous variables were assessed for normality both visually, using the q-q normal plot, and statistically, using the Shapiro-Wilk test. Continuous variables were compared using the t-test if normal and Wilcoxon rank-sum test if non-normal.

Our primary outcome was number of hospitalizations, which was calculated as both a mean and a rate of events per 100 person-years. The rate ratios for hospitalizations were compared between exposure groups using a negative binomial regression model due to the over-dispersion of the data. Percent attributable risk was calculated by subtracting the incidence rate in the unexposed group from the rate in the exposed group and dividing by the rate in the exposed. We calculated an adjusted attributable risk by taking regression postestimation to predict incident rates among our exposure group and subtracted the predicted value for this group had they not been exposed.³⁰

As we were interested in the effect of time on our outcome, we also constructed a time-to-event model using the Kaplan-Meier method. Group differences were compared using the log-rank test. Relative hazard of first hospitalization following echocardiogram was calculated using Cox proportional hazard models. We evaluated the proportional hazards assumptions graphically using the $-\log(-\log(\text{survival function}))$ plot and statistically using the Schoenfeld goodness-of-fit test. We performed a secondary time to event model with mortality as an

outcome using Cox models to adjust for covariates. Underlying cause of death was categorized as cardiovascular versus non-cardiovascular based on death certificate ICD-9 and ICD-10 codes.

Statistical significance for all comparisons was pre-specified with an alpha level of 0.05 (two-tailed). Statistical analysis was performed using Stata 10. (Stata Statistical Software: Release 10, StatCorp, College Station, TX, 2007.)

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RESULTS

Baseline Characteristics

Of the 2,622 participants from Jackson site who presented for the third ARIC visit, 2,445 underwent echocardiography. LV dysfunction was found in 61 of the 2,416 (2.5%) participants with evaluable data on left ventricular function. As compared to normal LV systolic function, LV dysfunction was associated with increased age (mean 60.7 vs. 58.8 years), lower educational attainment, and higher prevalence of hypertension (82.0% vs. 60.1%), diabetes (47.5% vs. 23.6%), coronary heart disease (31.2% vs. 4.1%), and heart failure (37.7% vs. 4.8%). Baseline characteristics are presented in Table 1.

Hospitalization Rates

During a mean follow up of 10.2 years, there were a total of 5,251 hospitalizations, with a mean of 2.2 hospitalizations per individual. Individuals with LV systolic dysfunction were hospitalized an average of 6.0 times during the study period, as compared to a mean of 2.1 hospitalizations for participants with normal LV function ($p < 0.001$). Discharge diagnoses were available for 4,660 (89%) of the hospitalizations. LV dysfunction was associated with increased numbers of both cardiovascular (mean 2.6 vs. 0.6; $p < 0.001$) and non-cardiovascular (mean 2.9 vs. 1.2; $p < 0.001$) admissions.

The overall hospitalization rate for participants with LV dysfunction was 127.0 per 100 person-years, while individuals with normal LV function had a rate of 25.4 per 100 person-years, for an adjusted incidence rate ratio (aIRR) of 3.11 (95% CI 2.22–4.35). Compared to their counterparts with normal LV function, adults with LV dysfunction were admitted to the hospital more frequently for both cardiovascular (aIRR 4.76; 95% CI 2.90–7.80) and non-cardiovascular (aIRR 2.67; 95% CI 1.82–3.90) disease. Individuals with LV dysfunction had significantly elevated rates of hospitalization for COPD (4.0 vs. 0.2 hospitalizations for 100 person-years; aIRR 18.24; 95% CI 5.06–65.70) and pulmonary diseases (aIRR 3.99; 95% CI 1.70–9.34) although not for pneumonia. LV dysfunction was also associated with increased hospitalization rates for gastrointestinal disease, kidney disease, and diabetes. (Table 2)

The attributable risk of LV dysfunction for all-cause, non-cardiovascular, and cardiovascular admissions was 101.6, 42.1, and 51.9 per 100 person-years, respectively. Non-cardiovascular admissions accounted for 41% of the additional hospitalizations observed in the LV dysfunction group, with cardiovascular admissions accounting for 51% of excess admissions.

