Depressive symptoms, cognitive impairment, and all-cause mortality among REGARDS participants with heart failure

Yulia Khodneva 1,*, Joanna Bryan Ringel2, Mangala Rajan2, Parag Goyal 2,3, Elizabeth A. Jackson 1, Madeline R. Sterling2, Andrea Cherrington1, Suzanne Oparil 1, Raegan Durant1, Monika M. Safford2, and Emily B. Levitan4

1Department of Medicine, School of Medicine, University of Alabama at Birmingham, MT509H 1717 11th Avenue South, Birmingham, AL 35294-4410, USA; 2Division of Internal Medicine, Weill Cornell University, 530 East 70st Street, New York, NY 10021, USA; 3Division of Cardiology, Weill Cornell University, 530 East 70st Street, New York, NY 10021, USA; and 4Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, 1720 University Blvd, Birmingham, Al 35294, USA

Received 29 June 2022; revised 6 September 2022; accepted 28 September 2022; online publish-ahead-of-print 3 October 2022

Handling Editor: Davide Stolfo

Aims
To ascertain whether depressive symptoms and cognitive impairment (CI) are associated with mortality among patients with heart failure (HF), adjusting for sociodemographic, comorbidities, and biomarkers.

Methods and results
We utilized Medicare-linked data from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study, a biracial prospective ongoing cohort of 30,239 US community-dwelling adults, recruited in 2003–07. HF diagnosis was ascertained in claims analysis. Depressive symptoms were defined as a score ≥4 on the four-item Center for Epidemiological Studies-Depression scale. Cognitive impairment was defined as a score of ≤4 on the six-item screener that assessed three-item recall and orientation to year, month, and day of the week. Sequentially adjusted Cox proportional hazard models were used to estimate the risk of death. We analyzed 1059 REGARDS participants (mean age 73, 48%—African American) with HF; of those 146 (14%) reported depressive symptoms, 136 (13%) had CI and 31 (3%) had both. Over the median follow-up of 6.8 years (interquartile range, 3.4–10.3), 785 (74%) died. In the socio-demographics-adjusted model, CI was significantly associated with increased mortality, hazard ratio 1.24 (95% confidence interval 1.01–1.52), compared with persons with neither depressive symptoms nor CI, but this association was attenuated after further adjustment. Neither depressive symptoms alone nor their comorbidity with CI was associated with mortality. Risk factors of all-cause mortality included: low income, comorbidities, smoking, physical inactivity, and severity of HF.

Conclusion
Depressive symptoms, CI, or their comorbidity was not associated with mortality in HF in this study. Treatment of HF in elderly needs to be tailored to cognitive status and includes focus on medical comorbidities.
Are depressive symptoms, cognitive impairment associated with all-cause mortality among REGARDS participants with heart failure?

Baseline comorbid depressive symptoms, cognitive impairment or presence of each of these syndromes alone was not associated with mortality among participants with heart failure.

Methods and Cohort
1,059 REGARDS participants with heart failure (HF)
Mean age - 73 years
48% - African American

Depressive symptoms –Center for Epidemiologic Studies Depression scale (CES-D-4, range 0-12) score ≥4
Cognitive impairment (CI) – Six-Item Screener (SIS) score ≥ 4
Analysis - Multivariable Cox proportional Regression Model

Findings
74% of participants died at median 6.8 years of follow-up
14% reported depressive symptoms, 13% had CI, 3% had both depression and CI at baseline
Only CI was associated with mortality in partially adjusted model:
Hazard Ratio 1.24, 95%CI (1.01-1.52)
This attenuated after further covariate adjustment

Mortality risk factors in HF
- Socio-Demographics: Age, Male Sex, Low income
- Comorbidities: Coronary Heart Disease, Prior Stroke, Diabetes, Proteinuria, Elevated C-reactive protein
- Behaviors: Physical Inactivity, Cumulative pack years of smoking
- Severity of HF: Lower physical health score (SF-12)

European Heart Journal Open
Yulia Khodneva, MD, PhD, University of Alabama, Birmingham

Keywords
Heart failure • Depression • Cognitive impairment • Mortality

Introduction
Heart failure (HF) is a chronic condition that affected 6.5 million Americans in 2013–16. Despite advances in treatment, HF is characterized by extremely poor prognosis irrespective of left ventricular ejection function, with 50–75% of patients dying within 5 years following their initial HF diagnosis. The majority of HF patients are older adults with multiple physical and psychiatric comorbidities. Both depression and cognitive impairment (CI) are common among HF patients with prevalence estimates of 20–40% for depression and 30–50% for CI, which increases as HF duration and severity increases. Depression and CI can exist as distinct syndromes but can also co-occur. Depression in older adults often presents with features of CI and vice versa, CI can be complicated by depression. A systematic review of general population samples estimated that 25% of persons with mild CI also had depression. Similarly, 47% of older adults—nursing home residents with depression—demonstrated CI. It has been shown that if CI is not addressed during late-life depression, then there is a poor response to antidepressant treatment.

Previous reports suggest that depression is associated with elevated all-cause mortality among adults with HF. Similarly, CI has been shown to be associated with adverse outcomes in HF, including increased mortality. Nevertheless, current HF guidelines do not offer specific screening or treatment interventions for HF patients with CI or their comorbidity with depression because of lack of evidence that such interventions can improve HF outcomes. Older adults with HF, complicated by comorbid CI and depression, are often excluded from major clinical trials. The prevalence of comorbid depressive symptoms and CI among HF patients and the effect of comorbid depressive symptoms and CI on mortality in HF are unknown.

To address this gap, we used data from the Reasons for Geographic and Racial Differences in Stroke (REGARDS), a biracial cohort of community-dwelling US adults, to explore the relationships of depressive symptoms, CI, and their comorbidity with all-cause mortality among persons with HF. We hypothesized that among REGARDS participants with HF at baseline, those with comorbid depressive symptoms and CI had higher all-cause mortality risk compared with those with depressive symptoms alone, CI alone, or neither.

