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Depression Increases the Risk of Mortality in Patients with Heart Failure: A Meta-Analysis

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Abstract

Background—Depression is a risk factor for mortality in cardiovascular diseases. Prior studies confirm that depression predicts adverse outcomes in patients with heart failure (HF). However, data were inconclusive regarding the effect of depression on mortality. This meta-analysis examines the relationship between depression and mortality in HF.

Methods—Prospective studies of depression and mortality in HF published between 1999 and April 2016 were located using PubMed, PsychINFO, and *MEDLINE*. Comprehensive Meta-Analysis software was used to compute an aggregated effect size estimates of hazard ratios and to conduct subgroup analyses.

Results—Eighteen studies met inclusion criteria. For 8 aggregated univariate and 14 multivariate estimates, depressive symptoms were related to all-cause mortality. A pooled HR of 3 multivariate analyses indicated that depressive symptoms were not linked to cardiovascular mortality. In subgroup analyses, depression predicted all-cause mortality in samples with a mean age > 65. The impact of depression on all-cause mortality also differed by follow-up duration, with samples with shorter follow-up durations demonstrating a larger effect.

Conclusions—In HF, depression is related to increased all-cause mortality risk, with stronger effects in samples with shorter follow-up and in older adults. In older adults, depression may serve as a marker of more severe HF. However, this possibility is difficult to examine given inconsistent adjustment for HF severity. Additional studies may assist in determining the relationship between depression and cardiovascular mortality, as the low number of studies examining cardiovascular mortality may have precluded detection of an effect.

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Keywords

heart failure; depression; mortality; meta-analysis

Depression in Heart Failure

Within the United States, 5.1 million persons have heart failure (HF) and 825,000 new HF cases are diagnosed each year.¹ Estimates indicate that the prevalence of HF will increase 46% by 2030, so that >8 million U.S. adults will have HF,² in part due to the aging population and improved survival rates following MI.³

Although survival rates have improved substantially, mortality in HF remains high. Fifty percent of HF patients die within five years of diagnosis.⁴⁻⁶ The contributors to mortality in HF are multifactorial. In addition to the pathophysiological effects of the disease itself, psychosocial factors may also play a role. Many individuals with HF experience depressive symptoms or clinical depression. Estimates indicate that approximately one in five patients with HF experience symptoms of a depressive disorder during the course of their illness⁷ and the prevalence of depression increases in concert with disease severity.^{7, 8}

Depression is well-established as a predictor of adverse clinical events such as negative health outcomes and increased healthcare usage. For example, depressed HF patients have a 2-fold risk of emergency room visits,⁹ and markedly higher hospital readmission rates.⁷ In a 3-year, retrospective analysis of health care utilization in 10,980 HF patients, Sullivan and colleagues¹⁰ reported that annual healthcare costs for HF patients with a chart-documented diagnosis of depression who were also prescribed antidepressants were 29% higher than for patients with no chart-documented evidence of depression (i.e., chart diagnosis or antidepressant prescription). The increase in cost is not attributable to mental health-related costs alone, but primarily stems from increased inpatient and outpatient medical visits.¹⁰

Existent data is incomplete or inconclusive regarding the correlation of depression and mortality in patients with HF. Although some contradictory evidence exists, findings generally indicate that depression predicts mortality in HF. A meta-analysis from a decade ago reported a 2-fold increased risk of death and associated cardiac events (e.g., heart transplantation, new cardiac events) for HF patients with elevated depressive symptoms or a diagnosis of a depressive disorder (relative risk: 2.1, 95% CI: 1.7 to 2.6).⁷ Rutledge et al. also reported that the association between depression and HF outcomes (mortality and clinical events) did not differ by study duration, though the studies included were limited by small sample sizes and likely underpowered to detect short-term differences in mortality and clinical events between depressed and non-depressed individuals. However, this was a small portion of a larger meta-analysis and only included eight studies. Furthermore, Rutledge et al. did not examine mortality alone, likely due to an insufficient number of studies solely estimating mortality risk. Exploration of the impact of depression on mortality independent of clinical events may differ given the added severity of reduced survival.

