ORIGINAL RESEARCH

Depressive Symptoms and Incident Heart Failure in the Jackson Heart Study: Differential Risk Among Black Men and Women

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BACKGROUND: Associations between depression, incident heart failure (HF), and mortality are well documented in predominately White samples. Yet, there are sparse data from racial minorities, including those who are women, and depression is underrecognized and undertreated in the Black population. Thus, we examined associations between baseline depressive symptoms, incident HF, and all-cause mortality across 10 years.

METHODS AND RESULTS: We included Jackson Heart Study (JHS) participants with no history of HF at baseline (n=2651; 63.9% women; median age, 53 years). Cox proportional hazards models tested if the risk of incident HF or mortality differed by clinically significant depressive symptoms at baseline (Center for Epidemiological Studies–Depression scores ≥16 versus <16). Models were conducted in the full sample and by sex, with hierarchical adjustment for demographics, HF risk factors, and lifestyle factors. Overall, 538 adults (20.3%) reported high depressive symptoms (71.0% were women), and there were 181 cases of HF (cumulative incidence, 0.06%). In the unadjusted model, individuals with high depressive symptoms had a 43% greater risk of HF (*P*=0.035). The association remained with demographic and HF risk factors but was attenuated by lifestyle factors. All-cause mortality was similar regardless of depressive symptoms. By sex, the unadjusted association between depressive symptoms and HF remained for women only (*P*=0.039). The fully adjusted model showed a 53% greater risk of HF for women with high depressive symptoms (*P*=0.043).

CONCLUSIONS: Among Black adults, there were sex-specific associations between depressive symptoms and incident HF, with greater risk among women. Sex-specific management of depression may be needed to improve cardiovascular outcomes.

Key Words: depression ■ heart failure ■ lifestyle ■ race ■ women

Heart failure (HF) affects an estimated 6 million people in the United States and is expected to increase in prevalence in the coming decade due to an aging population and an increase in risk factors for cardiovascular disease (CVD).[1] Black adults are more likely to develop HF compared with other racial or ethnic groups,[2] show a higher disease prevalence and incidence than patients who are White or Hispanic ethnicity,[1,3] and have a 50% greater likelihood of HF-related hospitalization than White, Hispanic, and Asian patients.[4]

Depression, another prevalent condition, may be an important risk factor for incident HF and related mortality.[5] Among patients with HF, elevated depressive symptoms are associated with greater functional impairment and symptom burden, poor self-care, worse quality of life, hospitalization, and death.[6,7] Black patients, in particular, are less likely to be diagnosed with a major depressive disorder or to receive treatment for depression, report higher levels of psychological distress, and experience greater functional impairment that is attributable to depression, compared with

CLINICAL PERSPECTIVE

What Is New?

- In this community-based cohort of Black men and women, high depressive symptoms conferred a 43% increase in the risk of incident heart failure (HF) over 10 years, but the association was attenuated in the model including lifestyle factors (smoking, obesity, and physical activity).
- Sex-stratified analyses showed that the effect of depressive symptoms on incident HF was specific to women, with high symptoms predicting a 53% greater risk of developing HF.
- Depressive symptoms were not related to all-cause mortality for the entire cohort or by sex.

What Are the Clinical Implications?

- Black women may be especially vulnerable to the adverse effects of depression on cardiovascular health.
- Sex-specific approaches to identify and manage depressive symptoms may be needed to improve cardiovascular outcomes.
- Addressing depressive symptoms among patients at a high risk of HF, or those with a HF diagnosis, may be most beneficial when also targeting lifestyle factors.

Nonstandard Abbreviations and Acronyms

aHR	adjusted hazard ratio
ARIC	Atherosclerosis Risk in Communities
CES-D	Center for Epidemiological Studies–Depression
JHS	Jackson Heart Study
LVIDD	left ventricular internal diameter during diastole
LVIDS	left ventricular internal diameter during systole

White patients.[8,9] These data raise important questions about how depression leads to incident HF and possibly worse health outcomes in Black patients, and whether comorbid conditions, such as diabetes and hypertension, may affect this relationship.

Associations between depressive symptoms, HF risk factors and symptoms, and related mortality also often differ by sex.[10,11] For example, women with HF are more likely to be depressed than men,[12] and depression has a greater impact on quality of life among women with HF.[13] These sex differences may be more profound among adults who are Black,[8,14] as Black women show worse symptoms of depression than Black men and have up to a 2-fold higher risk of lifetime major depression.[9,14] Significant associations between depression and incident CVD have already been described among Black women compared with men.[15–17] Understanding if there are sex-specific variations in the effect of depressive symptoms on incident HF among Black adults may have important implications for the primary prevention of HF in this vulnerable population.

The availability of long-term follow-up data in the JHS (Jackson Heart Study) provided an opportunity to examine the prospective associations between clinically significant depressive symptoms, incident HF, and all-cause mortality in a large, community-based cohort of Black men and women. We hypothesized that high baseline symptoms of depression would be associated with an increased risk of HF and all-cause mortality over 10 years. We also investigated the hypothesis that there are sex-specific effects of depressive symptoms on incident HF risk.

METHODS

Data Sources

The JHS is a single-site, community-based cohort study of CVD risk among Black adults. JHS data and study materials are available to other investigators for the purposes of reproducing the results or replicating these analyses by following the JHS publications, procedures, and data use agreements.[18] The original study cohort included individuals residing in the Jackson, MS, metropolitan area, and was designed to investigate risk factors for CVD. The cohort was composed of individuals aged 21 to 95 years, who were recruited from 4 groups: a random community sample of volunteers (30%), a commercially available list (Accudata Integrated Marketing) to aid random selection among Jackson residents (17%), participants in the Jackson site of the ARIC (Atherosclerosis Risk in Communities) cohort study (22%), and adult family members of ARIC study participants (31%).[19]

All participants completed a baseline examination between 2000 and 2004, which included the following: collection of a medical history and a physical examination, a survey of demographic and socioeconomic characteristics and lifestyle factors (eg, smoking status, height and weight, alcohol abuse, and level of physical activity), blood/urine analytes (eg, total cholesterol and estimated glomerular filtration rate [eGFR]), a CVD evaluation (eg, ECG and echocardiogram), and medications used. Deaths and nonfatal events were ascertained via annual telephone calls, review of death certificates, and abstraction of medical records for relevant *International Classification of Diseases,*

Ninth Revision, Clinical Modification (*ICD-9-CM*), and *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*), codes.[20] The JHS was approved by the Institutional Review Boards of the University of Mississippi Medical Center, Jackson State University, and Tougaloo College. All participants completed written informed consent.

Study Population

Overall, 5306 eligible JHS participants completed the baseline examination. The secondary analyses reported herein included participants who had completed at least 16 of 20 screening questions on the Center for Epidemiological Studies–Depression (CES-D) scale (n=3412). Self-reported disease and clinical measurement during the baseline examination were used to derive initial HF status, according to the modified Gothenburg criteria developed and validated in the ARIC study dataset.[21] Participants were excluded if they were deceased before January 1, 2005 (n=35), met criteria for HF with a modified Gothenburg score of ≥3 at baseline (n=249), were missing a baseline echocardiogram assessment (n=139), had a baseline left ventricular ejection fraction (LVEF) of ≤40% (n=19), or were missing HF hospitalization events at baseline (n=319). Altogether, complete data were available for 1305 participants. Following multiple imputation to address missing data (described below), the final analytic sample included 2651 participants (Figure 1).

Depressive Symptoms

The primary exposure was the presence or absence of clinically significant depressive symptoms based on the CES-D score at baseline.[22] The score is a sum of all 20 CES-D questions with a possible range of 0 to 60, which was then used to create a binary variable based on <16 and ≥16 to identify individuals at risk for clinical depression.[22,23] A higher CES-D score indicates a greater burden of depressive symptoms.

Outcome Ascertainment

The primary outcomes were HF hospitalization and all-cause mortality, both of which were time-varying. Time to hospitalization outcome classification began on January 1, 2005, when HF hospitalization surveillance began in the JHS cohort.[20] Time to death was calculated from the date of each baseline examination.[20] HF hospitalization and death were ascertained via direct patient queries during annual telephone follow-up and ongoing surveillance of hospitalizations, with subsequent transmission of hospital records and death certificates to a medical record abstraction unit for review. Computer-generated diagnoses, corroborated by physician adjudication, were used to classify HF hospitalizations.

Covariates

Covariates were selected a priori from the baseline examination, including demographic and socioeconomic characteristics (age, sex [a binary variable for men or women], education [college+ versus less than college], and individual income [upper-middle class/affluent versus lower-middle class/poor]), HF risk factors (hypertension, diabetes, coronary heart disease [CHD], eGFR, total cholesterol, and LVEF %), and lifestyle factors (smoking status, alcohol abuse, obesity, and physical activity).

Body mass index (BMI) was calculated as kg/m^2. Individuals were categorized as obese (BMI ≥30 kg/m^2) and non-obese (BMI <30 kg/m^2).

Baseline physical activity was categorized according to American Heart Association ideal cardiovascular health guidelines: poor physical activity: 0 minutes of moderate or vigorous physical activity per week; intermediate physical activity: <150 minutes of moderate physical activity, <75 minutes of vigorous physical activity, or <150 minutes of moderate and vigorous physical activity per week; and recommended physical activity: ≥150 minutes of moderate physical activity, ≥75 minutes of vigorous physical activity, or ≥150 minutes of moderate and vigorous physical activity per week.[24]

Smoking status was derived from a questionnaire. Participants were categorized as current smokers (self-report of having smoked >400 cigarettes in one's life and a positive response to the question, "Do you now smoke cigarettes?"), past smokers (smoked >400 cigarettes but quit at least 12 months ago), and never smokers (negative responses to both questions).