The remaining 7% of admissions were unclassified. The percent attributable risk of LV dysfunction was 80%, 74%, and 87% for all-cause, non-cardiovascular, and cardiovascular admissions, respectively, with values of 68%, 63%, and 79% after adjustment for covariates.

Survival Analysis

Of participants with LV dysfunction, 88.5% had at least one hospitalization during follow up, as compared to 63.6% of participants with normal LV function ($p<0.001$). The Kaplan-Meier curves for hospital free survival by LV functional status are shown in Figure 1a. LV systolic dysfunction was associated with a significant increase of cumulative risk of hospitalization ($p<0.0001$ by likelihood ratio test). After adjusting for covariates, LV dysfunction was associated with a hazard ratio of 3.39 (95% CI 2.49–4.91) for first hospitalization as compared to normal LV function. Among individuals with LV dysfunction, the adjusted relative hazard of first cardiovascular and non-cardiovascular hospitalization was 4.83 (95% CI 3.41–6.83) and 1.75 (95% CI 1.23–2.51), respectively. Survival curves for cardiovascular and non-cardiovascular hospitalizations are shown in Figures 1b and 1c.

In the analysis with mortality as outcome, the adjusted hazard ratio of all cause mortality was 3.49 (95% CI 2.35–5.19) for individuals with LV dysfunction as compared to those with normal LV function. LV dysfunction was associated with increased rates of death from both cardiovascular (adjusted HR 4.83; 95% CI 2.95–7.92) and non-cardiovascular (adjusted HR 2.04; 95% CI 1.00–4.21) causes.

Exclusion of Prevalent HF

In order to study the history of asymptomatic left ventricular systolic dysfunction, we repeated analyses after excluding individuals with prevalent HF ($n=136$) and obtained results that were similar to the larger cohort.

On average, individuals without prevalent HF were hospitalized 2.0 times during a mean of 10.3 years. As compared to asymptomatic individuals with normal LV function ($n=2,242$), individuals with asymptomatic LV dysfunction ($n=38$) had higher numbers of total hospitalizations (mean 4.9 vs 1.9; $p<0.001$), cardiovascular hospitalizations (1.8 vs. 0.5; $p<0.001$), and non-cardiovascular hospitalizations (2.8 vs. 1.2; $p=0.02$). As with the larger cohort, among individuals without prevalent HF, LV systolic dysfunction was associated with significantly increased rates of total hospitalizations and hospitalizations for cardiovascular, non-cardiovascular, pulmonary, COPD, gastrointestinal and kidney diagnoses. (Table 3)

With regard to the survival analysis for individuals without prevalent heart failure, 81.6% of individuals with asymptomatic LV systolic dysfunction and 62.2% of those with normal LV function were hospitalized during the study period. Following adjustment for covariates, individuals with asymptomatic LV systolic dysfunction had a hazard ratio for hospitalization of 3.02 (95% CI 2.04–4.49) in comparison to individuals with normal systolic function. Asymptomatic LV systolic dysfunction was associated with an adjusted relative hazard of 4.81 (95% CI 3.09–7.47) and 1.57 (95% CI 0.98–2.51) for cardiovascular and non-cardiovascular hospitalizations, respectively. The Kaplan Meier curves for individuals without prevalent heart failure were similar to those for the overall cohort.

DISCUSSION

In this study of 2,416 African American participants from the ARIC cohort, LV systolic dysfunction was associated with an increased rate of hospitalization due to both cardiovascular and non-cardiovascular causes. In fact, the absolute difference in number of hospitalizations related to LV dysfunction was similar for cardiovascular (mean 2.0) and non-cardiovascular

(mean 1.7) admissions and nearly half of excess hospitalizations were attributable to non-cardiovascular causes. Risk was independent of an array of potential confounders for both cardiovascular and non-cardiovascular diseases. These results were robust for both the hospitalization rate and time to event analyses and were present among asymptomatic individuals without diagnosed HF.