Present Study

Given the increasing prevalence of HF and the severity of the disruptions in the pathophysiology of the cardiovascular system, it is important to determine whether depression conveys similarly added risk in HF as in other presentations of cardiovascular disease such as myocardial infarction. For example, a meta-analysis of 29 studies spanning 25 years revealed that depression is associated with increased risk of cardiac events, cardiac mortality, and all-cause mortality within 24 months of MI.¹¹ Although one prior meta-analysis provided a valuable summary of the HF literature up to 2006, an updated meta-analysis may provide a more current and comprehensive estimate of the effect size of depression on mortality specifically. Thus, the objective of this paper is to summarize and systematically evaluate the influence of depression on mortality in HF patients. Based on previous research, we hypothesized that elevated depressive symptoms increase cardiovascular and all-cause mortality in HF patients. An additional purpose of the present study was to examine the impact of a number of moderators (i.e., mean age of sample, study location, recruitment setting, and follow-up duration) of the relationship between depression and mortality.

Method

The conduct of this meta-analysis was informed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.¹²

Selection of Studies

Only studies of individuals 18 years of age diagnosed with HF were selected for review. Studies that examined other types of cardiovascular disease were excluded unless specific statistics for a subset of the sample with HF were reported. Additional selection criteria included the following: (a) the study used a prospective design, (b) the study included and compared results of both depressed and non-depressed individuals, and (c) a univariate or multivariate hazard ratio reflecting the association between depression and all-cause and/or cardiovascular mortality was reported. For studies that reported data for both cardiovascular and all-cause mortality, data regarding all-cause mortality and cardiovascular mortality were analyzed separately. When two or more studies reported analyses of the same sample of participants, the study with a larger sample size was included in the primary meta-analysis. Studies reporting outcomes with different lengths of follow-up for the same sample of participants were included in subgroup analyses examining whether pooled effect sizes differed by length of follow-up.

Definition of Depression

Either clinical depression or depressive symptoms must have been assessed at baseline using a standardized clinical interview or standardized psychometric scales. Studies assessing depression prior to a cardiac procedure were excluded due to potential bias resulting from preoperative symptoms. Retrospective studies using previous documentation of depression were also excluded.

Literature Search and Data Sources

Only published journal articles and unpublished manuscripts (when available) were considered for inclusion. Literature searches were conducted using PsycINFO and *MEDLINE*, and PubMed to locate articles published in English from 1999-May 2016. Of note, the first study eligible for inclusion was published in 1999 and no earlier studies were excluded because of this date selection. Search terms included a combination of 1) “depression,” “depressive disorder,” or “depressive symptoms,” 2) “heart failure,” and 3) “mortality,” “death,” or “survival.” The references of review articles and retrieved studies were examined to identify additional potentially relevant studies. Full copies of all articles deemed potentially relevant based on the title and/or abstract were obtained for a thorough review. A follow-up computerized search of online databases was conducted with the names of the first authors of those studies; however, no additional potentially relevant studies were identified.

Data Management

The first and second authors thoroughly reviewed each manuscript. The following variables were coded for each article: 1) location (e.g., the country in which the study was conducted), 2) sample size, 3) mean age of the sample, 4) proportion of men in each sample expressed as a percentage, 5) recruitment setting (e.g., inpatient versus outpatient), 6) whether depression was assessed through a diagnostic clinical interview or a standardized self-report inventory (e.g., BDI or HADS), 7) study duration categorized as short-term (< 24 months), medium-term (> 24 – < 60 months), or long-term (≥ 60 months) follow-up, 8) primary outcome of the study (e.g., all-cause mortality or cardiovascular mortality), and 9) whether univariate and/or multivariate hazards ratios were reported.

Statistical Analysis

Univariate and/or multivariate hazard ratios (HRs) and 95% confidence intervals (CIs) were extracted from the eligible studies and combined to estimate an aggregated effect size. Univariate and multivariate hazard ratios were analyzed separately. For studies reporting multiple models, the adjusted HR from the final model was used.

Model selection and Heterogeneity—A random effects model was selected prior to statistically testing for heterogeneity because the included study protocols varied in potentially important ways (e.g., recruitment setting, length of follow-up).

