Journal of the American Heart Association

ORIGINAL RESEARCH

Depressive Symptoms and Incident Hospitalization for Heart Failure: Findings From the REGARDS Study

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BACKGROUND: Depressive symptoms are risk factors for several forms of cardiovascular disease including coronary heart disease (CHD). However, it is unclear whether depressive symptoms are associated with incident heart failure (HF), including hospitalization for HF overall or by subtype: HF with preserved (HFpEF) or reduced ejection fraction (HFrEF).

METHODS AND RESULTS: Among 26 268 HF-free participants in the REGARDS (Reasons for Geographic And Racial Differences in Stroke) study, a prospective biracial cohort of US community-dwelling adults ≥45 years, baseline depressive symptoms were defined as a score ≥4 on the 4-item Center for Epidemiologic Studies Depression scale. Incident HF hospitalizations were expert-adjudicated and categorized as HFpEF (EF ≥50%) and HFrEF, including mid-range EF (EF<50%). Over a median of 9.2 [IQR 6.2–10.9] years of follow-up, there were 872 incident HF hospitalizations, 526 among those without CHD and 334 among those with CHD. The age-adjusted HF hospitalization incidence rates per 1000 person-years were 4.9 (95% CI 4.0–5.9) for participants with depressive symptoms versus 3.2 (95% CI 3.0–3.5) for those without depressive symptoms (P<0.001). For overall HF, the elevated risk became attenuated after controlling for covariates. When HFpEF was assessed separately, depressive symptoms were associated with incident hospitalization after controlling for all covariates (hazard ratio [HR] 1.48, 95% CI 1.00–2.18) among those without baseline CHD. In contrast, depressive symptoms were not associated with incident HFrEF hospitalizations.

CONCLUSIONS: Among individuals free of CHD at baseline, depressive symptoms were associated with incident hospitalization for HFpEF, but not for HFrEF, or among those with baseline CHD.

Key Words: depression ■ incident heart failure ■ prevention ■ risk factors

Heart failure (HF) is the leading cause of hospitalizations in the United States.[1] The prevalence of HF is increasing: the National Health and Nutrition Examination Survey estimated that 6.2 million (2.2%) of US adults had HF between 2013 and 2016, compared to 5.7 million between 2009 and 2012.[2] Increase in HF prevalence has been attributed to the aging of the population, and, importantly, an increase in heart failure with preserved ejection faction (HFpEF) versus heart failure with reduced ejection fraction (HFrEF).[3–5] HFpEF and HFrEF are two distinct subtypes of HF with different sets of risk factors. HFrEF is more often associated with traditional cardiovascular risk factors and with coronary heart disease (CHD). HFpEF is more often associated with obesity and comorbidities, including both physical and emotional conditions.[6–8]

Patients with HF, especially HFpEF, suffer from multimorbidities, both physical and psychiatric, including depression. Depression is prevalent in all HF subtypes, with 20% to 40% of HF patients reporting depressive symptoms.[9] While depression is recognized as an important contributing factor to poor outcomes in patients

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Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.022818

For Sources of Funding and Disclosures, see page 10.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- In a large population-based cohort of US community-dwelling adults without prior coronary heart disease, depressive symptoms were associated with an increased risk of developing heart failure with preserved ejection fraction but not with heart failure with reduced or midrange ejection fraction.

What Are the Clinical Implications?

- Routine depression screening and targeted treatment interventions for depression among individuals without established coronary heart disease may reduce the risk of developing heart failure with preserved ejection fraction.

Nonstandard Abbreviations and Acronyms

CES-D	Center for Epidemiological Studies Depression scale
HFpEF	heart failure with preserve ejection fraction
HFrEF	heart failure with reduced ejection fraction

with established HF, it is unclear if depression is an independent risk factor for developing incident HF in the absence of prior HF,[10] and the previous literature results on this topic are mixed. For other cardiovascular diseases depressive symptoms are shown to be an independent risk factor for the new cardiovascular disease, especially for incident CHD.[11–13] The increased cardiovascular risk of depressive symptoms is explained by two potential mechanisms: behavioral and biological.[14] Behavioral mechanisms, linking depressive symptoms to cardiovascular disease, include smoking, physical inactivity and poor medication adherence.[14] Biological mechanism includes higher levels of chronic inflammation that occur in patients with chronic depression and is directly linked to cardiovascular disease.[14]

To address this gap this study objective was to explore the association of depressive symptoms with incident HF hospitalization, separately for HF subtypes. We utilized the data from the REGARDS (Reasons for Geographic and Racial Differences in Stroke) study, a large longitudinal prospective cohort of community dwelling adults in the US. We hypothesized that depressive symptoms are associated with incident HF hospitalization overall and association between depressive symptoms and incident HF is more pronounced for HFpEF than for HFrEF, given than both HFpEF and depressive symptoms are associated with chronic inflammation[14–16] and with more comorbidities.

METHODS

Study Cohort and Procedures

Manuscript raw data, analytic methods, and study materials are available to other researchers at request. The REGARDS study is an ongoing prospective cohort study of 30 239 community-dwelling adults from all 48 continental US states that examined regional and racial influences on stroke mortality. Details are described elsewhere; briefly, English-speaking adults aged 45 years and older residing in the continental US were enrolled between 2003 and 2007, with the help of commercially available lists combining mail and telephone contacts.[17] Race and sex were balanced by design, with oversampling from the Southeastern US. The final cohort composition included 58% women and 42% African Americans. Baseline data collection included computer-assisted telephone interviews on socio-demographics, medical history, and health status. In-home examinations by trained staff followed standardized, quality-controlled protocols to collect fasting blood and urine samples, electrocardiograms, blood pressure (BP), anthropometric measures, and data on medications via pill bottle review. Living participants or their next of kin were telephoned every 6 months with retrieval of medical records for reported hospitalizations. The REGARDS study procedures were approved by the Institutional Review Boards at the participating centers and all participants provided written informed consent.[17]