Hypertension was considered present if a participant had systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥80 mm Hg, or if use of blood pressure–lowering medications was reported at baseline.

Diabetes was considered present if the hemoglobin A1C was ≥6.5%, if a fasting plasma glucose was ≥126 mg/dL, or if use of diabetes medications was reported.

Coronary heart disease (*CHD*) was considered present at baseline if the participant reported a history of CHD, prior abnormal stress test result, coronary bypass graft surgery, or coronary angioplasty, or if there was ECG evidence of a prior myocardial infarction.

Estimated glomerular filtration rate (*eGFR*) was calculated from serum concentrations of creatinine and cystatin C measured at baseline using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation.[25]

Total cholesterol was evaluated based on fasting blood samples, which were assayed using the cholesterol oxidase method supplied by Boehringer
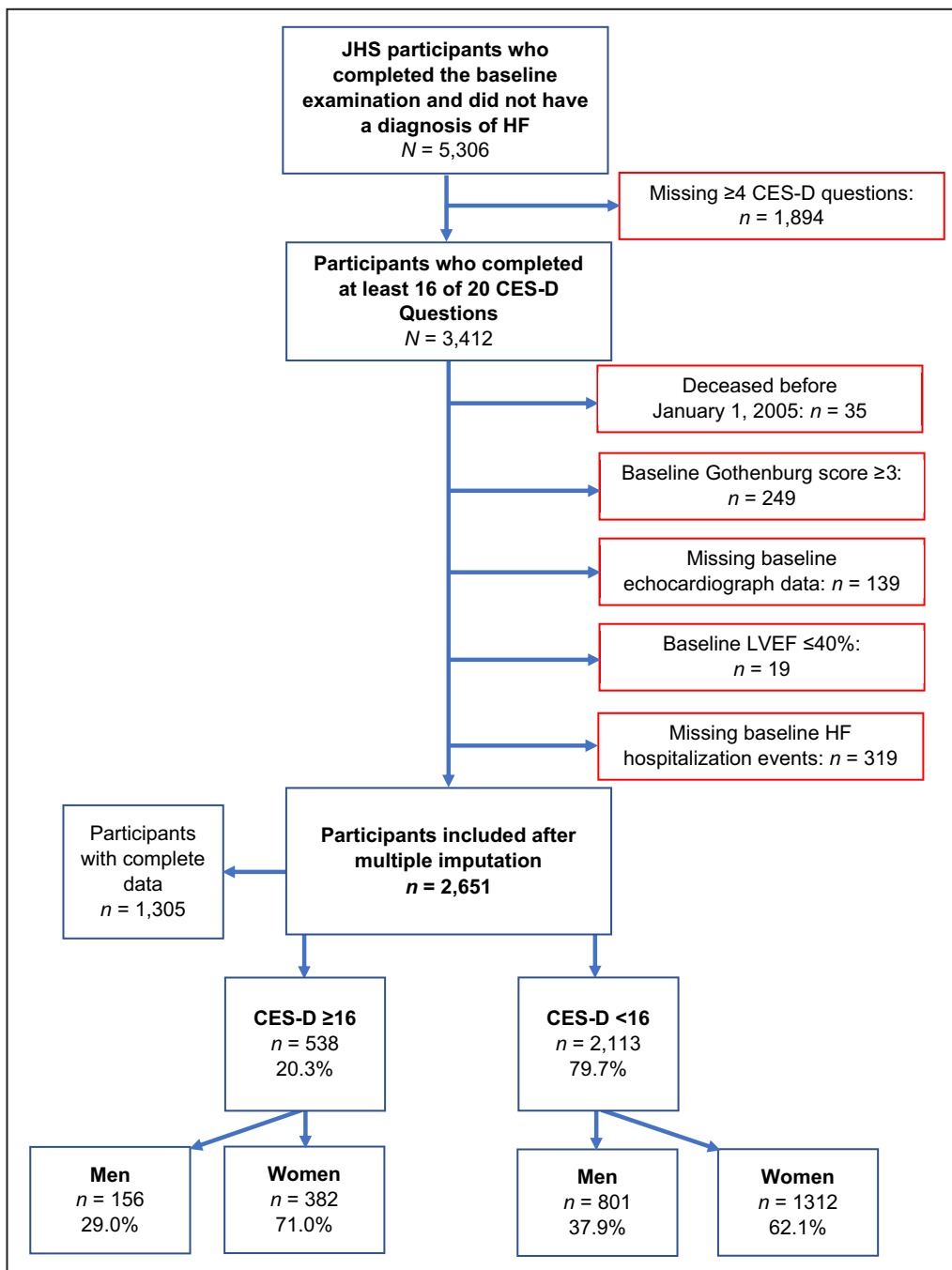
Figure 1. Flowchart of eligibility criteria for participants from the JHS (Jackson Heart Study).
CES-D indicates Center for Epidemiological Studies–Depression; HF, heart failure; and LVEF, left ventricular ejection fraction.

Mannheim Diagnostics on a Roche COBAS Fara analyzer (Indianapolis, IN).

Left ventricular ejection fraction (LVEF) was derived from echocardiograms conducted during the baseline examination by certified ultrasonography technicians (Sonos 4500 echocardiograph; Hewlett Packard, Andover, MA), according to recommendations from the American Society of Echocardiography.[26] LVEF was derived semiquantitatively using visual assessment of the left ventricular apex and a modified Quinones formula: $LVEF=(LVIDD^2-LVIDS^2)/LVIDD^2\times100\%$, where LVIDD represents left ventricular internal diameter during diastole and LVIDS represents left ventricular internal diameter during systole.

Statistical Analysis

Descriptive statistics (mean/SD, median/interquartile range [IQR], and frequency/percentage) were used to display patient characteristics for the overall sample and for those who did and did not meet study-defined criteria for depression. To test for differences between these defined groups, χ^2 tests were used for categorical variables and Student t tests or Kruskal-Wallis tests were used for normally and non-normally distributed continuous variables. A high proportion of participants did not complete the CES-D ($\approx$40%), and thus, baseline characteristics are first provided for those who completed the measure, followed by comparisons of those with and without complete CES-D data. Multiple imputation by chained equations was performed to account for uncertainty caused by missing values in covariates. Missingness was assumed to be random. Guided by the percentage of missingness, one imputed data set was needed for each percentage of maximal missingness in a variable, resulting in the creation of 50 imputed data sets with 20 iterations, and a trace plot was used to determine the minimal number of iterations required to reach a stable posterior distribution. Demographics, HF risk factors, lifestyle factors, hospitalization attributable to HF, and mortality were included, using a predictive mean matching method for continuous variables and a binary logistic regression model or discriminant methods for categorical variables. After multiple imputation, results were pooled with Rubin's rules.

Time of follow-up was defined as the length of time from the date of the first echocardiogram until the date of death from any cause/date of HF hospitalization, or the date of last follow-up (by December 31, 2011). With the presence of competing risk, conventional methods, such as a Kaplan-Meier curve (1–Kaplan-Meier) will yield a biased estimate of probability.[27] Therefore, the cumulative incidence of events was assessed by the presence of clinically significant depressive symptoms at baseline, and group differences were assessed using Gray's test. The cause-specific proportional hazards model is still a valid modeling approach to evaluate the impact of multiple risk factors on outcomes of interest in this situation, and interpretation of the results is limited to the association of risk factors and cause-specific hazards instead of probabilities.[28] Therefore, Cox proportional hazards models were used to estimate univariate- and covariate-adjusted associations between CES-D scores and outcomes of interest.

The following models were created in a hierarchical order: (1) in Model 1, depressive symptoms based on the CES-D were the only independent variable; (2) in Model 2, sociodemographic variables (age, sex, education, and income) were added; (3) in Model 3, HF risk factors (hypertension, diabetes, CHD, eGFR, total cholesterol, and LVEF %) were added; and (4) in Model 4, lifestyle factors (alcohol abuse, smoking status, obesity, and physical activity) were added. These models were also built separately for men and women. In all models, the proportional hazards assumption was tested by including a variable representing the interaction between CES-D and the log of survival time. There was no evidence that the proportional hazards assumption was violated in any model. For any significant results, sensitivity analyses were also conducted including only participants with complete CES-D data. A threshold of $P<0.05$ (2-tailed) and 95% CIs were used to establish statistical significance. All analyses were performed using SAS software, Version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

The final sample included 2651 individuals (63.9% women), who had a median age of 53 years. Those aged 50 to 59 years comprised the largest age group (26.5%). In the final sample, 538 individuals (20.3%) met criteria for clinically elevated depressive symptoms at baseline (Table 1). People with high depressive symptoms were younger, more likely to be women, less educated and had a lower income, were less physically active, and were significantly more likely to endorse current or previous smoking than those not meeting depression criteria (a CES-D score of ≥16 versus <16). When examining HF risk factors and related medications, individuals who reported high depressive symptoms were also more likely to have a history of CHD, a higher mean eGFR at baseline, and lower total cholesterol compared with those with low depressive symptoms. Table S1 provides data about those with and without CES-D data. Those without these data were 5 years older, had less education and a lower income, and they demonstrated a significantly higher prevalence of negative lifestyle factors (eg, alcohol use and smoking) and HF risk factors (eg, hypertension and diabetes).

Across 10 years, the cumulative incidence of HF was 0.06% (95% CI, 0.05%–0.07%; n=181 cases) and the cumulative all-cause mortality was 0.05% (95% CI, 0.04%–0.05%; n=293 cases). The cumulative incidence of HF was significantly greater among those with high versus low depressive symptoms (0.07 [95% CI, 0.05–0.09] versus 0.05 [95% CI, 0.04–0.06]; P=0.030). However, there was no difference in the cumulative incidence of all-cause mortality between those with high versus low depressive symptoms (0.04 [95% CI, 0.03–0.06] versus 0.05 [95% CI, 0.04–0.06]; P=0.73; Figures 2A and 2B).