Methods
Study participants and procedures
The REGARDS study is an ongoing prospective cohort study of 30,239 community-dwelling adults from 48 continental US states, designed to examine the causes of regional and racial disparities in 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. Race and gender were balanced by design, with oversampling from the Southeastern US. 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 pill bottle review of medications. The REGARDS study procedures were approved by the Institutional Review Boards at the participating centres and all participants provided written informed consent.20

This study included participants with a diagnosis of HF at baseline that was derived using Medicare claims from 2000 to 2006, prior to the REGARDS study baseline interview date. We utilized data from REGARDS participants who were linked to Medicare via social security number and date of birth.11,22 HF was defined as an ICD-9 code of 428.x in one or more inpatient hospital discharge claims and/or in two or more outpatient claims from different service dates.23–25 Deaths were recorded through 31 December 2017 by report of next of kin or through online resources (e.g. Social Security Death Index) and the National Death Index.

### Depressive symptoms and cognitive function in REGARDS

Depressive symptoms were defined using the four-item Center for Epidemiologic Studies Depression scale (CES-D-4) that was validated against the 20-item scale (r = 0.87).26,27 The CES-D-4 uses a four-point (0–3) scale to record the presence and frequency of depressive symptoms during the preceding week. Responses to four items were summed (Cronbach α = 0.80) with total score, ranging from 0 (no symptoms) to 12. The CES-D-4 was dichotomized, with scores of ≥4 signifying the presence of depressive symptoms, which had been reported to have 79.2% sensitivity and 86.4% specificity for meeting an established threshold of clinically significant depressive symptoms as assessed by the full 20-item CES-D.26,27

Patients were screened for probable CI by using the six-item screener (SIS), derived from the mini-mental state exam (MMSE), with the score range 0–6, that assessed three-item recall and orientation to year, month, and day of the week.28 A score of ≤4 correct items on SIS scale indicates screening positive for CI with 61% sensitivity and 99.2% specificity, validated against MMSE in the community samples.28 Six-item screener was used previously to identify CI among depressed individuals.29

### Covariates

Covariates were selected based on factors, reported in the literature to be associated with mortality in HF5–20,22 and with depressive symptoms and cognition.28 Baseline socio-demographics included age, race, sex, education, annual income (dichotomized at $35,000), marital status, and 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). Rural residence was derived from US census rural-urban commuting area codes and by using Federal Information Processing Standard codes representing rural counties in the ‘Black belt’.34 Social isolation was assessed via a self-report on how many people participants saw in a past month and defined as a visit with less than or equal to one person in past month. Health behaviours included: cumulative pack-years of smoking; and physical inactivity (none vs. any physical activity during average week, defined as 30 min of any moderate to strenuous activity producing sweat, at least once a week). Self-reported medication adherence was assessed with a four-item scale (perfect vs. not perfect adherence).35

Comorbidities were defined using established definitions in REGARDS and included coronary heart disease (CHD),36 diabetes, hypertenison, atrial fibrillation and stroke. The following physiological parameters were included: body mass index (kg/m²); systolic and diastolic BP (average of two measures, obtained after a 5 min rest, mmHg); high-sensitivity C-reactive protein (hs-CRP) (mg/L); total and high density lipoprotein cholesterol (mg/dL); and urinary albumin-to-creatinine ratio (ACR) (mg/g). Use of any anti-hypertensives, angiotensin converting enzyme inhibitors/angiotensin receptor blockers, statins and anti-depressant medications was determined via pill bottle review. Physical health status was ascertained via the short form 12 (SF-12) physical component summary score.37 Severity of baseline HF was determined by calculating the Acute Decompensated Heart Failure National Registry (ADHERE) score, which utilizes baseline systolic BP (SBP), blood urea nitrogen (BUN) and serum creatinine (sCr, mg/dL).38 If a person had BUN < 43 and SBP > 115, the risk of death was estimated as ‘low’. Participants with BUN ≥ 43 and SBP > 115 or BUN < 43 and SBP < 115 was categorized as ‘Intermediate risk 2–3’. Participants with BUN > 43, SBP < 115, and sCr < 2.75 were deemed to be in the ‘Intermediate risk 1’ group. Those with BUN ≥ 43, SBP < 115, and sCr > 2.75 comprised the ‘High risk’ group.

### Statistical analysis

Presence of both depressive symptoms and CI was defined as CES-D score ≥ 4 and SIS ≤ 4. Depressive symptoms alone were defined by CES-D score ≥ 4 and SIS > 4. Cognitive impairment alone was defined as CES-D score < 4 and SIS ≤ 4. The referent group included participants with neither depressive symptoms nor CI: CES-D score < 4 and SIS > 4.

Participant characteristics were compared according to depressive symptoms-cognition groups, using χ² and ANOVA tests. Kaplan–Meier curves were constructed to assess unadjusted associations between the four exposure groups and all-cause mortality. Age-adjusted incidence rates were calculated for each of the depressive symptoms-cognition group per 1000 person-years, using Poisson regression models. Next, we fitted sequentially adjusted Cox proportional hazards regression models of all-cause mortality. The crude model included only depressive symptoms-cognition groups. Model 1 added socio-demographics. Model 2 further adjusted for medical conditions, physiological variables and the ADHERE HF severity score. Proportionality assumption was satisfied in all models. Missing data in covariates were imputed in 10 datasets using the chained equations method. We also performed a sex-stratified analysis a priori. As a sensitivity analysis we repeated the modelling exercise using a different threshold for CI (SIS < 6) and having a least one symptom of depression (CES-D ≥ 1).

For all analyses we used STATA, Version 16.0 and SAS 9.4 (SAS Institute, Cary, NC, USA).