The current study excluded individuals with baseline HF based on the medication use algorithm. Baseline HF was considered present if the participant was taking HF medications such as digoxin in the absence of history of atrial fibrillation; angiotensin converting enzyme inhibitor/angiotensin receptor blocker plus beta-blocker in the absence of hypertension; carvedilol; spironolactone; loop diuretics including furosemide, bumetanide, or torsemide; and/or a combination of hydralazine and nitrates and/or use of inotropic agents.[18] This approach has been validated with a negative predictive value (NPV) of 0.995 to exclude both HFrEF and HFpEF in REGARDS, compared to Medicare–REGARDS linkage sub-cohort, which used medical claims data to identify baseline HF.[18]

Heart Failure Hospitalizations

Data from study baseline through December 31, 2015 were included. HF hospitalizations were adjudicated by a two-clinician team using medical records and established guidelines.[19] Charts were reviewed for symptoms

signs of HF and cardiac imaging data were abstracted for left ventricular ejection fraction (LVEF), diastolic dysfunction grade, filling pressures. Brain natriuretic peptide data were abstracted and considered in the case adjudication. HF was classified according to the lowest documented LVEF during the hospitalization, determined by transthoracic echocardiogram or other imaging modalities. HF with LVEF ≥50% was defined as HFpEF, and LVEF <50% was defined as HFrEF, including HF with mid-range EF of 40% to 50%. Previous research has shown that risk factors and patient characteristics of HF with mid-range EF are similar to those with HFrEF.[20] We have excluded individuals with indeterminate or missing LVEF from the analysis.

Depressive Symptoms

Depressive symptoms were obtained at baseline examination using the 4-item Center for Epidemiologic Studies Depression scale (CES-D-4) that was validated and found to correlate highly with original 20-item scale (r=0.87).[21,22] The CES-D-4 uses a four-point (0–3) scale to record the presence and frequency of specific symptoms of depression: (1) felt depressed, (2) felt lonely, (3) had crying spells, and (4) felt sad during the preceding week. Responses to 4 items were summed (Cronbach α=0.80) and total scored ranged from 0 (no symptoms) to 12. The CES-D-4 was dichotomized, with scores of ≥4 signifying the presence of "elevated depressive symptoms," which had been reported to have 79.2% sensitivity and 86.4% specificity for meeting a previously established threshold for having clinically significant depressive symptoms as assessed by the full 20-item CES-D.[21,22] Secondary analyses included a separate set of final models using depressive symptoms as a continuous score to capture the variability that might be missed in the dichotomous indicator.

Covariates

Covariate selection was guided by previous reports which delineated specific risk factors for the development of incident HF[6,23,24] and an association of those factors with depressive symptoms[24] as well as the Andersen Health Care Utilization model,[25] grouping covariates into predisposing (ie, socio-demographics), enabling (ie, primary care provider, health insurance, medication adherence), and need (ie, comorbidities) factors.

Baseline self-reported socio-demographic characteristics included age, race, sex, education, annual income (dichotomized at $35 000), marital status (married versus not), geographical region of residence (Stroke Buckle, defined as residence in coastal North and South Carolina and Georgia; Stroke Belt, defined as residence in the remainder of North and South Carolina and Georgia, plus Alabama, Mississippi, Louisiana, Arkansas, and Tennessee, and Non-Belt states), having a primary care provider, and having health insurance. Self-reported health behaviors included: pack-years of cigarette smoking; alcohol use (none, moderate, heavy, based on National Institutes of Drug and Alcohol Abuse sex-specific categories); and physical activity (never versus any during average week). Self-reported medication adherence was assessed with a 4-item scale (perfect versus not perfect adherence).[26] Self-reported physical health status was ascertained using the Short Form 12 (SF-12) physical component summary (PCS) score.[27]

Baseline CHD was defined as electrocardiographic evidence of myocardial infarction (MI) or self-reported history of coronary artery bypass surgery, percutaneous coronary intervention, or MI.[28] Diabetes was defined as use of insulin or oral hypoglycemic agents, or fasting blood glucose concentration of 126 mg/dL or higher or non-fasting random plasma glucose concentration of 200 mg/dL or higher. Hypertension was defined as blood pressure of 130/80 mm Hg or above and/or the intake of anti-hypertensive medications. The following baseline physiological parameters were included: body mass index (kg/m^2); systolic blood pressure (average of two measures, obtained after a 5-minute rest, mm Hg); high-sensitivity C-reactive protein (mg/L); and urinary albumin-to-creatinine ratio (mg/g). Use of anti-hypertensive, anti-depressant and benzodiazepine medications was determined via pill bottle review and/or self-report. Because CHD is one of the most important risk factors for developing HF, especially for ischemic cardiomyopathy and HFrEF, we examined associations between depressive symptoms and HF among those with and without CHD separately.

Accounting for Interim MI

MI events that occurred between baseline and incident HF hospitalization can attenuate the association of other baseline risk factors with incident HF hospitalization. MI is a risk factor for ischemic cardiomyopathy, which is the most common cause of HFrEF.[29] Therefore, incident MI may be in the causal pathway for HFrEF, but less likely for HFpEF. In a separate step in the analysis, we accounted for interim MI occurring between the baseline and the incident HF hospitalization. In the REGARDS study, MI cases included ST-elevation MIs and non-ST elevation MI and were expert-adjudicated based on chart review to detect signs or symptoms of ischemia; a rising and/or falling pattern in cardiac troponin or creatine phosphokinase-MB concentration over six or more hours with a peak concentration greater than twice the upper limit of normal; and/or electrocardiographic changes consistent with ischemia or MI, guided by the Minnesota code. Definite and probable MI events were included in analyses.[28,30]

Death as a Competing Risk

All-cause mortality was considered a competing risk. Deaths were recorded through December 31, 2015 by report of next of kin or through online sources (eg, Social Security Death Index) and the National Death Index.

Statistical Analysis

Participants with depressive symptoms were compared to those without depressive symptoms, overall and stratified by baseline CHD. Chi-square tests were used to compare categorical variables and t tests for continues variables. HF age-adjusted incidence rates were computed for those with and without depressive symptoms overall and stratified by baseline CHD.