Previous studies of LV systolic dysfunction and hospitalization risk have yielded mixed results, but they focused exclusively on readmissions among individuals with clinically diagnosed HF.^{8–11, 14} Community-wide studies have found an increased risk for cardiovascular hospitalization among individuals with asymptomatic LV systolic dysfunction;¹⁶ however, there exists limited information about the association between LV dysfunction and non-cardiovascular hospitalizations, which accounted for over half of the admissions in our study. For this reason, we quantified the extent to which previous studies may have underestimated the total hospitalization burden associated with LV dysfunction in the community.

We found that LV dysfunction was associated with hospitalizations for a variety of causes, including for pulmonary, gastrointestinal, and kidney diseases. Dunlay and colleagues recently examined the etiology of hospitalizations among heart failure patients in the community and found that non-cardiovascular hospitalizations accounted for substantial morbidity in an older population in Olmsted County, Minnesota.⁵ Of note, in that study LV dysfunction was not associated with increased risk of all-cause hospitalizations and the relationship of LV function to etiology of admission was not addressed. To our knowledge, no other studies have examined the reason for hospitalizations among individuals with LV dysfunction.

Participants with LV dysfunction had increased rates of both COPD and pulmonary admissions, a notable clinical finding as individuals with LV dysfunction are frequently admitted for HF which can present in a similar manner to pulmonary diseases.^{31, 32} Previous research among Medicare participants with HF have demonstrated high readmission rates for pulmonary diagnoses.^{4, 6} Studies have shown that 30% of heart failure patients have concurrent COPD, which is only partially due to common risk factors. Individuals with COPD have systemic inflammation which can lead to coronary disease and LV dysfunction, and both heart failure and COPD lead to muscle atrophy and worsening cardiopulmonary function.³¹ Our results of an association between LV dysfunction and COPD morbidity was, therefore, not surprising. Nonetheless, the overall proportion of COPD hospitalizations was small. Furthermore, we had expected to find a relationship between LV dysfunction and pneumonia. We hypothesize that the relatively few number of pulmonary hospitalizations may point to the diagnostic difficulty in differentiating HF, COPD, and pneumonia, with clinicians attributing a greater number of hospitalizations to HF in our study.

LV dysfunction was associated with increased rates of hospitalizations for admissions related to kidney disease and diabetes. Both are risk factors for LV dysfunction and cardiovascular diseases;³³ nevertheless, the results were significant even after adjustments for cardiovascular risk factors including diabetes status and eGFR.

We found LV dysfunction was associated with an increased rate of gastrointestinal admissions. The overlap between gastrointestinal diseases and HF in general has been less well recognized. HF may lead to intestinal ischemia and bowel edema with resulting bacterial and endotoxin translocation.³⁴ Indeed, gastroenteritis and gastrointestinal hemorrhage have been shown to be common admission diagnoses among HF patients.⁴ Our findings further support the association between gastrointestinal morbidity and HF in general.

Among individuals without prevalent HF at baseline, LV dysfunction was associated with an increased risk of total hospitalization, with similar increased rates for cardiovascular (2.84; 95% CI 1.47–5.51) and non-cardiovascular (aIRR 2.41; 95% CI 1.51–3.87) hospitalizations.

Previous population studies have demonstrated that asymptomatic left ventricular systolic dysfunction is associated with increased risk of cardiovascular morbidity and mortality.^{16, 17} Furthermore, clinical trials have shown that pharmacotherapy reduces cardiovascular events among individuals with asymptomatic LV dysfunction,^{12, 35, 36} which has led to discussion about screening in the community.^{37–39} Our study found a risk associated with asymptomatic LV dysfunction beyond cardiovascular disease, which implies that early detection may offer benefit to reduce morbidity associated with non-cardiovascular diseases. For instance, given their high incidence rate of pulmonary admissions, individuals with asymptomatic LV dysfunction may be an appropriate group for pneumococcal and influenza vaccinations to prevent hospitalization.

This study has several important strengths. The prospective, longitudinal nature of the study permitted for accurate assessment of hospitalization rates. We were able to follow a large, community-based cohort of middle aged African Americans who are at high risk of HF and often underrepresented in trials.³² The time of follow up was significant at a median of 10.8 years. Ejection fraction was assessed using a standard protocol with quality control which should have resulted in accurate measurement and classification of the primary exposure.