### Results

Among the 30,183 REGARDS study participants, 20,403 had Medicare-linked data and 1374 of them had HF at baseline and provided follow-up data. After excluding 315 participants who had either CES-D and/or SIS assessment missing, the final analytic sample was comprised of 1059 of persons with HF. At baseline, 31 participants (3%) had comorbid depressive symptoms and global CI; 146 (13.8%) had depressive symptoms alone, 136 (12.8%) had global CI alone, and 746 participants had neither.

### Characteristics of persons with comorbid depressive symptoms and cognitive impairment

The mean age of the study sample was 73, SD 8.3 years; 47.5% were African American and 54.8% were female (Table 1). Compared with persons without depression or CI, participants with comorbid depressive symptoms and CI were more likely to be African-American, live in the ‘Stroke Belt’, and have lower income and incomplete high school education. Participants with comorbid depressive symptoms and CI were also more likely to have medical comorbidities, such as prior stroke, hyperlipidaemia, diabetes, higher body mass index (BMI), and worse medication adherence. Participants with comorbid depressive symptoms and CI were less physically active. Further, those with comorbid depressive symptoms and CI were less likely to receive antidepresants compared with those with depressive symptoms alone.

### Association of comorbid depressive symptoms and cognitive impairment with all-cause mortality

End of follow-up for this study was 31 December 2017. Over the median follow-up of 6.8 years, interquartile range (3.4–10.3), 785 persons or 74% of the sample died. There were 21 deaths among persons with...
Table 1  Baseline characteristics of REGARDS participants with heart failure diagnosis

| Characteristic                              | Overall  | Neither depressive symptoms nor cognitive impairment | Cognitive impairment alone | Depressive symptoms alone | Cognitive impairment + depressive symptoms | P-value |
|---------------------------------------------|----------|------------------------------------------------------|---------------------------|--------------------------|--------------------------------------------|---------|
| | n                                           | 1059     | 746                                                  | 136                       | 146                      | 31                                         |         |
| **Socio-demographics**                      |          |                                                      |                           |                          |                                            |         |
| Age, mean (SD)                              | 73 (8.3) | 73 (8.0)                                             | 76 (8.0)                  | 70 (8.8)                 | 69 (9.4)                                   | <0.001  |
| African American                            | 503 (47.5%) | 316 (42.4%)                                          | 76 (55.9%)                | 90 (61.6%)               | 21 (67.7%)                                 | <0.001  |
| Female                                      | 580 (54.8%) | 387 (51.9%)                                          | 69 (50.7%)                | 107 (73.3%)              | 17 (54.8%)                                 | <0.001  |
| Stroke belt region                          | 360 (34.0%) | 243 (32.6%)                                          | 43 (31.6%)                | 56 (38.4%)               | 18 (58.1%)                                 | 0.03    |
| Rural residence                             | 376 (38.2%) | 250 (36.3%)                                          | 53 (42.1%)                | 60 (42.6%)               | 13 (43.3%)                                 | 0.35    |
| Annual income ≤$35 000                      | 622 (70.1%) | 425 (66.4%)                                          | 80 (75.5%)                | 96 (82.1%)               | 21 (87.5%)                                 | <0.001  |
| Education < high school                     | 270 (25.5%) | 160 (21.5%)                                          | 46 (33.8%)                | 49 (33.6%)               | 15 (48.4%)                                 | <0.001  |
| Married                                     | 492 (46.5%) | 370 (49.6%)                                          | 62 (45.6%)                | 43 (29.5%)               | 17 (54.8%)                                 | <0.001  |
| Social isolation                            | 159 (15.2%) | 105 (14.1%)                                          | 23 (17.6%)                | 27 (18.6%)               | 4 (13.3%)                                  | 0.45    |
| **Comorbidities**                           |          |                                                      |                           |                          |                                            |         |
| Stroke                                      | 173 (16.4%) | 99 (13.4%)                                           | 31 (22.8%)                | 31 (21.4%)               | 12 (38.7%)                                 | <0.001  |
| Diabetes                                    | 442 (43.7%) | 294 (41.2%)                                          | 54 (41.9%)                | 82 (58.2%)               | 12 (41.4%)                                 | 0.00    |
| Hypertension                                | 816 (77.6%) | 569 (76.6%)                                          | 99 (73.9%)                | 122 (84.1%)              | 26 (86.7%)                                 | 0.09    |
| Atrial fibrillation                         | 255 (25.0%) | 192 (26.6%)                                          | 22 (17.2%)                | 35 (24.8%)               | 6 (20.7%)                                  | 0.14    |
| Coronary artery disease (self-reported or ECG evidence) | 575 (55.3%) | 409 (55.7%)                                          | 64 (48.1%)                | 81 (57.4%)               | 21 (67.7%)                                 | 0.17    |
| Left ventricular hypertrophy                | 161 (15.5%) | 109 (14.9%)                                           | 24 (18.0%)                | 20 (13.9%)               | 8 (25.8%)                                  | 0.30    |
| **Self-reported physical health**           |          |                                                      |                           |                          |                                            |         |
| SF-12 physical component scale, median (IQR)| 39 (29, 48) | 39 (29, 49)                                          | 42 (30, 48)               | 31 (26, 42)              | 35 (28, 44)                                | <0.001  |
| **Physiological parameters**                |          |                                                      |                           |                          |                                            |         |
| Body mass index, kg/m², mean (SD)           | 30 (6.8) | 30 (6.8)                                             | 29 (5.8)                  | 32 (7.1)                 | 31 (7.8)                                   | <0.001  |
| Systolic blood pressure, mmHg, mean (SD)    | 132 (19) | 131 (18)                                             | 133 (17)                  | 135 (21)                 | 134 (19)                                   | 0.06    |
| Diastolic blood pressure, mmHg, mean (SD)   | 75 (11)  | 74 (10)                                               | 76 (10)                   | 77 (11)                  | 78 (13)                                    | 0.02    |
| Total cholesterol, mg/dL, mean (SD)         | 176 (42) | 174 (41)                                             | 173 (42)                  | 186 (45)                 | 184 (48)                                   | 0.01    |
| HDL, mg/dL, mean (SD)                       | 49 (16)  | 49 (16)                                               | 49 (15)                   | 50 (16)                  | 47 (12)                                    | 0.82    |
| Urinary albumin/creatinine ratio (mg/g), median (IQR) | 14 (6.7, 53.0) | 14 (6.8, 45.0)                                       | 20 (7.0, 156.0)           | 15 (7.1, 53.0)           | 15 (5.6, 53.0)                             | 0.13    |
| C-reactive protein (mg/L), median (IQR)     | 3.2 (1.3, 7.0) | 3.0(1.2, 6.0)                                        | 3.3 (1.2, 8.8)            | 4.9 (1.8, 9.7)           | 1.9 (1.0, 6.3)                             | <0.001  |
| **Medication use**                          |          |                                                      |                           |                          |                                            |         |
| Perfect medication adherence                | 717 (69.7%) | 502 (69.4%)                                          | 103 (78.0%)               | 97 (67.8%)               | 15 (50.0%)                                 | 0.02    |
| Statins                                     | 517 (48.9%) | 369 (49.5%)                                          | 66 (48.5%)                | 66 (45.2%)               | 16 (51.6%)                                 | 0.80    |
| Any antihypertensives                       | 962 (90.9%) | 676 (90.7%)                                          | 125 (91.9%)               | 134 (91.8%)              | 27 (87.1%)                                 | 0.83    |
| ACEi/ARBs                                   | 655 (61.9%) | 462 (62.0%)                                          | 87 (64.0%)                | 89 (61.0%)               | 17 (54.8%)                                 | 0.81    |
| Any antidepressants                         | 168 (15.9%) | 104 (14.0%)                                          | 20 (14.7%)                | 39 (26.7%)               | 5 (16.1%)                                  | <0.01    |
| **Behaviours**                              |          |                                                      |                           |                          |                                            |         |
| Physical inactivity (none in average week)  | 553 (53.6%) | 356 (48.4%)                                          | 81 (63.3%)                | 95 (67.4%)               | 21 (77.8%)                                 | <0.001  |
| Current smoker                              | 127 (12.1%) | 82 (11.0%)                                           | 14 (10.5%)                | 22 (15.3%)               | 9 (29.0%)                                  | 0.04    |
| Pack-years of smoking, mean (SD)            | 19 (30)  | 20 (30)                                               | 14 (23)                   | 19 (29)                  | 22 (49)                                    | 0.18    |
| Heavy alcohol use                           | 18 (1.7%)  | 11 (1.5%)                                             | 4 (3.0%)                  | 2 (1.4%)                 | 1 (3.3%)                                   | 0.73    |
| ADHERE in-hospital mortality predicted risk  |          |                                                      |                           |                          |                                            | 0.66    |