Sequentially adjusted Cox proportional hazards regression models were used to examine the association between baseline depressive symptoms and incident HF hospitalization overall and separately for HFpEF and HFrEF. First, we conducted unadjusted models of depressive symptoms and HF outcomes. Model 1 adjusted for depressive symptoms and sociodemographics. Model 2 added comorbidities, physiological variables, and health behaviors. Model 3 added having a primary care provider, health insurance, and self-reported physical health component score. Model 4 added intervening MI as a time-variant covariate. Finally, the last fully adjusted model utilized the Fine and Gray method to account for death from all causes as a competing risk of incident HF hospitalization and presented sub-distribution hazard ratios (SHR) for depressive symptoms.[31] This modeling exercise was performed first in the total analytic sample. We have tested an interaction between baseline CHD and CES-D ≥4 and then repeated analyses, stratified by baseline CHD. A *P*-value of 0.1 was considered statistically significant. Additionally, we tested interaction terms created between (1) sex and CES-D ≥4 and (2) race and CES-D ≥4 in the fully adjusted models of overall HF and then separately for HFpEF and HFrEF hospitalizations.

As a secondary analysis, fully adjusted models were fitted using the CES-D continuous score. Additionally, we constructed a competing risk model, in which HFpEF and HFrEF were considered competing risk outcomes, with estimation of the SHR for depressive symptoms. In separate sensitivity analyses we explored the role of antidepressant and benzodiazepines in the association between depressive symptoms and HF.

We tested the proportionality assumption by generating an interaction term between depressive symptoms and the log of time in each of the fully adjusted final models, which was satisfied for each HF outcome in overall and stratified samples. Missing data in covariates were imputed in 10 datasets using chained equations method that utilized regression models with sample bootstrapping. Descriptive analysis and incidence rate calculation were conducted using SAS software version 9.4 (SAS Institute, Cary, NC). Kaplan-Meier curves, multiple imputation, and Cox proportional hazards regression models were conducted in STATA version 14 (STATA Inc).

RESULTS

Figure 1 presents an exclusion cascade of the study participants. The final analytic sample included 26 268 REGARDS participants who were free of HF at baseline. Compared with the excluded participants, included participants did not differ in sex or geographic residence distribution, but were younger (mean age at baseline 64.5 versus 67.4, respectively, $P<0.001$), more likely to be White (59.8% versus 50.2%, respectively, $P<0.001$), married (59.6% versus 52.4%, respectively, $P<0.001$), and had higher annual family income. In our study, a total of 2725 (10.4%) participants had depressive symptoms.

Participant Characteristics

Compared to those without depressive symptoms, participants with elevated depressive symptoms (CES-D ≥4) were younger and were more likely to be African American, female, unmarried, have lower education and annual income, and live in the Stroke Belt and Buckle (Table 1). Having depressive symptoms at baseline was associated with more pack-years of smoking, physical inactivity, and medication nonadherence. Participants with depressive symptoms were also more likely to have diabetes, and had higher urinary albumin to creatinine ratios, higher levels of C-reactive protein, and lower physical health status scores. These differences persisted after stratification by baseline CHD status.

Depressive Symptoms and Incident HF Hospitalization

Over a median follow-up of 9.2 years [IQR 6.2–10.9] there were 872 incident HF hospitalizations (368 for HFpEF and 504 for HFrEF). Among persons with depressive symptoms at baseline, 53 experienced an incident HFpEF hospitalization and 54 an incident HFrEF hospitalization. Figure 2 presents unadjusted association of depressive symptoms and HFrEF and HFpEF. The median time from baseline to incident HF hospitalization was 4.8 years [IQR 2.4–7.3]. Among 872 participants with incident HF hospitalization, 70 individuals also had a MI event adjudicated during the study follow up period, prior to incident HF hospitalization.

We observed a significant interaction between baseline CHD and depressive symptoms in the models of

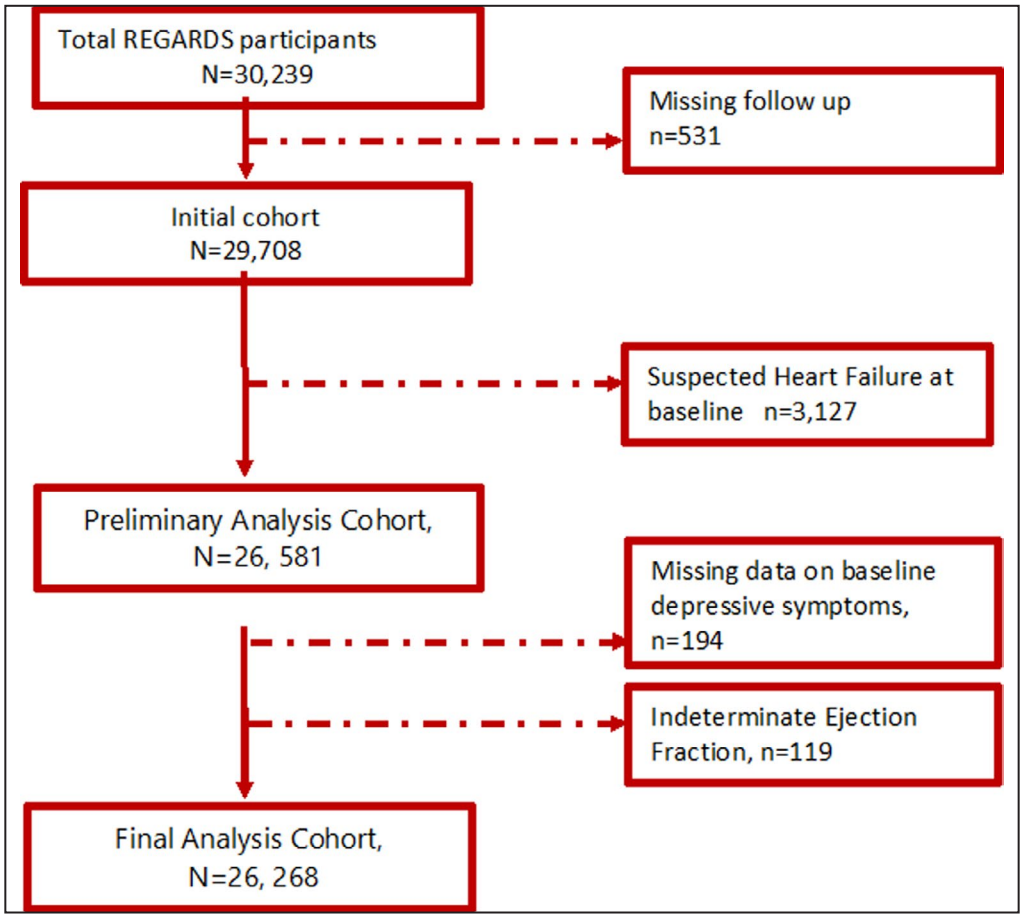

Figure 1. Exclusion cascade of the REGARDS (Reasons for Geographic and Racial Differences in Stroke) participants.

the incident HF overall (interaction *P*=0.08) and HFpEF (interaction *P*=0.05), but not HFrEF (interaction *P*=0.60). Therefore, results are presented overall, and also stratified by baseline CHD status (Table 2). Table S1 presents the full sequence of the models examining association of depressive symptoms with HF overall and HF subtypes.