Cochran’s Q statistic was used to assess heterogeneity. However, as the Q statistic is underpowered to detect the presence of heterogeneity when the number of studies is small¹³, the I^2 - statistic was included as an additional description of the amount of heterogeneity present. The I^2 statistic provides an estimate of the percentage of variation across studies that can be attributed to heterogeneity rather than chance alone and is not dependent on the number of studies.^{14,15} I^2 values greater than .75 or 75% were assumed to indicate high heterogeneity beyond sampling error alone.¹⁵

Moderator analyses—Subgroup analyses of categorical variables were conducted to explain observed heterogeneity. Potential explanatory variables were selected a priori. These

variables included mean age of the sample (categorized as < 65 or > 65), gender (< or > 50% male), recruitment setting (i.e., inpatient versus outpatient), and duration of follow-up. Moderating effects were defined as significantly different mean effect sizes between subgroups ($p < .05$) and presence of a reduction in within-subgroup variance compared to between-subgroup variance.

Publication Bias—Publication bias may especially affect the current meta-analysis as studies of mortality are often underpowered to detect significant results due to the large sample sizes required to have a sufficient base rate of events (i.e., deaths). Multiple measures of publication bias were assessed for each analysis. Rosenthal's classic fail-safe N was calculated to estimate the number of additional studies with non-significant results that would be necessary to nullify the current findings. Begg and Mazumdar's rank correlation was used to assess the rank correlation between the standardized effect size and the standard errors of the effects^{16, 17} (Begg and Mazumdar, 1994; Begg, 1994). When publication bias is present, high standard errors, presumably associated with small studies, are assumed to be associated with larger effect sizes. However, this test tends to have low power unless substantial bias is present^{18,19} (Sterne et al., 2000, 2001). Therefore, Egger's linear regression estimate was also examined^{19,20} (Egger et al., 1997; Sterne et al., 2001) which examines the actual values of the effect sizes and their precision instead of their ranks. Comprehensive Meta-Analysis version 2.0²¹ was used for analyses. STATA version 12.0 (Stata Corp LP, College Station) was used for creation of forest plots.

Results

Literature Search

A total of 67 studies were identified as potentially relevant to the current analysis based on the title and/or abstract. After review of the full manuscripts, 18 studies met the full inclusion criteria for one or more of the present analyses. See Figure 1 for a flow diagram of study selection and reasons for exclusion.

Of studies included in the meta-analysis, eight articles were based on studies conducted in the United States, whereas other studies were conducted in Japan ($N = 1$), the Netherlands ($N = 2$), Germany ($N = 2$), Spain ($N = 2$), Switzerland ($N = 1$), Norway ($N = 2$), and Italy ($N = 1$). In total, multivariate all-cause mortality results for 5,629 participants (3,488 for univariate estimates only) and multivariate cardiovascular mortality results for 1,696 participants were analyzed. Note that these totals include independent samples rather than the total number of included studies to account for overlapping samples. For overlapping samples, the study reporting the larger sample size was used to compute the total number of participants. Sample size ranged from $n = 111$ to $n = 1,082$. Publication dates ranged from 1999 to 2016. A description of the studies included in the meta-analysis is presented in Table 1.

Type of Participants

The mean age ranged from 53.2 to 79.2 years. Studies were primarily comprised of male HF patients. Of studies reporting minority status, most participants were Caucasian. However,

several studies, primarily studies conducted outside of the U.S., did not report minority composition of the sample. Most of the studies recruited participants from outpatient settings.

Study Characteristics

Measurement of Depression—Most studies assessed depressive symptoms using standardized self-report inventories, including the Beck Depression Inventory (BDI; multiple forms available), the Center for Epidemiologic Studies Depression Scale (CES-D), the Patient Health Questionnaire (PHQ; 9-items version and 2-item version), the Geriatric Depression Scale (GDS), the Zung Self-rating Depression Scale (SDS), a modified version of the GDS, and the Hospital Anxiety and Depression Scale (HADS).

Study Outcome—Of the 18 studies, all reported all-cause mortality results and 3 studies reported both cardiovascular and all-cause mortality. Two studies reported univariate analyses only, nine reported multivariate analyses only, and seven reported both univariate and multivariate findings. The range of follow-up varied from 12 months to 12 years.