Continued
In a recent meta-analysis, depression was associated with mortality in heart failure among persons with depressive symptoms, 112 deaths among those with CI alone, and 551 among those with neither depressive symptoms nor CI.

Kaplan–Meier curves depicted unadjusted association of depressive symptoms, CI, their comorbidity, and neither of them with all-cause mortality (Figure 1). In the crude model, only the group of HF participants with CI had increased risk of all-cause mortality compared with HF participants who had neither CI nor depressive symptoms [hazard ratio (HR) 1.34, 95% confidence interval (1.09–1.64)] (Table 2). This association remained statistically significant in the socio-demographics-adjusted model but became non-significant after adjusting for comorbidities and physiological parameters. Neither comorbid depressive symptoms and CI nor depressive symptoms alone was associated with all-cause mortality among REGARDS participants with HF.

**Factors associated with all-cause mortality in heart failure in REGARDS**

Of socio-demographics, male sex, age, and lower income were significantly associated with mortality in the multivariable-adjusted models (Table 3). CHD, prior stroke, diabetes, hs-CRP, and ACR were also associated with increased mortality in HF participants. Of health behaviours, physical inactivity and cumulative pack-years of smoking were significantly associated with mortality. Higher self-reported physical health, higher BMI, and use of statins had protective effects on mortality among these participants with HF. ADHERE categories of intermediate and high risk of predicted in-hospital mortality in HF had statistically significant dose-response association with all-cause mortality in REGARDS participants with HF (Table 3).

**Sensitivity analysis**

We performed sensitivity analyses where depressive symptoms were defined as CES-D ≥ 4 or any symptom of depression and CI was defined as SIS < 4. Using these definitions did not change the results: in adjusted models, neither depressive symptoms, CI, nor their combination was associated with mortality in this sample of adults with HF (see Supplementary material online, Table S1).

**Discussion**

In this prospective sample of community-dwelling US adults with HF, we found that CI was associated with increased risk of death among person with HF when the analysis was only adjusted for demographics. However, when chronic medical conditions, HF severity, and biomarkers were taking into account, this association became attenuated. Neither depressive symptoms alone nor comorbid depressive symptoms and CI were not associated with the increased risk of death. The increased mortality risk among adults with HF in this study was associated with age, gender, income, chronic medical conditions, and unhealthy behaviours, such as physical inactivity and smoking. We found a small proportion of REGARDS participants with HF who had comorbid depressive symptoms and CI. Participants with comorbid depressive symptoms and CI were more likely to be African Americans and demonstrated worse socioeconomic status, higher rate of comorbidities, and more unhealthy behaviours.