Participants with depressive symptoms had higher age-adjusted incidence of HF overall (4.9 per 1000 person-years [95% CI 4.0–5.9]) compared to participants with no depressive symptoms (3.2 per 1000 person-years [95% CI 3.0–3.5]), but this association became attenuated after adjustment for all covariates in the total sample (Table 2). There was no interaction between depressive symptoms and sex in the fully adjusted model of HF (interaction *P*=0.187) or depressive symptoms and race (interaction *P*=0.459).

Depressive Symptoms and HFpEF

In the total sample, we observed statistically significant associations between depressive symptoms and HFpEF that persisted after adjusting for demographics, physiological parameters, and health behaviors (HR 1.37, 95% CI 1.01–1.85). However, this association became attenuated after full adjustment (Table 2).

Among participants, free of CHD at baseline, depressive symptoms were significantly associated with incident HFpEF hospitalization even after adjustment for all covariates, including self-reported health and intervening MI (HR 1.54, 95% CI 1.06–2.23), and when death was accounted for as a competing risk (HR 1.48, 95% CI 1.00–2.18). Conversely, among those with CHD at baseline, there was no association between depressive symptom and incident HFpEF hospitalization (Table 2).

Depressive Symptoms and HFrEF

In the total sample, depressive symptoms were not associated with incident HFrEF hospitalization (Table 2). There was no interaction between depressive symptoms and sex in the fully adjusted model. Regardless of CHD status, depressive symptoms were not associated with incident HFrEF hospitalization.

Table 1. Baseline REGARDS Participants' Characteristics According to Depressive Symptoms Status

Characteristics, n (%)	Missing (n)	Total sample, n=26 268		Free of CHD n=21 888		CHD at baseline n=3879	
		No depressive symptoms (n=23 547)	Depressive symptoms (n=2725)	No depressive symptoms (n=19 724)	Depressive symptoms (n=2164)	No depressive symptoms (n=3388)	Depressive symptoms (n=491)
Socio-demographics							
Age, y, mean±SD	…	64.7±9.3	62.6±9.7	64.0±9.2	62.1±9.6	68.5±8.9	65.0±9.3
African American	…	9175 (39.0)	1388 (50.9)	7871 (39.9)	1119 (51.7)	1100 (32.5)	234 (47.7)
Female	…	12 583 (53.4)	1891 (69.4)	11 077 (56.2)	1568 (72.5)	1242 (36.7)	275 (56.0)
Region of residence							
Stroke belt		8027 (34.1)	1018 (37.4)	6669 (33.8)	808 (37.3)	1191 (35.2)	175 (35.6)*
Stroke buckle		4844 (20.6)	620 (22.8)	4090 (20.7)	500 (23.1)	683 (20.2)	111 (22.6)
Non-belt		10 672 (45.3)	1087 (39.9)	8965 (45.5)	856 (39.6)	1514 (44.7)	205 (41.8)
Married	…	14 595 (62.0)	1068 (39.2)	12 128 (61.5)	856 (39.6)	2236 (66.0)	191 (38.9)
Less than high school education	18	2424 (10.3)	608 (22.3)	1891 (9.6)	462 (21.4)	471 (13.9)	126 (25.7)
Annual income ≤$35 000	3201	9075 (43.8)	1651 (70.2)	7419 (42.7)	1276 (68.1)	1488 (49.6)	330 (77.5)
Had health Insurance	21	22 089 (93.9)	2366 (86.9)	18 414 (93.5)	1862 (86.1)	3282 (96.9)	441 (89.8)
Had a primary care provider	1929	17 421 (79.6)	1866 (76.4)	14 583 (79.5)	1475 (76.0)	2531 (80.1)	347 (78.9)†
Behaviors							
Smoking, pack-year, mean±SD	790	12.7±22.0	15.1±24.1	11.5±20.5	13.3±22.5	20.0±28.4	23.3±29.6
Heavy alcohol use	516	990 (4.3)	123 (4.6)	849 (4.4)	101 (4.8)	125 (3.8)	17 (3.6)
Physical Inactivity	380	7243 (31.2)	1207 (44.9)	5966 (30.7)	934 (43.8)	1127 (33.7)	240 (49.4)
Self-reported health status							
Short—Form 12 Physical Component Score, median [IQR]	1114	51.1 [43.2–55.3]	41.8 [31.6–52.3]	51.1 [43.2–55.2]	41.8 [31.6–52.3]	47.9 [38.0–53.7]	37.3 [28.2–46.2]
Comorbidities							
Hypertension	…	17 003 (72.3)	2062 (75.8)	13 900 (70.6)	1600 (74.0)	2781 (82.4)	413 (84.8)
Diabetes	961	4154 (18.3)	679 (25.8)	3156 (16.6)	492 (23.6)	897 (27.5)	169 (35.7)
Coronary heart disease	501	3388 (14.7)	491 (18.5)	…	…	…	…
Physiological parameters							
Systolic blood pressure, mm Hg, mean±SD	65	127.1±16.3	128.0±17.6	126.6±16.2	127.5±17.4	130.2±16.8	130.4±18.4‡
Body mass index, kg/m^2, mean±SD	143	28.8±5.8	30.0±6.7	28.9±5.9	30.0±6.7	28.7±5.6	29.9±6.4

(*Continued*)