Several weaknesses of the study deserve mention. First, our study is limited by the small number of individuals found to have LV systolic dysfunction: 2.5% among the entire cohort and 1.7% among individuals without symptomatic heart failure. These prevalences are about half of that observed in other population-based studies that defined LV systolic dysfunction as an ejection fraction of less than 50%.^{17, 23, 24, 39} Of note, these previous studies looked at populations that were predominantly white; African Americans are at higher risk of hypertension and left ventricular hypertrophy, which are strongly associated with diastolic dysfunction.³² Further research should address the differences in risk and prognosis of diastolic versus systolic dysfunction among the African-American population, which we were unable to assess due to significant limitations in echocardiographic evaluation of diastolic dysfunction in the ARIC study.²²

Second, although we used various methods to ensure the accuracy of number of hospitalizations, diagnoses were based on ICD-9 coding which is subject to misclassification. Misclassification could have occurred in the differentiation of pulmonary and cardiac causes of dyspnea, which frequently have similar clinical presentations. Some COPD hospitalizations may have therefore represented HF hospitalizations, and vice versa. This may limit the inferences from cause specific hospitalization data but strengthens the rationale for looking at all hospitalizations regardless of cause. Third, due to study protocol, information related to left ventricular function was categorical and we were unable to analyze ejection fraction as a continuous variable. Fourth, many of the study participants had zero hospital admissions, while some individuals had multiple admissions. This distribution may have skewed the results in the incident rates analyses as some individuals may have had a disproportionate effect on outcomes. However, the distribution of hospitalizations would not have affected the time to event analyses, which produced similar results. As we focused exclusively on African-Americans, a group which may be at increased risk of hospitalizations,⁴⁰ our results may not be generalizable to other races or ethnicities.

While we found that LV dysfunction was associated with increased risk of non-cardiovascular hospitalizations, we cannot determine the mechanism of risk. Concurrent increased rates of cardiovascular and non-cardiovascular hospitalizations may be a result of clustering tendencies, common risk factors, pathophysiologic overlap, or another mechanism. Further research will need to address whether measures such as screening for non-cardiovascular diseases or treatment of cardiovascular disease among individuals with LV dysfunction have efficacy in the prevention of non-cardiovascular hospitalizations.

The primary implication of our study is that LV systolic dysfunction confers an underappreciated risk of hospitalization due to non-cardiovascular disease. If additional studies confirm our results, initiatives to reduce hospitalizations should consider the impact of LV dysfunction on a broad array of diseases. Management of individuals with LV dysfunction should focus on prevention and treatment of both cardiovascular and non-cardiovascular comorbidities. Further research should examine a possible mechanism of an effect of left ventricular dysfunction on non-cardiovascular conditions, especially pulmonary and gastrointestinal diseases.

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Figure 1.

Kaplan Meier Curves for Hospitalizations. Graphs represent unadjusted time to event of first hospitalization for all-cause (1a), cardiovascular (1b), and non-cardiovascular (1c) admissions. Curves truncated to 5 years of follow-up since the risk in the LV dysfunction group was nearly 100% by this time.

Table 1

Baseline Characteristics

	Normal LV Function (n=2,355)	LV Dysfunction (n=61)	p-value
Age, years, mean (SD)	58.8 (5.7)	60.7 (5.8)	0.01
Female	64.9	41.0	<.001
Education Level			0.002
Less than 12th grade	37.5	57.4	
High School Degree or College	27.9	26.2	
Graduate School	34.6	16.4	
Health Insurance	84.6	78.7	0.21
Smoking Status			0.002
Current Smoker	19.6	26.2	
Former Smoker	31.5	47.5	
Never Smoker	48.9	26.2	
Current Drinker	29.7	29.5	0.97
Lung Disease	4.6	8.2	0.2
Asthma	5.6	8.2	0.39
Cancer	4.2	3.3	0.74
Hypertension	60.1	82.0	0.001
Diabetes	23.6	47.5	<.001
Coronary Heart Disease	4.1	31.2	<.001
Prevalent Heart Failure	4.8	37.7	<.001
Systolic Blood Pressure, mmHg, mean (SD)	139.4 (24.4)	149.5 (23.5)	0.001
BMI, kg/m ² , mean (SD)	30.5 (6.3)	28.1 (5.9)	<.001
Total cholesterol, mg/dl, mean (SD)	207.3 (39.6)	209.4 (41.4)	0.61
eGFR, ml/min/1.73 m ² , mean (SD)	94.8 (21.1)	81.7 (28.8)	0.003