Among these adults with HF, the prevalence of depressive symptoms was 14% and prevalence of CI was 13%, similar to previous data from the studies of community-dwelling adults, but generally lower than the respective estimates from the clinical trials. Several hypotheses have been suggested to explain why depression and CI are both prevalent among HF patients, including shared similar chronic inflammatory pathways. Proposed mechanisms underlying the association of HF with CI include cerebral hypo-perfusion, ischaemic, and cardiac-embolic phenomena, and an association with increased levels of brain-natriuretic peptide. The level of CI in HF tends to fluctuate, depending on the severity and duration of HF. Based on ADHERE scores, REGARDS participants with HF were likely to be generally ‘healthier’ than HF patients from clinical trials and, therefore, the prevalence of both CI and depressive symptoms was relatively lower in our study. Another potential explanation of the lower prevalence of depressive symptoms and CI in REGARDS is a relatively high proportion of persons who were married and lower proportion of those who reported social isolation.

To our knowledge, this is one of the first studies that evaluated the effect of comorbid depressive symptoms and CI on mortality in HF. Previous studies have addressed the associations of depression or impaired cognition with mortality in HF, separately for each of these syndromes. In a recent meta-analysis, depression was associated with all-cause mortality in HF (pooled HR 1.20); however, this association was statistically significant only for adults >65 years old. Similarly, a meta-analysis of eight studies showed CI was associated with all-cause mortality in HF (pooled HR 1.75). Limitations of both meta-analyses included large heterogeneity in the study designs and variability in HF severity among included studies. Unlike most previous reports, in this study, neither depressive symptoms alone, CI alone, nor their comorbidity was associated with all-cause mortality among persons with HF. Potential explanation for the lack of these associations in our study is that we were able to adjust for a

| Characteristic | Overall | Neither depressive symptoms nor cognitive impairment | Cognitive impairment alone | Depressive symptoms alone | Cognitive impairment + depressive symptoms | P-value |
|----------------|---------|-----------------------------------------------------|---------------------------|--------------------------|---------------------------------------------|---------|
| Intermediate 2.3 | 183 (21.8%) | 134 (22.4%) | 21 (21.6%) | 26 (21.8%) | 2 (8.3%) | |
| Low | 646 (77.0%) | 455 (76.0%) | 76 (78.4%) | 93 (78.2%) | 22 (91.7%) | |

Depressive symptoms defined as CES-D ≥ 4. Global cognitive impairment defined as SIS < 4.

ACEi/ARBs, angiotensin converting enzyme inhibitors/aldosterone receptor blockers; ADHERE, Acute Decompensated Heart Failure National Registry; BUN, blood urea nitrogen; CES-D, Center for Epidemiological Studies Depression Scale; HDL, high density lipoprotein; IQR, inter-quartile range; sCr, serum creatinine; SD, standard deviation; SF-12, short form 12; SIS, six item screeners.

ADHERE risk categories: Low, BUN < 43 and SBP > 115; Intermediate risk 2–3, BUN ≥ 43 and SBP ≥ 115 or BUN < 43 and SBP < 115; Intermediate risk 1, BUN ≥ 43, SBP < 115 and sCr ≥ 2.75; High, BUN ≥ 43, SBP < 115 and sCr < 2.75.
number of covariates, including a variety of comorbidities, behaviours, and the ADHERE score that are not readily available in other studies. It is likely that other factors, such as comorbidities and unhealthy behaviours, confound the association between cognition-depression and mortality in HF. Similar to our report, depression did not predict all-cause mortality in the Danish nationwide population cohort of persons with HF after adjustment for similar covariates. Additionally, the group with comorbid depressive symptoms and CI was relatively small, making it harder to detect statistically significant differences.

Some previous studies have attempted to examine separately at specific features of depression, including affective, cognitive vs.
The CES-D-4 instrument is a somatic symptoms of depression, not cognitive-affective symptoms, were associated with all-cause mortality. The CES-D-4 assesses primarily affective symptoms of depression, and our finding of the lack of an association between the comorbid depressive symptoms (affective symptoms on CES-D-4) and CI and mortality is consistent with this line of research. Even though we were not able to assess somatic depressive symptoms, in our study the physical health component score of SF-12 was one of the strongest predictors of mortality, likely reflecting the burden of somatic symptoms in participants with HF.

Our study limitations include observational design that does not allow us to establish causality. Some data, such as smoking, physical activity, income, and education, were self-reported with potential bias. Data on baseline left ventricular ejection fraction or medication dosages are not available in REGARDS. The SIS instrument that was used to evaluate the CI has a known limitation of potentially missing mild CI while capturing moderate CI or dementia. The CES-D-4 instrument is a truncated version of the 16-item CES-D scale and potentially may miss some variability in depressive symptoms. Our study’s strengths include the large diverse sample of community-dwellers, HF diagnosis confirmed by Medicare claims analysis, long follow-up, availability of many physiologic and patient-reported characteristics, and rigorous adjudication of deaths.

Our study has important implications for future research and clinical practice. This study’s findings suggest that optimizing treatment for HF medical comorbidities as well as addressing unhealthy behavioural practices may represent an important approach to prevent premature mortality in HF. Clinical approach to HF patients should also take patient cognitive status into consideration. Increasing support to HF patients via caregiver education and availability of home health services may be an important avenue to improve health outcomes of HF patients.