Table 1. Continued

Characteristics, n (%)	Missing (n)	Total sample, n=26 268		Free of CHD n=21 888		CHD at baseline n=3879	
		No depressive symptoms (n=23 547)	Depressive symptoms (n=2725)	No depressive symptoms (n=19 724)	Depressive symptoms (n=2164)	No depressive symptoms (n=3388)	Depressive symptoms (n=491)
Urinary albumin to creatinine ratio, median [IQR], mg/g	1190	7.1 [4.5–15.4]	7.8 [4.9–17.2]	6.8 [4.4–13.5]	7.3 [4.8–15.2]	9.1 [5.3–22.1]	10.0 [5.8–28.7]
High sensitivity C-reactive protein, median [IQR], mg/L	1605	2.1 [0.9–4.7]	2.8 [1.1–6.5]	2.1 [0.9–4.6]	2.8 [1.1–6.4]	2.1 [0.9–4.7]	2.7 [1.1–6.8]
Medication use							
Antihypertensives	70	12 837 (54.7)	1629 (60.0)	9998 (50.8)	1216 (56.4)	2581 (76.3)	381 (77.6)[§]
Antidepressants	70	2289 (9.7)	645 (23.7)	1891 (9.6)	501 (23.2)	348 (10.3)	128 (26.1)
Medication adherence (perfect vs not)	2631	15 122 (71.5)	1547 (62.0)	12 587 (71.8)	1223 (62.4)	2244 (69.7)	281 (59.7)

Depressive symptoms: CESD ≥4. CES-D indicates Center for Epidemiological Studies Depression scale; CHD, coronary heart disease; IQR, interquartile range; and REGARDS (Reasons for Geographic and Racial Differences in Stroke).

All comparisons have *P* value <0.05 except for: *P=0.35; †P=0.55; ‡P=0.78; §P=0.52.

Sensitivity Analyses

Results were similar when both HFpEF and HFrEF were assessed as simultaneous competing risks (Table S2). Among those free of CHD depressive symptoms were associated with HFpEF in the presence of HFrEF assessed as competing risk (SHR 1.52, 95% CI 1.05–2.11). The analyses of CES-D as a continuous measure of depressive symptoms were similar to those with the CES-D modeled dichotomously (Table S3). A one-point increase in the CES-D score (worsening severity of depression) was associated with 6% increased risk for HFpEF in the total sample and a 7% increased risk for HFpEF among those free of CHD. This was not observed for HFrEF. We have additionally explored the role of antidepressants and benzodiazepines in the association of depressive symptoms with HF. Among antidepressants, only the tricyclics were significantly associated with HF in unadjusted models. However, when depressive symptoms were added into the models, association of tricyclic antidepressants became nonsignificant. Benzodiazepine use was significantly associated with HF in both unadjusted and fully adjusted models, but it did not change our main results (data not shown).

DISCUSSION

In this large geographically diverse cohort of the US, Black and White adults, who were free of CHD at baseline, participants with depressive symptoms had a 1.5-fold increased risk of incident hospitalization for HFpEF that persisted after controlling for other cardiovascular risk factors. Depressive symptoms were not associated with incident HF hospitalization when the HF subtype or CHD history were not distinguished. To our knowledge this is one of the first studies to report a difference in the association of depressive symptoms and incident HF hospitalization by HF subtype.

For participants with prevalent CHD we did not find an association between depressive symptoms and incident HF hospitalization, regardless of HF subtype. The lack of association with depression may reflect the differences in risk factors for HF for those with preceding CHD event. Prior MI may cause direct myocyte injury and subsequent scarring, resulting in ischemic cardiomyopathy. After the initial insult to myocytes, the pathogenesis of HF may have a different trajectory, not involving extra-cardiac factors such as depression.

The literature to date about the relationship between depressive symptoms and the incidence of HF is limited and mixed. A cohort study of more than 60 000 community dwelling adults in Norway showed that participants with severe depressive symptoms had a 1.4-fold increased risk of incident hospitalization for