Table 1. Baseline Characteristics of the Study Population Overall, and by CES-D Depressive Symptoms

Variable	CES-D depressive symptoms		Total (N=2651)	P value
	High (≥16) (n=538)	Low (<16) (n=2113)		
Demographics				
Age, median (IQR), y	52 (43–63)	54 (45–63)	53 (44–63)	0.015
21–29	18 (3.3)	56 (2.7)	74 (2.8)	0.16
30–39	348 (13.1)	267 (15.1)	274 (10.3)	
40–49	153 (28.4)	523 (24.8)	676 (25.5)	
50–59	136 (25.3)	566 (26.8)	702 (26.5)	
60–69	110 (20.4)	547 (25.9)	657 (24.8)	
≤70	058 (10.8)	210 (9.9)	268 (10.1)	
Sex				
Men	156 (29.0)	801 (37.9)	957 (36.1)	<0.001
Women	382 (71.0)	1312 (62.1)	1694 (63.9)	
Education				
Less than high school	90 (16.7)	229 (10.8)	319 (12.0)	<0.001
High school/GED	138 (25.7)	349 (16.5)	487 (18.4)	
College or trade school	310 (57.6)	1531 (72.5)	1841 (69.4)	
Missing	0	4 (0.2)	4 (0.2)	
Income				
Poor	107 (19.5)	160 (7.6)	267 (10.1)	<0.001
Lower-middle	120 (22.3)	359 (17.0)	479 (18.1)	
Upper-middle	140 (26.0)	585 (27.7)	725 (27.3)	
Affluent	89 (16.5)	731 (34.6)	820 (30.9)	
Missing	82 (15.2)	278 (13.2)	360 (13.6)	
Lifestyle factors				
Alcohol abuse				
No	287 (53.3)	1109 (52.5)	1396 (52.7)	0.78
Yes	251 (46.7)	997 (47.2)	1248 (47.1)	
Missing	0	7 (0.3)	7 (0.3)	
Smoking status				
Current	90 (16.7)	184 (8.7)	274 (10.3)	<0.001
Past	8 (1.5)	25 (1.2)	33 (1.2)	
Never	431 (80.1)	1868 (88.4)	2299 (86.7)	
Missing	9 (1.7)	36 (1.7)	45 (1.7)	
BMI, median (IQR), kg/m^2	30.8 (26.8–35.7)	30.2 (26.8–34.6)	30.3 (26.8–34.9)	0.09
Non-obese (<30 kg/m^2)	236 (43.9)	1025 (48.5)	1261 (47.6)	0.05
Obese (≥30 kg/m^2)	302 (56.1)	1085 (51.3)	1387 (52.3)	
Missing	0	3 (0.1)	3 (0.1)	
Physical activity				
Poor	289 (53.7)	898 (42.5)	1187 (44.8)	<0.001
Intermediate	165 (30.7)	730 (34.5)	895 (33.7)	
Recommended	84 (15.6)	484 (22.9)	568 (21.4)	
Missing	0	1 (0.1)	1 (0.1)	
Heart failure risk factors				
Heart rate, bpm				
Mean (SD)	64.4 (10.1)	63.7 (10.0)	63.8 (10.0)	0.14
Missing		1 (0.1)	1 (0.1)	

(Continued)

Table 1. Continued

| Variable | CES-D depressive symptoms | | | P value |
	High (≥16) (n=538)	Low (<16) (n=2113)	Total (N=2651)	
Systolic blood pressure, mm Hg				
Mean (SD)	126.2 (16.0)	125.9 (15.5)	125.9 (15.6)	0.72
Missing	5 (0.9)	4 (0.2)	9 (0.3)	
Hypertension				
No	257 (47.8)	1045 (49.5)	1302 (49.1)	0.48
Yes	281 (52.2)	1068 (50.5)	1349 (50.9)	
Diabetes				
No	409 (76.0)	1688 (79.9)	2097 (79.1)	0.08
Yes	122 (22.7)	411 (19.5)	533 (20.1)	
Missing	7 (1.3)	14 (0.7)	21 (0.8)	
CHD				
No	505 (93.9)	2045 (96.8)	2550 (96.2)	0.002
Yes	33 (6.1)	68 (3.2)	101 (3.8)	
eGFR, mL/min per 1.73 m²				
Mean (SD)	87.6 (19.0)	85.6 (17.5)	86.0 (17.9)	0.029
Missing	10 (1.9)	22 (1.0)	32 (1.2)	
Total cholesterol, mg/dL				
Mean (SD)	196.0 (38.5)	200.5 (38.8)	199.6 (38.8)	0.022
Missing	44 (8.2)	140 (6.6)	184 (6.9)	
LVEF, %				
Mean (SD)	62.3 (6.5)	62.1 (6.6)	62.1 (6.6)	0.50

Data are given as number (percentage), unless otherwise indicated. BMI indicates body mass index; bpm, beats per minute; CES-D, Center for Epidemiological Studies–Depression scale; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; GED, general equivalency diploma; IQR, interquartile range; LVEF, left ventricular ejection fraction; and SD, standard deviation.

Incident HF and All-Cause Mortality

Table 2 shows factors that were independently associated with incident HF. In the unadjusted model (ie, Model 1), high depressive symptoms were associated with a 43% increase in incident HF (hazard ratio [HR], 1.43; 95% CI, 1.03–1.98; $P=0.035$). This association remained significant after adjusting for demographics (adjusted HR [aHR], 1.41; 95% CI, 1.04–2.05; $P=0.027$; Model 2) and established HF risk factors (aHR, 1.44; 95% CI, 1.02–2.02; $P=0.036$; Model 3), but was no longer significant after adjusting for lifestyle factors (aHR, 1.23; 95% CI, 0.84–1.81; $P=0.28$; Model 4). In this fully adjusted model, age, CHD, and eGFR remained associated with a greater risk of incident HF, with diabetes emerging as the strongest predictor (aHR, 2.31; 95% CI, 1.65–3.23; $P<0.001$), whereas never smoking and physical activity were protective factors. Finally, in the unadjusted model, depressive symptoms were not associated with all-cause mortality (HR, 1.04; 95% CI, 0.81–1.32; $P=0.77$; Table S2). Despite a lack of power to appropriately test interaction terms and a focus on analyses by sex, in an exploratory analysis the CES-D×Sex interaction was also tested, but results were nonsignificant for HF hospitalization and all-cause mortality ($P=0.62$ and 0.63).

Subgroup Analyses by Sex

Across the 10-year time frame, there was no difference in the cumulative incidence of HF or all-cause mortality between men and women (Figures 3A and 3B). On the basis of the unadjusted model, high depressive symptoms were not associated with incident HF (HR, 1.26; 95% CI, 0.69–2.32; $P=0.45$) or all-cause mortality (HR, 0.96; 95% CI, 0.62–1.48; $P=0.86$) for men (Tables S3 and S4). For women, high depressive symptoms were associated with incident HF in the unadjusted model (HR, 1.52; 95% CI, 1.02–2.26; $P=0.039$; Table 3, Model 1), an association which remained significant in the fully adjusted model that included demographics, HF risk factors, and lifestyle factors (aHR, 1.53; 95% CI, 1.01–2.30; $P=0.043$; Model 4). As observed with the full sample, the final model of women also showed significant effects of age, diabetes, eGFR, and smoking on incident HF. As observed for men, in the unadjusted model, depressive symptoms were not associated with all-cause mortality among women (HR, 1.10; 95% CI, 0.82–1.47; $P=0.53$; Table S5).
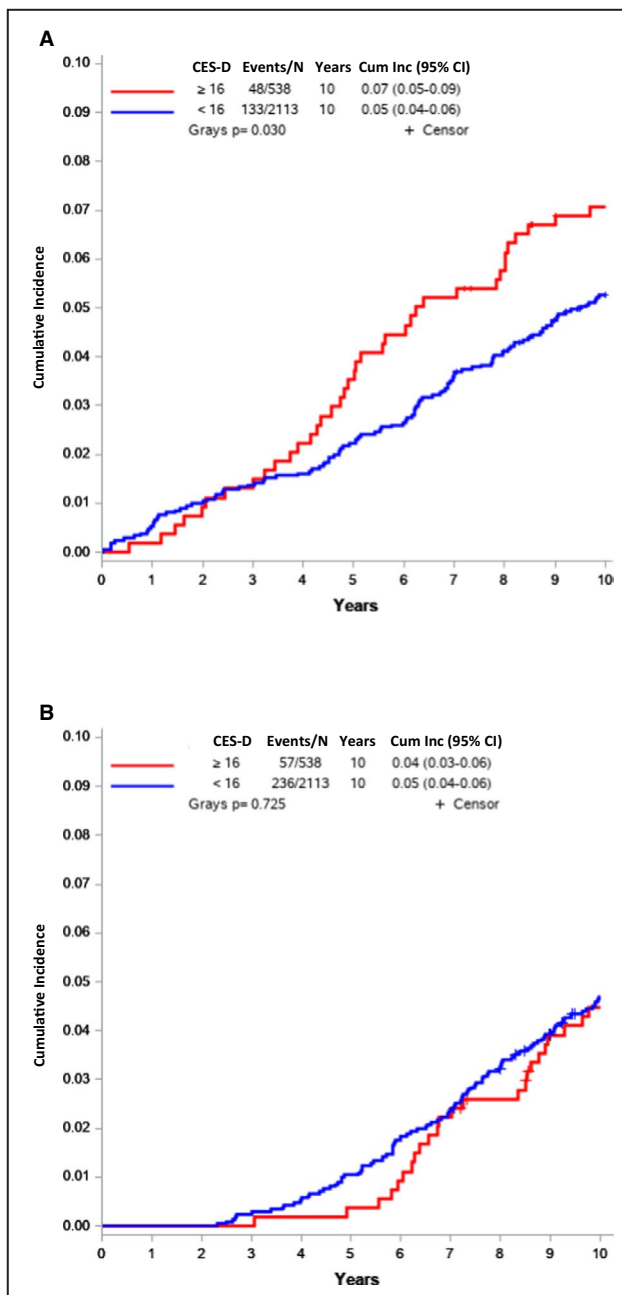
Figure 2. The unadjusted cumulative incidence (cum inc) of heart failure (HF) hospitalization or incident HF (A) and all-cause mortality (B), according to high and low depressive symptoms on the Center for Epidemiological Studies–Depression (CES-D) scale.