**Table 3** Multivariable model of factors associated with all-cause mortality among heart failure participants in REGARDS

| Characteristics                        | HR  | 95% CI   | P-value |
|----------------------------------------|-----|----------|---------|
| **Depression-cognition groups**        |     |          |         |
| Cognitive impairment alone             | 1.02| 0.82–1.26| 0.83    |
| Depressive symptoms alone              | 0.91| 0.72–1.14| 0.41    |
| Both                                   | 0.91| 0.58–1.44| 0.69    |
| Neither                                | ref |          |         |
| **Demographics**                       |     |          |         |
| Male sex                               | 1.51| 1.25–1.81| <0.001  |
| African American                       | 0.93| 0.78–1.11| 0.44    |
| Age, per 1 year increase               | 1.05| 1.04–1.06| <0.001  |
| Education < high school                 | 1.03| 0.86–1.23| 0.75    |
| Annual income ≤35,000                   | 1.31| 1.09–1.59| 0.005   |
| Married                                | 0.88| 0.74–0.94| 0.14    |
| Social isolation                       | 1.09| 0.90–1.33| 0.38    |
| ‘Stroke belt’ Region (sampling variable)| 1.04| 0.88–1.24| 0.64    |
| **SF-12 Physical health score, per 1 unit increase** | 0.99| 0.98–1.00| 0.001   |
| **Comorbidities, physiological factors, medications** |     |          |         |
| Coronary artery disease                | 1.34| 1.14–1.56| <0.001  |
| History of stroke                      | 1.29| 1.06–1.56| 0.01    |
| Atrial fibrillation                    | 1.12| 0.95–1.33| 0.17    |
| Diabetes                               | 1.25| 1.06–1.48| 0.009   |
| Body mass index, per 1 unit increase   | 0.98| 0.96–0.99| 0.001   |
| Systolic blood pressure, per 1 mmHg    | 1.00| 1.00–1.01| 0.11    |
| Use of any anti-HTN medication         | 0.79| 0.60–1.05| 0.10    |
| Use of ACEi/ARBs                       | 0.97| 0.83–1.15| 0.75    |
| Use of a statin                        | 0.81| 0.69–0.95| 0.009   |
| Log-transformed albumin to creatinine ratio | 1.16| 1.10–1.22| <0.001  |
| Log transformed high sensitivity protein | 1.07| 1.01–1.15| 0.04    |
| Use of antidepressants                 | 1.20| 0.98–1.47| 0.08    |
| **Behaviours**                         |     |          |         |
| Physical inactivity                    | 1.40| 1.19–1.63| <0.001  |
| Pack years of smoking, per 1 pack-year increase | 1.00| 1.00–1.01| 0.03    |
| ADHERE in-hospital mortality predicted risk |     |          |         |
| High, Intermediate 1                   | 2.37| 1.17–4.80| 0.01    |
| Intermediate 2,3                       | 1.43| 1.13–1.79| 0.003   |
| Low                                    | ref |          |         |

somatic symptoms, and their association with mortality in HF. The data from the Rural Education to Improve Outcomes in Heart Failure clinical trial has shown that only the change in somatic symptoms of depression, not affective and cognitive symptoms, was associated with mortality among 457 HF patients. Somatic symptoms included change in appetite, sleep problems, psychomotor agitation or retardation, and fatigue. Another study of 366 outpatients with HF also showed that only somatic symptoms of depression, not cognitive-affective symptoms, were associated with all-cause mortality. The CES-D-4 assesses primarily affective symptoms of depression, and our finding of the lack of an association between the comorbid depressive symptoms (affective symptoms on CES-D-4) and CI and mortality is consistent with this line of research. Even though we were not able to assess somatic depressive symptoms, in our study the physical health component score of SF-12 was one of the strongest predictors of mortality, likely reflecting the burden of somatic symptoms in participants with HF.

Our study limitations include observational design that does not allow us to establish causality. Some data, such as smoking, physical activity, income, and education, were self-reported with potential bias. Data on baseline left ventricular ejection fraction or medication dosages are not available in REGARDS. The SIS instrument that was used to evaluate the CI has a known limitation of potentially missing mild CI while capturing moderate CI or dementia. The CES-D-4 instrument is a truncated version of the 16-item CES-D scale and potentially may miss some variability in depressive symptoms. Our study’s strengths include the large diverse sample of community-dwellers, HF diagnosis confirmed by Medicare claims analysis, long follow-up, availability of many physiologic and patient-reported characteristics, and rigorous adjudication of deaths.

Our study has important implications for future research and clinical practice. This study’s findings suggest that optimizing treatment for HF medical comorbidities as well as addressing unhealthy behavioural practices may represent an important approach to prevent premature mortality in HF. Clinical approach to HF patients should also take patient cognitive status into consideration. Increasing support to HF patients via caregiver education and availability of home health services may be an important avenue to improve health outcomes of HF patients.

**Conclusions**

In this diverse sample of US community-dwelling adults, participants with HF, who were prospectively observed for a median of 7 years, demonstrated a high rate (74%) of all-cause mortality. Baseline comorbid depressive symptoms and CI or presence of each of these syndromes alone were not associated with increased risk of death among this study’s HF population.

**Authors’ contributions**

Study concept and design by Y.K., M.R.S., M.M.S., E.B.L., P.G., E.A.J., and A.C. Data analysis by J.B.R. and M.R., with additional statistical expertise provided by E.B.L. The drafting of the manuscript by Y.K. and S.O. All authors read and approved the final manuscript and provided critical revisions.

**Ethics approval and consent to participate**

The study protocol was reviewed and approved by the University of Alabama at Birmingham Institutional Review Board and all participants provided written informed consent.
Lead author biography

Yulia Khodneva a Board-certified internal medicine clinician and an Assistant Professor in the Division of Preventive Medicine and Internal Medicine, Department of Medicine, University of Alabama in Birmingham. Her research interests include cardiovascular epidemiology and health promotion intervention development. The overarching goal of her research is to improve quality of life and other health outcomes of patients suffering from HF. She is specifically interested in HF with preserved ejection fraction and developing interventions that improve treatment of both medical and psychological comorbidities of HF with preserved ejection fraction.

Data availability

The data analyzed during the current study belong to REGARDS and further inquiry can be made at http://www.regardsstudy.org.

Supplementary material

Supplementary material is available at European Heart Journal Open online.

Acknowledgements

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/sopf/ regardsstudy/.

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, 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, 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, or interpretation of the data.

Conflict of interest: E.B.L. 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 HF. All other authors reported no conflict of interest.