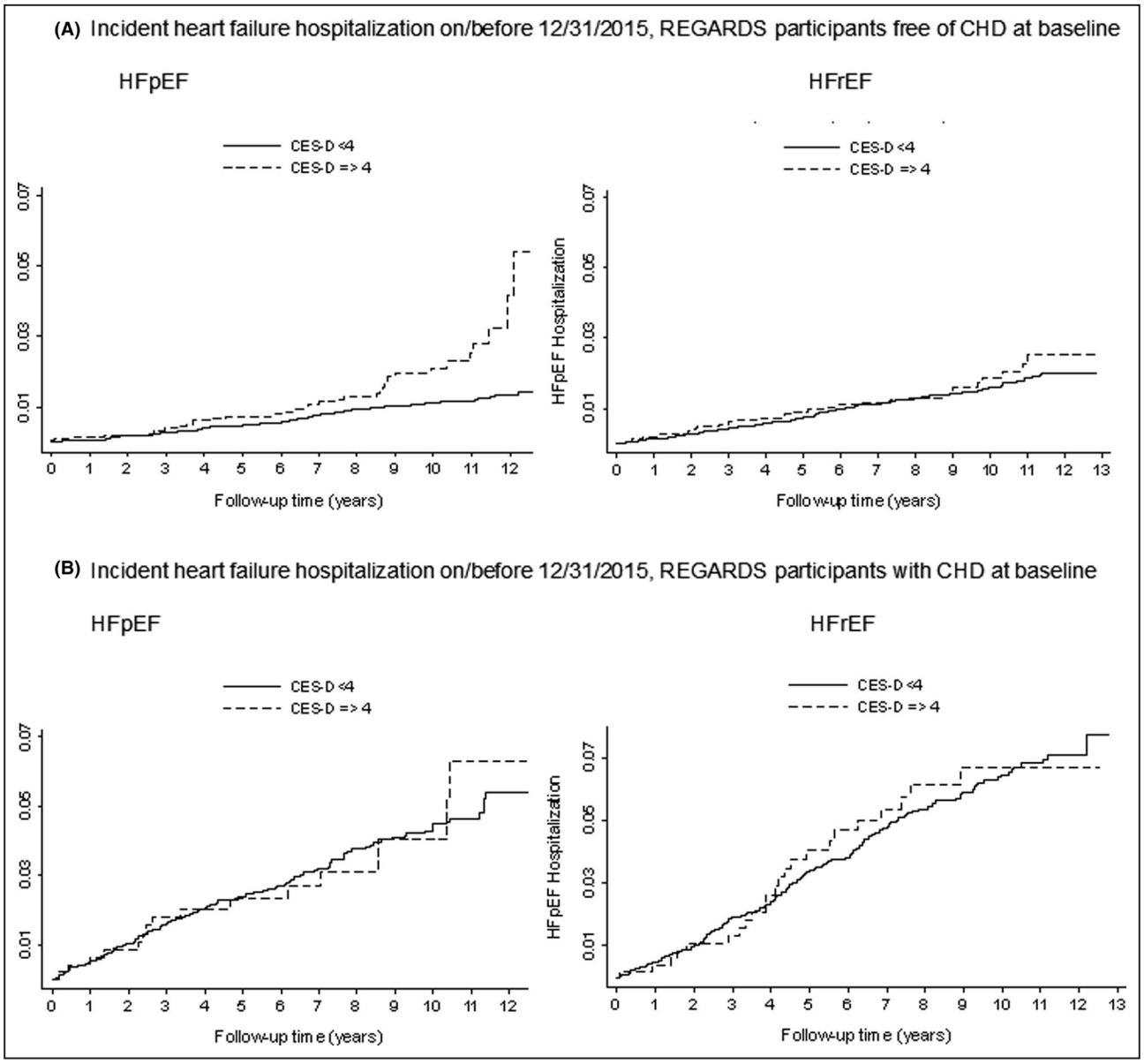

Figure 2. Incident heart failure hospitalization for HFpEF and HFrEF according to baseline depressive symptoms and CHD status.

The graphs present unadjusted Kaplan Meier curves for depressive symptoms associated with incident hospitalization for heart failure with preserved ejection function (HFpEF) and heart failure with reduced ejection function (HFrEF) stratified by absence (**A**) or presence (**B**) of coronary heart disease at baseline in REGARDS. CES-D indicates Center for Epidemiological Studies Depression scale; CHD, coronary heart disease; and REGARDS, Reasons for Geographic and Racial Differences in Stroke.

HF, controlling for a variety of risk factors.[32] Conversely, among US adults enrolled in the MESA (Multi-Ethnic Study of Atherosclerosis) study there was no association between depressive symptoms and incident HF.[33] Notably, none of the above-mentioned studies made a distinction between HFpEF and HFrEF. The methods of these two studies differed, without adjudication of events in the Norwegian study and a HF detection strategy designed to include only events with very high specificity for HF in MESA. A study of patients with type 2 diabetes mellitus showed that people with depressive symptoms were 2.5 times as likely to develop incident HF hospitalization compared to non-depressed individuals.[34] Similarly, depressive symptoms were associated with 2.5-fold increased risk of developing incident HF hospitalization in a study of patients with hypertension.[35] Importantly, none of the cited reports examined differences between HF subtypes, which could contribute to the mixed evidence on the association between depression and HF.

A novel finding of the current study is that among individuals without baseline CHD depressive symptoms

Table 2. Association of Depressive Symptoms With Incident Heart Failure Hospitalization in REGARDS (End of Follow-Up, December 31, 2015)

	Overall HF		HFpEF (EF ≥50%)		HFrEF (EF <50%)	
	No depressive symptoms	Depressive symptoms	No depressive symptoms	Depressive symptoms	No depressive symptoms	Depressive symptoms
Total sample, n=26 268						
Hospitalizations, n	765	107	315	53	450	54
Age-adjusted IR, [95%CI]	3.2 [3.0–3.5]	4.9 [4.0–5.9]	1.3 [1.1–1.4]	2.3 [1.8–3.0]	2.0 [1.8–2.2]	2.5 [1.9–3.2]
HR, 95% CI						
Crude	REF	1.37 (1.12–1.68)*	REF	1.65 (1.24–2.21)*	REF	1.17 (0.88–1.55)
Fully adjusted†		1.07 (0.87–1.32)		1.27 (0.93–1.72)		0.91 (0.68–1.22)
+ Death as CR‡		1.00 (0.80–1.25)		1.21 (0.88–1.67)		0.87 (0.64–1.16)
Free of CHD at baseline, n=21 888						
Hospitalizations, n	459	67	187	36	272	31
Age-adjusted IR, [95% CI]	2.3 [2.1–2.5]	3.7 [2.9–4.8]	0.9 [0.8–1.1]	2.0 [1.4–2.7]	1.4 [1.2–1.6]	1.8 [1.2–2.5]
HR, 95% CI						
Crude	REF	1.49 (1.18–1.92)*	REF	1.98 (1.40–2.84)*	REF	1.15 (0.79–1.66)
Fully adjusted†		1.24 (0.96–1.62)		1.54 (1.06–2.23)*		1.00 (0.69–1.47)
+ Death as CR‡		1.17 (0.89–1.53)		1.48 (1.00–2.18)*		0.95 (0.65–1.40)
Baseline CHD, n=3879§						
Hospitalizations, n	295	39	122	16	173	23
Age-adjusted IR, [95% CI]	10.5 [9.3–11.8]	12.5 [9.1–17.1]	4.1 [3.4–5.0]	5.0 [3.1–8.3]	6.3 [5.4–7.4]	7.3 [4.9–11.1]
HR, [95% CI]						
Crude	REF	1.02 (0.73–1.43)	REF	1.01 (0.60–1.70)	REF	1.03 (0.67–1.59)
Fully adjusted†		0.86 (0.60–1.22)		0.90 (0.52–1.56)		0.81 (0.50–1.29)
+ Death as CR‡		0.79 (0.54–1.15)		0.86 (0.49–1.52)		0.78 (0.48–1.27)

Depressive symptoms are present when CESD ≥4. CES-D indicates Center for Epidemiological Studies Depression Scale; CHD, coronary heart disease; CR, competing risk; EF, ejection fraction; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazards ratio; IR, incident rate per 1000 person-years; REF, reference group; REGARDS, Reasons for Geographic and Racial Differences in Stroke; and SHR, sub-distribution hazard ratio.

+ This means death was added as a competing risk outcome to the fully adjusted model.