Sensitivity Analyses

Sensitivity analyses were conducted to examine the observed associations between depressive symptoms and incident HF hospitalization among only those with complete data, prior to imputation. For the entire sample, both the unadjusted and adjusted associations between depressive symptoms and risk

of HF hospitalization were not significant (Table S6). For women, in the unadjusted model, high depressive symptoms were not significantly associated with HF (HR, 1.70; 95% CI, 0.92–3.13; P=0.09; Table S7). However, in the final, adjusted model, high depressive symptoms were associated with a significantly greater risk of HF for women (aHR, 1.94; 95% CI, 1.01–3.74; P=0.047; Model 4).

DISCUSSION

To our knowledge, the current analysis is the first to examine the prospective associations between clinically significant depressive symptoms, incident HF, and all-cause mortality over a 10-year period in a large, community-based cohort of Black men and women. There are several notable findings. First, 1 in 5 participants reported clinically elevated depressive symptoms at the study baseline. These individuals were younger, had less years of education, a lower income, and were more likely to smoke, to be obese, and to be inactive, and to have a diagnosis of CHD compared with those without clinically significant depressive symptoms. Second, depressive symptoms contributed to a 43% increase in the risk for incident HF in unadjusted models, but the strength of this association was attenuated in fully adjusted models that included lifestyle factors. Third, analyses by sex showed that the effect of depression on incident HF was specific to women, with high depressive symptoms predicting a 53% greater risk of HF. Depressive symptoms were not significantly related to all-cause mortality for the entire sample or by sex, which is concordant with other data from Black adults.[29]

Our finding that greater depressive symptoms only conferred HF risk among Black women aligns with previous evidence highlighting women's unique vulnerability to HF. For example, hypertension is shown to triple the risk of HF in women, but only doubles HF risk in men.[30] In other work, depression was only associated with a risk of HF among women, although that sample was composed of mostly White individuals and was about 20 years older than the age of the JHS sample.[17] HF presentation also differs by sex, as women are more prone to developing HF with preserved ejection fraction.[1] Women, particularly women of color, remain underrepresented in clinical trials.[31] This lack of representation is concerning given observations of sex-specific HF correlates, particularly among Black women,[31] which may necessitate distinct risk mitigation strategies. Although age-specific analyses were not an objective of this investigation, HF-related mortality may be particularly high for younger patients who are Black compared with those who are older.[32] Thus,

Table 2. Multivariate Models of CES-D Depressive Symptoms and Risk of Incident HF

Variable	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	P value	aHR (95% CI)	P value	aHR (95% CI)	P value	aHR (95% CI)	P value
CES-D depressive symptoms*	1.43 (1.03–1.98)	0.035	1.41 (1.04–2.05)	0.027	1.44 (1.02–2.02)	0.036	1.23 (0.84–1.81)	0.28
Demographics								
Age			1.08 (1.07–1.10)	<0.001	1.07 (1.05–1.09)	<0.001	1.07 (1.05–1.09)	<0.001
Men			1.27 (0.94–1.73)	0.12	1.29 (0.92–1.73)	0.14	1.35 (0.96–1.91)	0.09
Education			0.81 (0.58–1.14)	0.22	0.85 (0.61–1.20)	0.36	0.97 (0.67–1.42)	0.89
Income			0.90 (0.63–1.28)	0.56	0.91 (0.64–1.30)	0.61	0.95 (0.60–1.22)	0.38
HF risk factors								
Hypertension					1.25 (0.97–1.55)	0.21	1.24 (0.85–1.80)	0.26
Diabetes					2.23 (1.64–3.02)	<0.001	2.31 (1.65–3.23)	<0.001
CHD					1.55 (0.94–2.56)	0.09	2.02 (1.20–3.40)	0.009
eGFR					0.99 (0.98–1.00)	0.12	0.99 (0.98–1.00)	0.019
Total cholesterol					1.00 (1.00–1.01)	0.35	1.00 (1.00–1.01)	0.41
LVEF					0.98 (0.96–1.00)	0.048	0.98 (0.95–1.00)	0.07
Lifestyle factors								
Alcohol abuse							0.85 (0.60–1.22)	0.38
Former smoker							0.97 (0.22–4.22)	0.97
Never smoker							0.58 (0.36–0.96)	0.033
Obesity							0.72 (0.46–1.14)	0.16
Physical activity							0.71 (0.51–0.98)	0.038

HRs and 95% CIs are given. aHR indicates adjusted HR; CES-D, Center for Epidemiological Studies–Depression; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; and LVEF, left ventricular ejection fraction.

*High CES-D depressive symptoms (≥16) vs low CES-D depressive symptoms (<16).
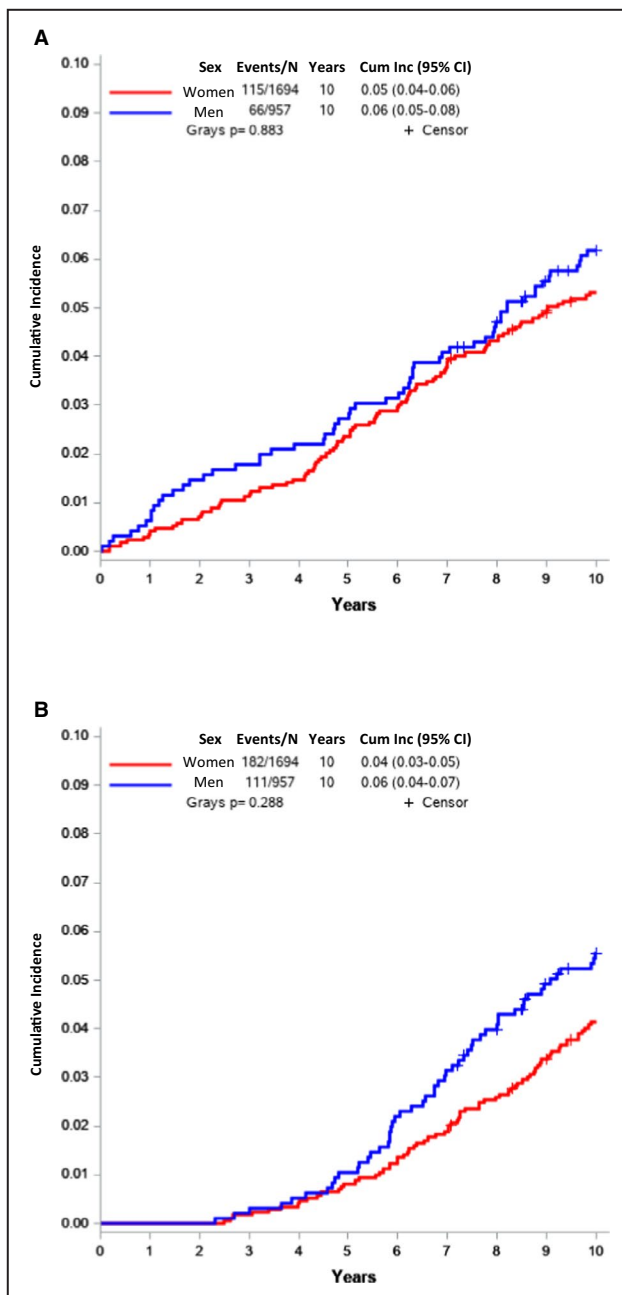
A

B

Figure 3. The unadjusted cumulative incidence (cum inc) of heart failure (HF) hospitalization or incident HF (A) and all-cause mortality (B) for men and women separately.

subgroup analyses of depression and risk of HF by age represent a valuable direction for future inquiry.

To understand the associations between depression and HF in Black women, one must consider the pathophysiological mechanisms that differentiate depression among women compared with men. The higher prevalence of depression among women is well documented.[11,33–37] Systemic differences that drive this distinction may involve sex hormones; long-term

elevations in sympathetic nervous system, inflammatory cytokine, and/or hypothalamic-pituitary-adrenal axis activity; and alterations in neurotrophic or metabolic factors, among others.[36] Chronic depressive symptoms have been associated with greater vulnerability to developing left ventricular dysfunction, a precursor to HF, with stronger effects observed for women.[38] These physiological processes might be particularly active among women of color, who show more persistent symptoms of depression than women who are White[39] or Black men.[9,14] Although JHS data do not provide for a powered testing of these pathways, identifying the relevant mechanisms is central to understanding cardiovascular risk in different racial groups.