References

1. Benjamin EJ, Munter P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Das SR, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Jordan LC, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longeonecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, O’Flaherty M, Pandey A, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Spartano NL, Stokes A, Tirschwell DL, Tsao CW, Turakhia MP, VanWagner LB, Wilkins JT, Wong SS, Virani SS; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. Circulation 2019;139:e56–e66.
2. Shah KS, Xu H, Matsusaka RA, Bhatt DL, Heidenreich PA, Hernandez AF, Devore AD, Yancy CW, Fonarow GC. Heart failure with preserved borderline, and reduced ejection fraction: 5-year outcomes. J Am Coll Cardiol 2017;70:2476–2486.
3. Lam PH, Dooley DJ, Deedwania P, Singh SN, Bhatt DL, Morgan CJ, Butler J, Mohammed SF, Wu VW, Panprag G, Zile MR, White M, Arndel C, Love TE, Blackman MR, Allman RM, Aronow WS, Anker SD, Fonarow GC, Ahmed A. Heart rate and outcomes in hospitalized patients with heart failure with preserved ejection fraction. J Am Coll Cardiol 2017;70:1861–1871.
4. Ko DT, Alter DA, Austin PC, You JJ, Lee DS, Qu F, Stukel TA, Tu JV. Life expectancy after an index hospitalization for patients with heart failure: a population-based study. Am Heart J 2008;155:324–331.
5. Regan JA, Kitzman DW, Leifer ES, Kraus WE, HoJ L, Forman DE, Whellan DJ, Woyda D, Parikh K, O’Connor CM, Mentz RJ. Impact of age on comorbidities and outcomes in heart failure with reduced ejection fraction: JACC Heart Fail 2019;7:1056–1065.
6. Lu MLR, De Venecia TA, Goyal A, Rodriguez Ziccardi M, Kanjanahattakij N, Shah MK, Davila CD, Figueroedo VM. Psychiatric conditions as predictors ofrehospitalization among further American patients hospitalized with heart failure. Circ Clin Cardiol 2017;40:1020–1025.
7. Murad K, Goff D, Morgan TM, Burke GL, Bartz TM, Kizer JR, Chaudhry SI, Gottlieber JS, Kitzman DW. Burden of comorbidities and functional and cognitive impairments in elderly patients at the initial diagnosis of heart failure and their impact on total mortality: the cardiovascular health study. JACC Heart Fail 2015;3:542–550.
8. 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.
9. Angermann CE, Ertl G. Depression, anxiety, and CI: comorbid mental health disorders in heart failure. Curr Heart Fail Rep 2018;15:398–410.
10. Li CL, Chiu YC, Bai YB, Lin JD, Stanaway F, Chang HY. The co-occurrence of depressive symptoms and CI and its relationship with self-care behaviors among community dwelling older adults with diabetes. Diabetes Res Clin Pract 2017;129:73–81.
11. Ismail Z, Elbayoumi H, Fischer CE, Hogan DB, Milkin CF, Schweizer T, Morbry ME, Smith EE, Patton SB, Fiest KM. Prevalence of depression in patients with mild cognitive impairment: a systematic review and meta-analysis. JAMA Psychiatry 2017;74:58–67.
12. Ulbricht CM, Rothschild AJ, Huncinjc NT, Lapane KL. Depression and CI among newly admitted nursing home residents in the USA. Int J Geriatr Psychiatry 2017;32:1172–1181.
13. Morimoto S, Kanellopoulos D, Manning KJ, Alexopoulos GS. Diagnosis and treatment of depression and CI in late life. Ann N Y Acad Sci 2015;1345:36–46.
14. van den Broek KC, Defilippi CR, Christenson RH, Seliger SL, Gottdiener JS, Kop WJ. Predictive value of depressive symptoms and 8-type natriuretic peptide for new-onset heart failure and mortality. Am J Cardiol 2011;107:723–729.
15. Newhouse A, Jiang W. Heart failure and depression. Curr Heart Fail Rep 2016;13:295–304.
16. Cannon JA, Moffitt P, Perez-Moreno AC, Walters MR, Broomfield NM, McMurray JJV, Quinn TJ. CI and heart failure: systematic review and meta-analysis. J Card Fail 2017;23:464–475.
17. Cannon JA, Shen L, Jhund PS, Kristensen SL, Kober L, Chen F, Gong J, Jelkowitiz MP, Rouleau JL, Shi VC, Swedberg K, Zile MR, Solomon SD, Parker M, McMurray JJ. PARADIGM-HF Investigators and Committees. Dementia-related adverse events in PARADIGM-HF and other trials in heart failure with reduced ejection fraction. Eur J Heart Fail 2019;11:209–137.
18. Huyhn QL, Negishi K, Blizard L, Saito M, De Pasquale CG, Hare JL, Leung D, Stanton T, Sanderson K, Venn AJ, Marwick TH. Mild CI predicts death and readmission within 30 days of discharge for heart failure. Int J Cardiol 2016;221:212–217.
19. Chaudhry SI, Wang Y, Gill TM, Krumholz HM. Geriatric conditions and subsequent mortality in older patients with heart failure. J Am Coll Cardiol 2010;55:309–316.
20. Howard VJ, Cushman M, Pulley L, Gomez CR, Go RC, Prineas RJ, Graham A, Moy CS, Howard G. The reasons for geographic and racial differences in study objective and design. Neuropolimicini 2005;25:135–143.
21. Xie F, Colantonio LD, Curtis JR, Safoon MM, Levitan EB, Howard G, Munter P. Linkage of a population-based cohort with primary data collection to Medicare claims: the reasons for geographic and racial differences in study objective. Am J Epidemiol 2016;184:532–544.
22. Kumamaru H, Judd Suzanne E, Curtis Jeffrey R, Ramachandran R, Hardy NC, Rhodes JD, Safoon Monika, Kissela Brett, Howard G, Jalbert Jessica J, Broth Thomas G, Setoguchi S. Validity of claims-based stroke algorithms in contemporary Medicare data. Circ Cardiovasc Qual Outcomes 2014;7:611–619.
23. Bertoni AG, Hundley WG, Massing MW, Bonds DE, Burke GL, Goff D. Heart failure prevalence, incidence, and mortality in the elderly with diabetes. Diabetes Care 2014; 37:699–703.