*$P<0.05$.

† Model adjusted for age, race, sex, region, education, income, marital status, systolic blood pressure, body mass index, use of any antihypertensive medication, diabetes, log-transformed urinary albumin to creatinine ratio, log-transformed high sensitivity C-reactive protein, baseline coronary artery disease for models in total sample, medication adherence, pack-years of smoking, alcohol use, and physical inactivity, health insurance, primary care provider, self-reported physical health component score of SF-12 scale, and interim nonfatal myocardial infarction on/before incident HF hospitalization as a time-dependent covariate.

‡Fully-adjusted SHR for depressive symptoms when death from all causes is accounted for as a competing risk outcome.

§501 missing baseline CHD status.

were associated exclusively with incident hospitalization for HFpEF but not HFrEF. This underscores the important differences in pathophysiology of HFpEF versus HFrEF. Whereas HFrEF results from an insult to the myocardium leading to myocyte death, HFpEF results from abnormal processes in the endothelial layer, with subsequent alterations in myocyte structure without actual cell death.[36] Recent data suggest that several inflammatory cytokines, such as C-reactive protein and interleukin-6, are involved in the pathogenesis of HFpEF.[15] Another body of research found an association between the same inflammatory markers and depressive symptoms.[16] This raises the intriguing possibility that shared chronic inflammation pathways could explain the association between depressive symptoms and HFpEF. Although not fully comparable with our design, other studies noted a signal that depressive symptoms may be associated with HFpEF but not HFrEF. Depressive symptoms predicted readmissions for HFpEF but not HFrEF in a Japanese study.[37] Importantly, in that study, patients with HFpEF had more comorbid medical conditions than those with HFrEF.[38]

Several other mechanisms have been proposed to explain why depressive symptoms may be associated with incident HF hospitalization. Depressive symptoms are associated with less self-care, medication nonadherence, and withdrawal from social support.[10] For example, a Swedish study of patients with incident HF hospitalization showed that participants with depressive symptoms were more likely to delay seeking care from the onset of HF symptoms to hospital admission.[39] The MESA study also showed a moderate signal for an association between depressive symptoms and incident HF hospitalization among participants with poor self-reported health, but not among those with good, very good, or excellent self-reported health.[33]

Strengths of our study include a large diverse sample of community-dwellers, long follow-up, availability of many physiologic and patient-reported characteristics, and expert-adjudicated HF events and cardiovascular disease outcomes. This study also has several limitations, including the observational design with limited opportunity for drawing causal inferences. Data for depressive symptoms and some covariates (health behaviors, medication adherence) were self-reported, with known biases. Data on baseline ejection fraction are unavailable in REGARDS. Participants on antidepressants with prior or remote medical history of depression that has resolved at the time of baseline CESD-4 assessment and who did not report depressive symptoms were not distinguished from those without history of depression and not reporting depressive symptoms at baseline assessment. Participants with remote history of depression may potentially represent a different group than those who were never experiencing lifetime depressive symptoms, but REGARDS cohort can identify this group of participants. Baseline HF status was identified based on use of HF medications, but this approach showed a high negative predictive value.

The primary prevention of HF and reducing the risk of hospitalization for HF are one of the major challenges in the modern medicine. The possibility that depressive symptoms are an independent risk factor of incident HF hospitalization underscores the importance of screening and treatment of depressive symptoms. Our study results suggest an important opportunity for primary prevention of HFpEF by addressing depressive symptoms.

CONCLUSION

Depressive symptoms were independently associated with risk of incident hospitalization for HFpEF but not for HFrEF in the absence of prevalent coronary heart disease. Identifying patients with depressive symptoms in the ambulatory or inpatient setting via screening may offer an important opportunity to intervene early and improve patients' mental and cardiovascular health.

ARTICLE INFORMATION

Received June 8, 2021; accepted January 26, 2022.

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Acknowledgments

The authors thank the other investigators, the staff, and the participants of the REGARDS study for their valuable contributions. A full list of participating REGARDS investigators and institutions can be found at: https://www.uab.edu/soph/regardsstudy/.

Sources of Funding

This research project is supported by cooperative agreement U01 NS041588 co-funded by the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute on Aging (NIA), National Institutes of Health, Department of Health and Human Service. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NINDS or the NIA. Representatives of the NINDS were involved in the review of the manuscript but were not directly involved in the collection, management, analysis or interpretation of the data. Additional funding was provided by R01 HL08477, K24 HL111154 from the National Heart, Lung, and Blood Institute (NHLBI). Representatives from the NHLBI did not have any role in the design and conduct of the study, the collection, management, analysis, and interpretation of the data, or the preparation or approval of the manuscript. Dr Khodneva has been supported by the Agency For Healthcare Research And Quality (AHRQ) training grant to the University of Alabama at Birmingham (T32HS013852-16) and NHLBI T32 HL007457 "Mechanisms of Hypertension and Cardiovascular Diseases."

Disclosures

Dr Levitan has research funding from Amgen, have served on Amgen advisory boards, and as a scientific consultant for a research project funded by Novartis, all related to cardiovascular therapies including heart failure. The remaining authors have no disclosures to report.

Supplemental Material

Tables S1–S3

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SUPPLEMENTAL MATERIAL

Table S1. Association of depressive symptoms with incident heart failure hospitalization in REGARDS, (End of follow-up 12/31/2015). Full sequence of the Cox proportional hazards regression models.