Based on these data, screening for depression among Black adults, especially those with HF, may be warranted.[40] A meta-analysis revealed that 34% of patients with HF report clinically significant depressive symptoms on questionnaires like the CES-D scale, with up to a 44% prevalence rate among minorities.[41] Yet, evidence to date has not established that depression screening is beneficial for patients with HF, or definitively, that these patients with clinically significant depressive symptoms may benefit from treatment for depression. In small-sample, randomized clinical trials, cognitive behavioral therapy has been associated with improved depressive symptoms, self-care, and quality of life for patients with HF.[42] In addition, a patient preference (medication versus psychotherapy), stepped-care treatment approach for depression after acute coronary syndrome was shown in 2 small trials to be associated with reduced depression and lower cardiac recurrent event rate at the end of treatment,[43,44] an effect on recurrent events that was lost at 1-year follow-up,[45] and there is evidence that women and Black adults prefer psychotherapy to antidepressant medication.[46] As depressive symptoms show greater chronicity among Black adults,[8] the testing of algorithms for frequent screening and longer-term depression management may offer guidance for best strategies to reduce depression and improve HF outcomes.[47]

As previously reported for diverse samples, and for samples of Black individuals exclusively,[48,49] medical and lifestyle factors also predicted incident HF. For example, diagnoses of diabetes and CHD were each associated with a 2-fold greater risk of HF. Among the lifestyle risk factors for HF, physical activity and "never smoking" were significant protective factors, associated with 71% and 58% lower risks, respectively. Yet, there was no significant effect of obesity on incident HF, suggesting that physical activity, rather than depressive symptoms or body mass index, may be a more important prognostic factor for HF among Black adults.[50] Clinical efforts to manage depressive symptoms among patients at a high risk of HF, or those

Table 3. Multivariate Models of CES-D Depressive Symptoms and Risk of Incident HF Among Women

Variable	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	P value	aHR (95% CI)	P value	aHR (95% CI)	P value	aHR (95% CI)	P value
CES-D depressive symptoms*	1.52 (1.02–2.26)	0.039	1.56 (1.04–2.33)	0.031	1.57 (1.04–2.36)	0.030	1.53 (1.01–2.30)	0.043
Demographics								
Age			1.08 (1.06–1.10)	<0.001	1.07 (1.04–1.09)	<0.001	1.07 (1.05–1.09)	<0.001
Education			0.71 (0.46–1.08)	0.11	0.73 (0.47–1.12)	0.14	0.97 (0.67–1.42)	0.89
Income			1.00 (0.64–1.55)	0.99	1.09 (0.69–1.70)	0.72	0.95 (0.60–1.22)	0.38
HF risk factors								
Hypertension					1.16 (0.74–1.82)	0.52	1.15 (0.73–1.81)	0.55
Diabetes					2.46 (1.67–3.61)	<0.001	2.46 (1.66–3.63)	<0.001
CHD					1.22 (0.60–2.46)	0.58	1.12 (0.55–2.28)	0.76
eGFR					0.99 (0.98–1.00)	0.034	0.99 (0.98–1.00)	0.034
Total cholesterol					1.00 (1.00–1.01)	0.37	1.00 (1.00–1.01)	0.36
LVEF					0.98 (0.95–1.01)	0.13	0.98 (0.95–1.00)	0.10
Lifestyle factors								
Alcohol abuse							0.80 (0.51–1.25)	0.33
Former smoker							2.61 (0.68–9.96)	0.16
Never smoker							0.50 (0.27–0.91)	0.024
Obesity							1.03 (0.69–1.52)	0.90
Physical activity							0.79 (0.54–1.17)	0.24

HRs and 95% CIs are given. aHR indicates adjusted HR; CES-D, Center for Epidemiological Studies–Depression; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; and LVEF, left ventricular ejection fraction.

*High depressive symptoms on the CES-D (≥16) vs low depressive symptoms (<16).

with an HF diagnosis, may yield the greatest benefit from dually addressing lifestyle factors, such as encouraging physical activity and smoking cessation, which were also significant predictors of HF in earlier analyses.[32,51]

There are several limitations to our investigation and the JHS data. First, the CES-D scale was designed to measure the current level of depressive symptoms but does not sufficiently capture the necessary features required for a diagnosis of major depression disorder.[22,23] Relatedly, the analyses included baseline symptoms of depression and did not account for change in depressive symptoms over time. Second, although symptoms of depression were assessed with the CES-D scale, a high percentage of JHS participants did not complete this assessment (≈40%), and there were notable differences between participants with and without CES-D scale data. JHS participants who were excluded on the basis of missing CES-D scale data were distinct, both socioeconomically and in terms of their health, from those who were included in the present analyses. Thus, results from the analytic cohort cannot be extrapolated to those who were excluded. These missing CES-D scale data may represent patient reluctance to disclose mental health information because of concerns about cultural stigma.[52] Third, the size of the CIs for the effects of high depressive symptoms, for the entire sample and among women alone, are somewhat wide. This statistical variability may limit our ability to draw conclusions about the potential effect of depression on risk for HF. Fourth, data about the effect of treatment for depression (eg, antidepressant medications and psychotherapy) on the relationship between depression and HF, as well as the percentages of adults who developed different subtypes of HF, were unavailable for this analysis. Fifth, we cannot discount the possibility that some HF diagnoses, hospitalizations, and deaths may have been missed or misclassified, which could alter these findings. Last, the socioeconomic status of the JHS cohort is higher than that of Black adults nationwide, and the sample was limited to the "greater" Jackson, MS, area. Therefore, findings may not reflect the health of all Black men or women in the general US population and merit replication. Finally, despite adjustment for multiple time-varying covariates, residual confounding cannot be ruled out.

To conclude, in a sample of Black adults, high depressive symptoms were associated with risk of incident HF, which persisted after multivariable adjustment for clinical risk factors, but was eliminated after controlling for lifestyle factors. Further investigation revealed that the effect of greater depressive symptoms on HF was specific to Black women only. Future work is merited concerning changes in the sex-specific burden of depression over time and testing of algorithms for assessing and monitoring depression status, and for treating depression, as potential strategies to mitigate the associated risk of HF among Black men and women.

ARTICLE INFORMATION

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Acknowledgments

Sources of Funding

Disclosures

Supplemental Material

Tables S1–S7

REFERENCES

1. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Cheng S, Delling FN, et al. Heart disease and stroke statistics—2021 update: a report from the American Heart Association. *Circulation*. 2021;143:e254–e743. doi: 10.1161/CIR.0000000000000950

2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017;136:e137–e161. doi: 10.1161/CIR.0000000000000509

3. Bahrami H, Kronmal R, Bluemke DA, Olson J, Shea S, Liu K, Burke GL, Lima JA. Differences in the incidence of congestive heart failure by ethnicity: the multi-ethnic study of atherosclerosis. *Arch Intern Med*. 2008;168:2138–2145. doi: 10.1001/archinte.168.19.2138

4. Brown DW, Haldeman GA, Croft JB, Giles WH, Mensah GA. Racial or ethnic differences in hospitalization for heart failure among elderly adults: Medicare, 1990 to 2000. *Am Heart J*. 2005;150:448–454. doi: 10.1016/j.ahj.2004.11.010

5. Celano CM, Villegas AC, Albanese AM, Gaggin HK, Huffman JC. Depression and anxiety in heart failure: a review. *Harv Rev Psychiatry*. 2018;26:175. doi: 10.1097/HRP.0000000000000162

6. Graven LJ, Grant JS, Vance DE, Pryor ER, Grubbs L, Karioth S. Predicting depressive symptoms and self-care in patients with heart failure. *Am J Health Behavior*. 2015;39:77–87. doi: 10.5993/AJHB.39.1.9

7. Sokoreli I, de Vries JJG, Pauws SC, Steyerberg EW. Depression and anxiety as predictors of mortality among heart failure patients: systematic review and meta-analysis. *Heart Fail Rev*. 2016;21:49–63. doi: 10.1007/s10741-015-9517-4

8. Barnes DM, Bates LM. Do racial patterns in psychological distress shed light on the Black-White depression paradox? A systematic review. *Soc Psychiatry Psychiatr Epidemiol*. 2017;52:913–928. doi: 10.1007/s00127-017-1394-9

9. Tobin CST. Distinguishing distress from disorder: black-white patterns in the determinants of and links between depressive symptoms and major depression. *J Affect Disord*. 2020;279:510–517. doi: 10.1016/j.jad.2020.10.035

10. Bryant KB, Jannat-Khah DP, Cornelius T, Khodneva Y, Richman J, Fleck EM, Torres-Deas LM, Safford MM, Moise N. Time-varying depressive symptoms and cardiovascular and all-cause mortality: does the risk vary by age or sex? *J Am Heart Assoc*. 2020;9:e016661. doi: 10.1161/JAHA.120.016661

11. Kubicki DM, Xu M, Akwo EA, Dixon D, Muñoz D, Blot WJ, Wang TJ, Lipworth L, Gupta DK. Race and sex differences in modifiable risk factors and incident heart failure. *JACC Heart Fail*. 2020;8:122–130. doi: 10.1016/j.jchf.2019.11.001

12. Gottlieb SS, Khatta M, Friedmann E, Einbinder L, Katzen S, Baker B, Marshall J, Minshall S, Robinson S, Fisher ML, et al. The influence of age, gender, and race on the prevalence of depression in heart failure patients. *J Am Coll Cardiol*. 2004;43:1542–1549. doi: 10.1016/j.jacc.2003.10.064

13. Lesman-Leegte I, Jaarsma T, Coyne JC, Hillege HL, Van Veldhuisen DJ, Sanderman R. Quality of life and depressive symptoms in the elderly: a comparison between patients with heart failure and age- and gender-matched community controls. *J Card Fail*. 2009;15:17–23. doi: 10.1016/j.cardfail.2008.09.006

14. Sims M, Glover LSM, Gebreab SY, Spruill TM. Cumulative psychosocial factors are associated with cardiovascular disease risk factors and management among African Americans in the Jackson Heart Study. *BMC Public Health*. 2020;20:1–11. doi: 10.1186/s12889-020-08573-0

15. Lewis TT, Guo H, Lunos S, Mendes de Leon CF, Skarupski KA, Evans DA, Everson-Rose SA. Depressive symptoms and cardiovascular mortality in older black and white adults: evidence for a differential association by race. *Circ Cardiovasc Qual Outcomes*. 2011;4:293–299. doi: 10.1161/CIRCOUTCOMES.110.957548

16. Williams DR, Haile R, González HM, Neighbors H, Baser R, Jackson JS. The mental health of Black Caribbean immigrants: results from the National Survey of American Life. *Am J Public Health*. 2007;97:52–59. doi: 10.2105/AJPH.2006.088211

17. Williams SA, Kasl SV, Heiat A, Abramson JL, Krumholz HM, Vaccarino V. Depression and risk of heart failure among the elderly: a prospective community-based study. *Psychosom Med*. 2002;64:6–12. doi: 10.1097/00006842-200201000-00002

18. Jackson Heart Study. Data access [internet]. 2015. Available at: https://www.jacksonheartstudy.org/Research/Study-Data/Data-Access. Accessed November 16, 2021.