24. Colantonio LD, Levitan EB, Yun H, Kilgore ML, Rhodes JD, Howard G, Safford MM, Munter P. Use of Medicare claims data for the identification of myocardial infarction: the reasons for geographic and racial differences in stroke study. Med Care 2018;56:1051–1059.

25. Mefford MT, Sephel A, Van Dyke MK, Chen L, Durant RW, Brown TM, Fiolot M, Maya J, Goyal P, Safford MM, Levitan EB. Medication-taking behaviors and perceptions among adults with heart failure (from the REasons for Geographic And Racial Differences in Stroke Study). Am J Cardiol 2019;123:1667–1674.

26. Radiolf LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1977;1:385–401.

27. Melchior LA, Hula GJ, Brown VB, Reback CJ. A short depression index for women. Educ Psychol Meas 1993;53:1117–1125.

28. Callahan CM, Unverzagt FW, Hui SL, Perkins AJ, Hendrie HC. Six-item screener to identify CI among potential subjects for clinical research. Med Care 2002;40:771–781.

29. Steffens DC, Snowden M, Fan M-Y, Hendrie H, Katon WJ, Unützer J. IMPACT Investigators. Cognitive impairment and depression outcomes in the IMPACT study. Am J Geriatr Psychiatry 2006;14:401–409.

30. Rahimi K, Bennett D, Conrad N, Williams TM, Basu J, Dwight J, Woodward M, Patel A, McMurray J, MacMahon S. Risk prediction in patients with heart failure: a systematic review and analysis. JACC Heart Fail 2014;2:440–446.

31. Sterling MR, Ringel JB, Pinheiro LC, Safford MM, Levitan EB, Phillips E, Brown TM, Goyal P. Social determinants of health and 90-day mortality after hospitalization for heart failure in the REGARDS study. J Am Heart Assoc 2020;9:e014836.

32. Calvillo-King L, Arnold D, Eubank KJ, Lo M, Yungyongying P, Stiglitz H, Halm EA. Impact of social factors on risk of readmission or mortality in pneumonia and heart failure: systematic review. J Gen Intern Med 2013;28:269–282.

33. Gilsippet SR, Thacker EL, Letter AJ, McClure LA, Wadley VG, Unverzagt FW, Kissela BM, Kennedy RE, Glasser SP, Levine DA, Cushman M. Correlates of incident CI in the REasons for Geographic and Racial Differences in Stroke (REGARDS) study. Clin Neuropsychol 2015;29:466–486.

34. Summer JA, Khodireva Y, Munter P, Redmond N, Lewis MW, Davidson KW, Edmondson D, Richman J, Safford MM. Effects of concurrent depressive symptoms and perceived stress on cardiovascular risk in low- and high-income participants: findings from a large UK general population-based cohort. J Psychosom Res 2019;120:134–140.

35. Lan H, Hawkins LA, Kashner M, Perez E, Finkel J, Silvet H. CI predicts mortality in out-patient veterans with heart failure. Heart Lung 2018;47:346–352.

36. Gathright EC, Goldstein CM, Josephson RA, Hughes JW. Depression increases the risk of acute coronary mortality in patients with atrial fibrillation and heart failure. Circulation 2009;120:134–140.

37. Sterling MR, Jannat-Khah D, Bryan J, Banerjee S, McClure LA, Wadley VG, Unverzagt FW, Levitan EB, Peterson JC, Manly JJ, Levine DA, Safford MM. The prevalence of CI among adults with incident heart failure: the “reasons for geographic and racial differences in stroke” (REGARDS) study. J Card Fail 2019;25:130–136.

38. Wint LS, Rotter J, Steans SC, Gottesman RF, Kucharska-Newton AM, Richay Sharrett A, Wruck LM, Bressler J, Sueta GA, Chang PP. Heart failure and CI in the atherosclerosis risk in communities (ARIC) study. J Gen Intern Med 2018;33:1721–1728.

39. Adelborg K, Schmidt M, Sundbøll J, Pedersen L, Videbech P, Bøtker Hans E, Egstrup K, Sørensen Henrik T. Mortality risk among heart failure patients with depression: a nationwide population-based cohort study. J Am Heart Assoc 2016;5:e004137.

40. Warrach HJ, Kitzman DW, Whelan DJ, Duncan PV, Mentz RJ, Pastva AM, Nelson MB, Lippadthy B, Reeves GR. Physical function, frailty, cognition, depression, and quality of life in hospitalized adults ≥60 years with acute decompensated heart failure with preserved versus reduced ejection fraction. Circ Heart Fail 2018;11:e005254.

41. Chiala O, Vellone E, Klompstra L, Ortaí GA, Stromberg A, Jaarsma T. Relationships between exercise capacity and anxiety, depression, and cognition in patients with heart failure. Heart Lung 2018;47:465–470.

42. Warraich HJ, Kitzman DW, Whellan DJ, Duncan PV, Mentz RJ, Pastva AM, Nelson MB, Lippadthy B, Reeves GR. Physical function, frailty, cognition, depression, and quality of life in hospitalized adults ≥60 years with acute decompensated heart failure with preserved versus reduced ejection fraction. Circ Heart Fail 2018;11:e005254.

43. Bauer LC, Johnson JK, Pozehl BJ. Cognition in heart failure: an overview of the concepts and their measures. J Am Acad Nurse Pract 2011;23:577–585.