Hazard ratios, 95% confidence intervals for CES-D score ≥ 4

	Overall HF HR,95%CI	**HFpEF (EF ≥50 %)** HR,95%CI	**HFrEF (EF < 50 %)** HR,95%CI
Total sample, N=26,268			
Crude	**1.37(1.12-1.68)**	**1.65(1.24-2.21)**	1.17(0.88-1.55)
Model 1[a]	**1.36(1.11-1.68)**	**1.58(1.17-2.13)**	1.21(0.90-1.61)
Model 2[b]	1.16(0.94-1.43)	**1.37(1.01-1.85)**	1.00(0.75-1.34)
Model 3[c]	1.07(0.86-1.33)	1.26(0.93-1.72)	0.92(0.69-1.24)
Model 4[d]	1.07(0.87-1.32)	1.27(0.93-1.72)	0.91(0.68-1.22)
Model 5 SHR, 95%CI	1.00(0.80-1.25)	1.21(0.88-1.67)	0.87(0.64-1.16)
Free of CHD at baseline, n=21,888			
Crude	**1.49(1.18-1.92)**	**1.98(1.40-2.84)**	1.15(0.79-1.66)
Model 1	**1.40(1.08-1.82)**	**1.72(1.19-2.47)**	1.14(0.78-1.67)
Model 2	**1.31(1.01-1.70)**	**1.62(1.12-2.33)**	1.06(0.72-1.55)
Model 3	1.23(0.95-1.60)	**1.53(1.06-2.22)**	1.00(0.68-1.47)
Model 4	1.24(0.96-1.62)	**1.54(1.06-2.23)**	1.00(0.69-1.47)
Model 5 SHR, 95%CI	1.17(0.89-1.53)	**1.48(1.00-2.18)**	0.95(0.65-1.40)
Baseline CHD, n=3,879*			
Crude	1.02(0.73-1.43)	1.01(0.60-1.70)	1.03(0.67-1.59
Model 1	1.08(0.76-1.53)	1.11(0.65-1.91)	1.05(0.67-1.66)
Model 2	0.97(0.68-1.38)	1.00(0.58-1.73)	0.85(0.53-1.36)
Model 3	0.87(0.61-1.23)	0.89(0.51-1.54)	0.85(0.53-1.36)
Model 4	0.86(0.60-1.22)	0.90(0.52-1.56)	0.81(0.50-1.29)
Model 5 SHR, 95%CI	0.79(0.54-1.15)	0.86(0.49-1.52)	0.78(0.48-1.27)

CES-D – CI-confidence interval, CHD-coronary heart disease, EF – ejection fraction, IR- incident rate, HR-hazards ratio, SHR- Sub-distribution Hazard Ratio

Model 1 adjusts for depressive symptoms, age, race, sex, region, education, income, marital status

Model 2 adjusts for model 1 plus systolic blood pressure, body mass index, use of any antihypertensive medication, diabetes, log-transformed urinary albumin to creatinine ratio, log-transformed high sensitivity C-reactive protein, baseline coronary artery disease for models in total sample, medication adherence, pack-years of smoking, alcohol use and physical inactivity

Model 3 adjusts for model 3 covariates plus having health insurance, primary care provider and self-reported physical health component score of SF-12 scale

Model 4 adjusts for Model 3 covariates and adds intervening non-fatal myocardial infarction on/before incident HF hospitalization as a time-varient covariate

Model 5 adjusts for Model 3 covariates and presents SHR for depressive symptoms when death from all causes is accounted for as a competing risk outcome.

Bolded p <.05

*501 missing baseline CHD status

Table S2 Association of depressive symptoms with incident heart failure hospitalization in REGARDS, (End of follow-up 12/31/2015). Sub-distribution Hazards Ratio for Depressive Symptoms associated with Heart Failure with preserved Ejection Fraction and Heart Failure with reduced Ejection Fraction, assessed together as competing risk.

	Total sample, N=26,268		Free of CHD, n=21,888		CHD at baseline n= 3,879	
Incident hospitalization, Heart Failure subtype	CES-D < 4 N=23547	CES-D > 4 N=2725	CES-D < 4 n=19724	CES-D ≥ 4 n=2164	CES-D < 4 n=3388	CES-D ≥ 4 n=491
		aSHR,95%CI		aSHR,95%CI		aSHR,95%CI
HFpEF	REF	1.28(0.93-1.77)	REF	**1.52(1.05-2.11)**	REF	0.95(0.55-1.68)
HFrEF	-	0.92(0.68-1.41)	-	0.99(0.68-1.45)	-	0.85(0.52-1.37)

CES-D – Center for epidemiological studies depression scale, CI-confidence interval, CHD-coronary heart disease, HFpEF –Heart failure with preserved ejection fraction, HFrEF–Heart failure with reduced ejection fraction, aSHR-Adjusted Sub-distribution Hazard Ratio.

All models estimates sub-distribution hazard ratio for incident HFpEF hospitalization in the presence of HFrEF as a competing risk and vice versa and adjusts for depressive symptoms, age, race, sex, region, education, income, marital status, systolic blood pressure, body mass index, use of any antihypertensive medication, diabetes, log-transformed urinary albumin to creatinine ratio, log-transformed high sensitivity C-reactive protein, baseline coronary artery disease (only for model in total sample), medication adherence, pack-years of smoking, alcohol use, physical inactivity, health insurance, primary care provider and self-reported physical health component score of SF-12 scale.

Table S3 Association of depressive symptoms as a continuous CES-D score with incident heart failure hospitalization in REGARDS, (End of follow-up 12/31/2015).

	Total sample, N-26,268	Free of CHD n=21,888	CHD at baseline n= 3,879
Incident hospitalization, Heart Failure subtype	CES-D Score (per 1 point increase in score)	CES-D Score (per 1 point increase in score)	CES-D Score (per 1 point increase in score)
	aHR,95%CI	aHR,95%CI	aHR,95%CI
Overal Heart Failure	1.03(0.99-1.06)	1.04(1.00-1.09)	1.00(0.95-1.06)
HFpEF	**1.06(1.01-1.10)**	**1.07(1.01-1.14)**	1.02(0.96-1.08)
HFrEF	1.00(0.96-1.05)	1.03(0.95-1.12)	0.99(0.92-1.07)

CES-D – Center for epidemiological studies depression scale (score range 0-12), CI-confidence interval, CHD-coronary heart disease, HFpEF–Heart failure with preserved ejection fraction, HFrEF–Heart failure with reduced ejection fraction, aHR- Adjusted Hazard Ratio.

All models adjust for depressive symptoms, age, race, sex, region, education, income, marital status, systolic blood pressure, body mass index, use of any antihypertensive medication, diabetes, log-transformed urinary albumin to creatinine ratio, log-transformed high sensitivity C-reactive protein, baseline coronary artery disease (only for models in total sample), medication adherence, pack-years of smoking, alcohol use, physical inactivity, health insurance, primary care provider and self-reported physical health component score of SF-12 scale.