In percentage points unless otherwise specified

Table 2

Incidence Rate Ratios for Hospitalizations

	Hospitalization Rate*		Unadjusted Rate Ratio			Adjusted [†] Rate Ratio		
	Normal LV Function	LV Dysfunction	IRR	95% CI	p-value	IRR	95% CI	p-value
All Hospitalizations	25.4	127.0	4.87	3.39	7.02	3.11	2.22	4.35
Non-cardiovascular	14.7	56.8	3.62	2.42	5.43	2.67	1.82	3.90
Pulmonary	1.5	5.6	4.82	1.99	11.67	3.99	1.70	9.34
COPD	0.2	4.0	27.26	6.46	115.15	18.24	5.06	65.70
Pneumonia	0.5	0.4	1.01	0.20	5.10	0.75	0.14	3.88
Cancer	2.0	1.0	0.78	0.28	2.22	0.83	0.29	2.36
Infection	0.9	3.1	4.47	1.18	16.92	2.26	0.64	7.91
Mental Illness	0.3	1.7	5.26	0.98	28.29	2.18	0.36	13.23
Gastrointestinal	1.8	8.2	3.79	2.01	7.15	3.17	1.67	6.03
Kidney Disease	0.2	1.7	6.78	0.97	47.32	8.02	1.16	55.89
Diabetes	1.7	18.0	10.03	3.17	31.70	2.71	1.15	6.40
Musculoskeletal	1.0	0.7	1.14	0.40	3.21	2.09	0.73	6.01
Cardiovascular	7.7	59.6	7.62	4.38	13.28	4.76	2.90	7.80

* Rates are per 100 person-years

[†] Adjusted for age, gender, education, insurance, smoking status, alcohol use, bmi, total cholesterol, eGFR, systolic blood pressure, edical history (lung disease, asthma, diabetes, hypertension, coronary heart disease, cancer)

Table 3
Incidence Rate Ratios for Hospitalizations for Individuals free of Prevalent Heart Failure

	Hospitalization Rate*		Unadjusted Rate Ratio			Adjusted [†] Rate Ratio		
	Normal LV Function	LV Dysfunction	IRR	95% CI	p-value	IRR	95% CI	p-value
All Hospitalizations	22.8	64.6	3.13	2.00	4.89	2.49	1.63	3.81
Non-cardiovascular	13.7	33.2	2.75	1.69	4.50	2.41	1.51	3.87
Pulmonary	1.4	6.0	5.45	1.81	16.40	3.84	1.35	10.97
COPD	0.1	3.9	31.97	5.72	178.50	13.51	3.01	60.65
Pneumonia	0.5	0.2	0.72	0.08	6.60	0.53	0.06	5.11
Cancer	2.0	1.1	0.80	0.22	2.89	0.79	0.22	2.82
Infection	0.8	3.3	4.71	0.82	27.02	2.87	0.55	15.01
Mental Illness	0.3	2.7	8.13	1.03	64.00	2.94	0.34	25.30
Gastrointestinal	1.7	4.3	3.17	1.45	6.94	2.97	1.33	6.66
Kidney Disease	0.2	0.6	3.29	0.28	39.71	14.95	1.05	213.59
Diabetes	1.5	2.9	2.27	0.47	11.02	1.59	0.43	5.95
Musculoskeletal	1.0	1.2	1.66	0.54	5.07	3.59	1.16	11.08
Cardiovascular	6.4	25.3	4.40	2.17	8.90	2.84	1.47	5.51

* Rates are per 100 person-years

[†] Adjusted for age, gender, education, insurance, smoking status, alcohol use, bmi, total cholesterol, eGFR, systolic blood pressure medical history (lung disease, asthma, diabetes, hypertension, coronary heart disease, cancer)