19. Taylor HA Jr, Wilson JG, Jones DW, Sarpong DF, Srinivasan A, Garrison RJ, Nelson C, Wyatt SB. Toward resolution of cardiovascular health disparities in African Americans: design and methods of the Jackson Heart Study. *Ethn Dis*. 2005;15:S6-4-17.

20. Keku E, Rosamond W, Taylor HA Jr, Garrison R, Wyatt SB, Richard M, Jenkins B, Reeves L, Sarpong D. Cardiovascular disease event classification in the Jackson Heart Study: methods and procedures. *Ethn Dis*. 2005;15:S6–S62.

21. Rosamond WD, Chang PP, Baggett C, Johnson A, Bertoni AG, Shahar E, Deswal A, Heiss G, Chambless LE. Classification of heart failure in the atherosclerosis risk in communities (ARIC) study: a comparison of diagnostic criteria. *Circ Heart Fail*. 2012;5:152–159. doi: 10.1161/CIRCHEARTFAILURE.111.963199

22. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Applied Psychol Measurement*. 1977;1:385–401. doi: 10.1177/014662167700100306

23. Vilagut G, Forero CG, Barbaglia G, Alonso J. Screening for depression in the general population with the Center for Epidemiologic Studies Depression (CES-D): a systematic review with meta-analysis. *PLoS One*. 2016;11:e0155431. doi: 10.1371/journal.pone.0155431

24. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic impact goal through 2020 and beyond. *Circulation*. 2010;121:586–613. doi: 10.1161/CIRCULATIONAHA.109.192703

25. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med*. 2012;367:20–29. doi: 10.1056/NEJMoa1114248

26. Carpenter MA, Crow R, Steffes M, Rock W, Skelton T, Heilbraun J, Evans G, Jensen R, Sarpong D. Laboratory, reading center, and coordinating center data management methods in the Jackson Heart Study. *Am J Med Sci*. 2004;328:131–144. doi: 10.1097/00000441-200409000-00001

27. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med*. 1999;18:695–706. doi: 10.1002/(SICI)1097-0258(19990330)18:6<695:AID-SIM60>3.0.CO;2-O

28. Putter H, Schumacher M, van Houwelingen HC. On the relation between the cause-specific hazard and the subdistribution rate for competing risks data: the Fine-Gray model revisited. *Biom J*. 2020;62:790–807. doi: 10.1002/bimj.201800274

29. Assari S. Depressive symptoms increase the risk of mortality for white but not black older adults. *Healthcare*. 2018;6:36. doi: 10.3390/healthcare6020036

30. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. *JAMA*. 1996;275:1557–1562. doi: 10.1001/jama.1996.03530440037034

31. Colvin M, Sweitzer NK, Albert NM, Krishnamani R, Rich MW, Stough WG, Walsh MN, Westlake Canary CA, Allen LA, Bonnell MR, et al. Heart failure in non-Caucasians, women, and older adults: a white paper on special populations from the Heart Failure Society of America Guideline Committee. *J Card Fail*. 2015;21:674–693. doi: 10.1016/j.cardfail.2015.05.013

32. Nayak A, Hicks AJ, Morris AA. Understanding the complexity of heart failure risk and treatment in black patients. *Circ Heart Fail*. 2020;13:e007264. doi: 10.1161/CIRCHEARTFAILURE.120.007264

33. Maciejewski PK, Prigerson HG, Mazure CM. Sex differences in event-related risk for major depression. *Psychol Med*. 2001;31:593–604. doi: 10.1017/S0033291701003877

34. Sinha A, Ning H, Carnethon MR, Allen NB, Wilkins JT, Lloyd-Jones DM, Khan SS. Race- and sex-specific population attributable fractions of incident heart failure: a population-based cohort study from the lifetime risk pooling project. *Circ Heart Fail*. 2021;14:e008113. doi: 10.1161/CIRCHEARTFAILURE.120.008113

35. Lam CS, Arnott C, Beale AL, Chandramouli C, Hilfiker-Kleiner D, Kaye DM, Ky B, Santema BT, Sliwa K, Voors AA. Sex differences in heart failure. *Eur Heart J*. 2019;40:3859c–3868c. doi: 10.1093/eurheartj/ehz835

36. Labaka A, Goñi-Balentziaga O, Lebeña A, Pérez-Tejada J. Biological sex differences in depression: a systematic review. *Biol Res Nurs*. 2018;20:383–392. doi: 10.1177/1099800418776082

37. Altemus M. Sex differences in depression and anxiety disorders: potential biological determinants. *Horm Behav*. 2006;50:534–538. doi: 10.1016/j.yhbeh.2006.06.031

38. Gustad LT, Bjerkeset O, Strand LB, Janszky I, Salvesen Ø, Dalen H. Cardiac function associated with previous, current and repeated depression and anxiety symptoms in a healthy population: the HUNT study. *Open Heart*. 2016;3:e000363. doi: 10.1136/openhrt-2015-000363

39. Spence NJ, Adkins DE, Dupre ME. Racial differences in depression trajectories among older women: socioeconomic, family, and health

influences. *J Health Soc Beh*. 2011;52:444–459. doi: 10.1177/0022146511410432

40. Elderon L, Smolderen KG, Na B, Whooley MA. Accuracy and prognostic value of American Heart Association–recommended depression screening in patients with coronary heart disease: data from the Heart and Soul Study. *Circ Cardiovasc Qual Outcomes*. 2011;4:533–540. doi: 10.1161/CIRCOUTCOMES.110.960302

41. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure: a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *J Am Coll Cardiol*. 2006;48:1527–1537. doi: 10.1016/j.jacc.2006.06.055

42. Ishak WW, Edwards G, Herrera N, Lin T, Hren K, Peterson M, Ngor A, Liu A, Kimchi A, Spiegel B. Depression in heart failure: a systematic review. *Innov Clin Neurosci*. 2020;17:27. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7413333/pdf/icns_17_4-6_27.pdf

43. Davidson KW, Bigger JT, Burg MM, Carney RM, Chaplin WF, Czajkowski S, Dornelas E, Duer-Hefele J, Frasure-Smith N, Freedland KE, et al. Centralized, stepped, patient preference–based treatment for patients with post–acute coronary syndrome depression: CODIACS vanguard randomized controlled trial. *JAMA Intern Med*. 2013;173:997–. doi: 10.1001/jamainternmed.2013.915

44. Davidson KW, Rieckmann N, Clemow L, Schwartz JE, Shimbo D, Medina V, Albanese G, Kronish IM, Hegel M, Burg MM. Enhanced depression care for acute coronary syndrome patients with persistent depressive symptoms: Coronary Psychosocial Evaluation Studies randomized controlled trial. *Arch Intern Med*. 2010;170:600–608. doi: 10.1001/archinternmed.2010.29

45. Ye S, Shaffer JA, Rieckmann N, Schwartz JE, Kronish IM, Ladapo JA, Whang W, Burg MM, Davidson KW. Long-term outcomes of enhanced depression treatment in patients with acute coronary syndromes. *Am J Med*. 2014;127:1012–1016. doi: 10.1016/j.amjmed.2014.05.004

46. Burg MM, Rieckmann N, Clemow L, Medina V, Schwartz J, Davidson KW. Treatment preferences among depressed patients after acute coronary syndrome: the COPES observational cohort. *Psychother Psychosom*. 2011;80:380–382. doi: 10.1159/000323615

47. Freedland KE, Hesseler MJ, Carney RM, Steinmeyer BC, Skala JA, Dávila-Román VG, Rich MW. Major depression and long-term survival of patients with heart failure. *Psychosom Med*. 2016;78:896. doi: 10.1097/PSY.0000000000000346

48. Vardeny O, Gupta DK, Claggett B, Burke S, Shah A, Loehr L, Rasmussen-Torvik L, Selvin E, Chang PP, Aguilar D, et al. Insulin resistance and incident heart failure: the ARIC study (Atherosclerosis Risk in Communities). *JACC Heart Fail*. 2013;1:531–536. doi: 10.1016/j.jchf.2013.07.006

49. Rørth R, Jhund PS, Mogensen UM, Kristensen SL, Petrie MC, Køber L, McMurray JJ. Risk of incident heart failure in patients with diabetes and asymptomatic left ventricular systolic dysfunction. *Diabetes Care*. 2018;41:1285–1291. doi: 10.2337/dc17-2583

50. Lavie CJ, Ventura HO. Impact of obesity on the prevalence and prognosis of heart failure-it is not always just black and white. *J Card Fail*. 2016;22:598–599. doi: 10.1016/j.cardfail.2016.06.003

51. Jha MK, Qamar A, Vaduganathan M, Charney DS, Murrough JW. Screening and management of depression in patients with cardiovascular disease: JACC state-of-the-art review. *J Am Coll Cardiol*. 2019;73:1827–1845. doi: 10.1016/j.jacc.2019.01.041

52. Menke R, Flynn H. Relationships between stigma, depression, and treatment in white and African American primary care patients. *J Nerv Ment Dis*. 2009;197:407–411. doi: 10.1097/NMD.0b013e3181a6162e

SUPPLEMENTAL MATERIAL

Table S1. Baseline Characteristics of Included and Excluded Participants based on CES-D Completion

	CES-D Completion			
	*Included Participants** (*n* = 2651)	*Excluded Participants* (*n* = 1894)	*Total*[†] (*N* = 4545)	*P* Value
Demographics				
Age, Median (IQR)	53.0 (44.0 – 63.0)	58.0 (47.0 – 67.0)	55.0 (45.0 – 64.0)	<0.001
21-29	74 (2.8%)	38 (2.0%)	112 (2.5%)	<0.001
30-39	274 (10.3%)	159 (8.4%)	433 (9.5%)	
40-49	676 (25.5%)	370 (19.5%)	1046 (23.0%)	
50-59	702 (26.5%)	451 (23.8%)	1153 (25.4%)	
60-69	657 (24.8%)	520 (27.5%)	1177 (25.9%)	
70+	268 (10.1%)	356 (18.8%)	624 (13.7%)	
Sex				
Men	957 (36.1%)	754 (39.8%)	1711 (37.7%)	0.011
Women	1694 (63.9%)	1140 (60.2%)	2834 (62.4%)	
Education				
Less than high school	319 (12.0%)	520 (27.5%)	839 (18.5%)	<0.001
High school/GED	487 (18.4%)	423 (22.3%)	910 (20.0%)	
College or trade school	1841 (69.4%)	939 (49.6%)	2780 (61.2%)	
Missing	4 (0.2%)	12 (0.6%)	16 (0.3%)	
Income				
Poor	267 (10.1%)	290 (15.3%)	557 (12.3%)	<0.001
Lower-middle	479 (18.1%)	445 (23.5%)	924 (20.3%)	
Upper-middle	725 (27.3%)	431 (22.8%)	1156 (25.4%)	
Affluent	820 (30.9%)	387 (20.4%)	1207 (26.6%)	
Missing	360 (13.6%)	341 (18.0%)	701 (15.4%)	
Lifestyle Factors				
Alcohol Abuse				
No	1396 (52.7%)	1070 (56.5%)	2466 (54.3%)	0.005
Yes	1248 (47.1%)	807 (42.6%)	2055 (45.2%)	
Missing	7 (0.2%)	17 (0.9%)	24 (0.5%)	
Smoking Status				
Current	274 (10.5%)	285 (15.3%)	559 (12.3%)	<0.001
Past	33 (1.3%)	21 (1.1%)	54 (1.2%)	
Never	2299 (88.2%)	1554 (83.6%)	3853 (84.8%)	

Table S1. Baseline Characteristics of Included and Excluded Participants based on CES-D Completion

	CES-D Completion			
	Included Participants[*] (*n* = 2651)	*Excluded Participants* (*n* = 1894)	*Total*[†] (*N* = 4545)	*P* Value
Missing	45 (1.7%)	34 (1.8%)	79 (1.7%)	
BMI (kg/m², Median (IQR)	30.3 (26.8 – 34.9)	30.50 (26.5 – 35.4)	30.4 (26.7 – 35.1)	0.66
Non-obese (<30)	1261 (47.6%)	885 (46.9%)	2146 (47.2%)	0.64
Obese (≥30)	1387 (52.4%)	1001 (53.1%)	2388 (52.5%)	
Missing	3 (0.1%)	8 (0.4%)	11 (0.2%)	
Physical Activity				
Poor	1187 (44.8%)	1045 (55.2%)	2232 (49.1%)	<0.001
Intermediate	895 (33.8%)	533 (28.2%)	1428 (31.4%)	
Recommended	568 (21.4%)	314 (16.6%)	882 (19.4%)	
Missing	1 (0.1%)	2 (0.1%)	3 (0.1%)	
Heart Failure Risk Factors				
Heart Rate (bpm)				
Mean (SD)	63.83 (10.0)	64.79 (11.1)	64.23 (10.5)	0.003
Missing	1 (0.1%)	17 (0.9%)	18 (0.4%)	
Systolic Blood Pressure				
Mean (SD)	125.94 (15.6)	129.51 (18.3)	127.43 (16.9)	<0.001
Missing	9 (0.3%)	7 (0.4%)	16 (0.4%)	
Hypertension				
No	1302 (49.1%)	754 (39.8%)	2056 (45.3%)	<0.001
Yes	1349 (50.9%)	1139 (60.2%)	2488 (54.8%)	
Diabetes				
No	2097 (79.7%)	1391 (73.4%)	3488 (76.7%)	<0.001
Yes	533 (20.3%)	473 (25.0%)	1006 (22.1%)	
Missing	21 (0.8%)	30 (1.6%)	51 (1.1%)	
CHD				
No	2550 (96.2%)	1713 (90.4%)	4263 (93.8%)	<0.001
Yes	101 (3.8%)	181 (9.6%)	282 (6.2%)	
eGFR (ml/min/1.73m²)				
Mean (SD)	85.98 (17.9)	82.54 (20.6)	84.56 (19.1)	<0.001
Missing	32 (1.2%)	47 (2.5%)	79 (1.7%)	
Total Cholesterol (mg/dL)				

Table S1. Baseline Characteristics of Included and Excluded Participants based on CES-D Completion

	CES-D Completion			
	Included Participants[*] (n = 2651)	*Excluded Participants* (n = 1894)	*Total*[†] (N = 4545)	*P* Value
Mean (SD)	199.62 (38.8)	199.59 (41.6)	199.60 (40.0)	0.98
Missing	184 (6.9%)	217 (11.5%)	401 (8.8%)	
LVEF (%)				
Mean (SD)	62.13 (6.6)	61.68 (8.2)	61.95 (7.3)	0.05

Abbreviations. BMI, body mass index; CES-D, Center for Epidemiological Studies-Depression scale,

CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range;

LVEF, left ventricular ejection fraction; SD, standard deviation.

[*]Participants who completed at least 16 of 20 screening questions on the baseline CES-D.

[†]Before applying other exclusion criteria.

Table S2. Multivariate Models of CES-D Depressive Symptoms and Risk of All-Cause Mortality

	Model 1		Model 2		Model 3		Model 4	
	HR	*P* value	aHR	*P* value	aHR	*P* value	aHR	*P* value
CES-D Depressive Symptoms[*]	1.04 (0.81-1.32)	0.77	0.96 (0.75-1.23)	0.75	0.92 (0.71-1.18)	0.50	0.87 (0.68-1.12)	0.27
Demographics								
Age			1.09 (1.08-1.10)	<0.001	1.08 (1.06-1.09)	<0.001	1.08 (1.06-1.09)	<0.001
Male			1.47 (1.20-1.81)	<0.001	1.47 (1.19-1.82)	<0.001	1.45 (1.17-1.81)	<0.001
Education			0.86 (0.68-1.08)	0.20	0.90 (0.72-1.14)	0.40	0.94 (0.74-1.19)	0.62
Income			0.61 (0.48-0.77)	<0.001	0.59 (0.47-0.75)	<0.001	0.63 (0.49-0.81)	<0.001
HF Risk Factors								
Hypertension					1.22 (0.97-1.55)	0.09	1.24 (0.98-1.58)	0.07
Diabetes					1.68 (1.36-2.07)	<0.001	1.80 (1.45-2.24)	<0.001
CHD					1.48 (1.04-2.11)	0.028	1.53 (1.08-2.18)	0.018
eGFR					0.99 (0.98-1.00)	0.012	0.99 (0.98-1.00)	0.004
Total cholesterol					1.00 (1.00-1.00)	0.64	1.00 (1.00-1.00)	0.82

LVEF%	0.99 (0.97-1.00)	0.17	0.99 (0.97-1.00)	0.18
Lifestyle Factors				
Alcohol abuse			0.97 (0.77-1.21)	0.79
Former smoker			0.65 (0.20-2.10)	0.47
Never smoker			0.56 (0.41-0.77)	<0.001
Obesity			0.97 (0.74-1.27)	0.80
Physical activity			0.85 (0.69-1.05)	0.14

Hazard ratios and 95% CIs are presented.

Abbreviations: aHR, adjusted hazard ratio; CES-D, Center for Epidemiological Studies-Depression scale; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction.

[*]High depressive symptoms on the CES-D (≥16) versus low depressive symptoms (<16).

Table S3. Multivariate Models of CES-D Depressive Symptoms and Risk of HF Hospitalization Among Men

	Model 1		Model 2		Model 3		Model 4	
	HR	*P* value	aHR	*P* value	aHR	*P* value	aHR	*P* value
CES-D Depressive Symptoms[*]	1.26 (0.69-2.32)	0.45	1.27 (0.69-2.36)	0.45	1.29 (0.69-2.41)	0.43	1.24 (0.66-2.35)	0.50
Demographics								
Age			1.09 (1.06-1.11)	<0.001	1.08 (1.05-1.11)	<0.001	1.09 (1.05-1.12)	<0.001
Education			1.03 (0.58-1.83)	0.91	1.14 (0.64-2.04)	0.65	1.16 (0.65-2.09)	0.61
Income			0.74 (0.41-1.35)	0.32	0.66 (0.36-1.20)	0.17	0.71 (0.38-1.33)	0.28
HF Risk Factors								
Hypertension					1.39 (0.79-2.43)	0.26	1.34 (0.76-2.37)	0.30
Diabetes					1.97 (1.18-3.31)	0.010	1.95 (1.15-3.31)	0.013
CHD					2.23 (1.06-4.67)	0.034	2.28 (1.07-4.84)	0.032
eGFR					1.00 (0.99-1.02)	0.67	1.00 (0.99-1.02)	0.78
Total cholesterol					1.00 (0.99-1.01)	0.70	1.00 (0.99-1.01)	0.65
LVEF%					0.98 (0.94-1.01)	0.23	0.98 (0.94-1.01)	0.21

Lifestyle Factors

Alcohol abuse	0.82 (0.48-1.38)	0.45
Former smoker	0.62 (0.08-4.57)	0.64
Never smoker	0.56 (0.27-1.17)	0.12
Obesity	1.32 (0.79-2.19)	0.29
Physical activity	0.80 (0.48-1.33)	0.39

Hazard ratios and 95% CIs are presented.

Abbreviations: aHR, adjusted hazard ratio; CES-D, Center for Epidemiological Studies-Depression scale; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction.

[*]High depressive symptoms on the CES-D ($\geq$16) versus low depressive symptoms (<16).

Table S4. Multivariate Models of CES-D Depressive Symptoms and Risk of All-Cause Mortality Among Men

	Model 1		Model 2		Model 3		Model 4	
	HR	*P* value	aHR	*P* value	aHR	*P* value	aHR	*P* value
CES-D Depressive Symptoms[*]	0.96 (0.62-1.48)	0.86	0.86 (0.55-1.34)	0.51	0.85 (0.54-1.34)	0.48	0.84 (0.53-1.33)	0.45
Demographics								
Age			1.10 (1.08-1.11)	<0.001	1.09 (1.07-1.11)	<0.001	1.09 (1.07-1.11)	<0.001
Education			0.76 (0.53-1.10)	0.15	0.83 (0.57-1.21)	0.33	0.85 (0.58-1.24)	0.40
Income			0.68 (0.46-0.99)	0.042	0.59 (0.40-0.88)	0.009	0.60 (0.40-0.90)	0.015
HF Risk Factors								
Hypertension					1.39 (0.79-2.43)	0.26	1.24 (0.86-1.79)	0.26
Diabetes					1.97 (1.18-3.31)	0.010	1.95 (1.37-2.76)	<0.001
CHD					2.23 (1.06-4.67)	0.034	1.83 (1.11-3.01)	0.018
eGFR					1.00 (0.99-1.02)	0.67	0.99 (0.98-1.01)	0.28
Total cholesterol					1.00 (0.99-1.01)	0.70	1.00 (0.99-1.00)	0.60
LVEF%					0.98 (0.94-1.01)	0.23	0.98 (0.95-1.00)	0.10

Lifestyle Factors

Alcohol abuse	1.15 (0.81-1.63)	0.43
Former smoker	0.62 (0.08-4.57)	0.64
Never smoker	0.56 (0.27-1.17)	0.037
Obesity	1.32 (0.79-2.19)	0.36
Physical activity	0.80 (0.48-1.33)	0.17

Hazard ratios and 95% CIs are presented.

Abbreviations: aHR, adjusted hazard ratio; CES-D, Center for Epidemiological Studies-Depression scale; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction.

[*]High depressive symptoms on the CES-D ($\geq$16) versus low depressive symptoms (<16).

Table S5. Multivariate Models of CES-D Depressive Symptoms and Risk of All-Cause Mortality Among Women

	Model 1		Model 2		Model 3		Model 4	
	HR	*P* value	aHR	*P* value	aHR	*P* value	aHR	*P* value
CES-D Depressive Symptoms[*]	1.10 (0.82-1.47)	0.53	1.02 (0.76-1.38)	0.88	1.01 (0.74-1.36)	0.97	0.99 (0.73-1.34)	0.92
Demographics								
Age			1.08 (1.07-1.10)	<0.001	1.07 (1.05-1.09)	<0.001	1.07 (1.05-1.09)	<0.001
Education			0.95 (0.71-1.27)	0.72	0.99 (0.73-1.33)	0.93	1.03 (0.76-1.38)	0.86
Income			0.56 (0.41-0.76)	<0.001	0.57 (0.42-0.77)	<0.001	0.60 (0.44-0.82)	0.001
HF Risk Factors								
Hypertension					1.16 (0.85-1.58)	0.34	1.18 (0.86-1.61)	0.30
Diabetes					1.58 (1.20-2.07)	0.001	1.63 (1.24-2.16)	<0.001
CHD					1.18 (0.70-1.99)	0.53	1.17 (0.69-1.97)	0.56
eGFR					0.99 (0.98-1.00)	0.008	0.99 (0.98-1.00)	0.014
Total cholesterol					1.00 (1.00-1.00)	0.91	1.00 (1.00-1.00)	0.96
LVEF%					1.00 (0.98-1.02)	0.70	0.99 (0.97-1.01)	0.53

Lifestyle Factors

Alcohol abuse	0.84 (0.62-1.15)	0.28
Former smoker	0.81 (0.19-3.41)	0.64
Never smoker	0.50 (0.34-0.75)	<0.001
Obesity	0.90 (0.69-1.16)	0.41
Physical activity	0.87 (0.67-1.14)	0.31

Hazard ratios and 95% CIs are presented.

Abbreviations: aHR, adjusted hazard ratio; CES-D, Center for Epidemiological Studies-Depression scale; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction;

[*]High depressive symptoms on the CES-D ($\geq$16) versus low depressive symptoms (<16).

Table S6. Multivariate Models of CES-D Depressive Symptoms and Risk of HF Hospitalization

	Model 1		Model 2		Model 3		Model 4	
	HR	*P* value	aHR	*P* value	aHR	*P* value	aHR	*P* value
CES-D Depressive Symptoms[*]	1.35 (0.79-2.29)	0.27	1.52 (0.89-2.60)	0.13	1.49 (0.86-2.58)	0.16	1.42 (0.81-2.49)	0.22
Demographics								
Age			1.08 (1.05-1.10)	<0.001	1.07 (1.04-1.09)	<0.001	1.07 (1.04-1.10)	<0.001
Male			1.17 (0.73-1.88)	0.51	1.12 (0.69-1.81)	0.65	1.19 (0.72-1.97)	0.50
Education			0.79 (0.46-1.34)	0.38	0.87 (0.50-1.51)	0.62	0.96 (0.55-1.66)	0.87
Income			0.77 (0.45-1.31)	0.33	0.75 (0.44-1.28)	0.29	0.95 (0.47-1.40)	0.46
HF Risk Factors								
Hypertension					1.34 (0.80-2.25)	0.27	1.30 (0.77-2.20)	0.33
Diabetes					2.14 (1.32-3.47)	0.002	2.08 (1.27-3.42)	0.004
CHD					2.21 (1.03-4.76)	0.042	2.13 (0.96-4.73)	0.06
eGFR					0.99 (0.98-1.01)	0.36	0.99 (0.97-1.01)	0.26
Total cholesterol					1.00 (0.99-1.00)	0.54	1.00 (0.99-1.00)	0.55

LVEF%	0.98 (0.94-1.01)	0.21	0.98 (0.94-1.01)	0.17
Lifestyle Factors				
Alcohol abuse			0.95 (0.57-1.58)	0.79
Former smoker			1.72 (0.36-8.23)	0.50
Never smoker			0.64 (0.30-1.34)	0.23
Obesity			1.25 (0.52-2.97)	0.62
Physical activity			0.72 (0.44-1.18)	0.19

Hazard ratios and 95% CIs are presented.

Abbreviations: aHR, adjusted hazard ratio; CES-D, Center for Epidemiological Studies-Depression scale; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction.

[*]High depressive symptoms on the CES-D (≥16) versus low depressive symptoms (<16).

Table S7. Multivariate Models of CES-D Depressive Symptoms and Risk of HF Hospitalization in Complete Cases for Women

	Model 1		Model 2		Model 3		Model 4	
	HR	*P* value	aHR	*P* value	aHR	*P* value	aHR	*P* value
CES-D Depressive Symptoms[*]	1.70 (0.92-3.13)	0.09	2.00 (1.08-3.73)	0.03	2.03 (1.07-3.87)	0.03	1.94 (1.01-3.74)	0.04
Demographics								
Age			1.07 (1.05-1.10)	<0.001	1.06 (1.03-1.09)	<0.001	1.06 (1.02-1.09)	0.002
Education			0.68 (0.35-1.35)	0.27	0.74 (0.37-1.48)	0.40	0.82 (0.41-1.62)	0.57
Income			0.89 (0.46-1.72)	0.72	0.95 (0.49-1.86)	0.88	1.02 (0.52-1.98)	0.96
HF Risk Factors								
Hypertension					1.43 (0.73-2.79)	0.29	1.43 (0.73-2.79)	0.29
Diabetes					1.88 (0.99-3.54)	0.05	1.88 (0.99-3.54)	0.05
CHD					2.12 (0.79-5.67)	0.13	2.12 (0.79-5.67)	0.13
eGFR					0.99 (0.97-1.00)	0.14	0.99 (0.97-1.00)	0.14
Total cholesterol					1.00 (0.99-1.01)	0.75	1.00 (0.99-1.01)	0.75
LVEF%					0.98 (0.94-1.02)	0.34	0.98 (0.94-1.02)	0.34
Lifestyle Factors								

Alcohol abuse	0.87 (0.45-1.68)	0.67
Former smoker	5.96 (1.07-33.29)	0.04
Never smoker	0.83 (0.32-2.18)	0.71
Obesity	1.30 (0.68-2.50)	0.42
Physical activity	0.58 (0.30-1.12)	0.11

Hazard ratios and 95% CIs are presented.

Abbreviations: aHR, adjusted hazard ratio; CES-D, Center for Epidemiological Studies-Depression scale; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction.

[*]High depressive symptoms on the CES-D (≥16) versus low depressive symptoms (<16).