Effect of Depressive Symptoms

All-Cause Mortality—Among studies that reported a univariate HR, depressive symptoms were predictive of increased mortality risk (HR = 1.75; 95% CI: 1.33 – 2.30; see Figure 2). Substantial heterogeneity was observed between effect sizes ($Q(7) = 44.77, p < .001, I^2 = 84.36\%$). Subgroup analyses revealed that both samples with a mean age < 65 (HR = 1.95; 95% CI: 1.17 – 3.25) and samples with a mean age ≥ 65 (HR = 1.72; 95% CI: 1.31 – 2.51) yielded significant effects. The difference between effect sizes was not significant, $p = .71$. In addition, effect sizes did not differ by study location (i.e., U.S. vs. non-U.S.), $p = .65$. Subgroup analyses examining inpatient/outpatient and length of follow-up differences were not conducted due to limited variability on these characteristics for studies that reported univariate HRs.

Also, analysis of aggregated multivariate HRs indicated that baseline depressive symptoms were associated with increased mortality risk, (HR = 1.20; 95% CI: 1.10–1.31; see Figure 3). Substantial heterogeneity was noted between effect sizes ($Q(13) = 57.51, p < .001, I^2 = 77.40\%$).

Moderator variables were examined to explore possible contributors to the observed heterogeneity in multivariate analyses. Both U.S.-based and non-U.S. based studies demonstrated pooled increased mortality risk associated with depressive symptoms. There was not a significant difference between effect sizes, $p = .36$. Subgroup analyses also revealed that depression significantly predicted mortality in inpatient (HR = 1.36; 95% CI: 1.09 – 1.62) and outpatient (HR = 1.11; 95% CI: 1.03 – 1.20) samples. No difference emerged between the effect sizes, $p = .11$.

Analyses indicated that depression significantly increased mortality risk in samples with a mean age ≥ 65 (HR: 1.26; 95% CI: 1.12 – 1.42), but not < 65 years. Differences in length of follow-up were also tested. There was a significant short-term effect of depressive symptoms on all-cause mortality (HR = 3.24; 95% CI: 2.21–4.74), a significant medium-term effect

(HR = 1.13; 95% CI: 1.03–1.24), and a significant long-term effect (HR = 1.13; 95% CI: 1.03–1.24) of depressive symptoms on all-cause mortality. The difference between effect sizes was significant, ($Q(2) = 28.38, p < .001$). See Table 2 for a summary of moderator analyses.

Publication Bias: All-Cause Mortality—Rosenthal’s classic fail-safe N suggested that 128 additional studies with non-significant results would be necessary to attenuate the current findings to the null value. Additionally, Begg and Mazumdar’s rank correlation (Kendall’s tau) test was non-significant, $p = .62$, supporting the absence of bias. However, Egger’s linear regression suggested the possible presence of bias, $p < .01$.

Publication bias in the multivariate analyses was also examined. Rosenthal’s fail-safe N indicated that 252 non-significant studies would be necessary to reduce the current findings to the null value. However, both Begg and Mazumdar’s rank correlation test ($p < .01$) and Egger’s linear regression ($p < .01$) indicated the presence of possible bias.

Cardiovascular Mortality—Only one study reported a univariate HR for cardiovascular mortality²³. Three studies reported multivariate HRs for cardiovascular mortality. After adjustment for cardiovascular risk factors, depressive symptoms did not demonstrate an impact on cardiovascular mortality (HR = 1.64; 95% CI: .88 – 3.06; see Figure 4). Among studies of cardiovascular mortality, significant heterogeneity was observed among effect sizes, ($Q(2) = 10.02, p < .01; I^2 = 80.04\%$). However, given small number of primary studies, moderator analyses were not conducted for cardiovascular mortality.

Publication Bias: Cardiovascular Mortality—Neither Begg and Mazumdar’s rank correlation test ($p > .05$) nor Egger’s linear regression test ($p > .05$) indicated the presence of bias. However, these tests have low power when the number of studies is small. Therefore, the possibility of publication bias cannot fully be excluded.

Discussion

The current meta-analysis investigated the impact of depressive symptoms on all-cause and cardiovascular mortality in HF patients. Compared with a prior meta-analysis on this topic, the current analysis was expanded to include additional reports and provide a more comprehensive look into study characteristics that may create heterogeneity in effect sizes. Four potential moderating variables were examined (age, study location, recruitment setting, and length of follow-up).

Consistent with Rutledge et al.,⁷ the current meta-analysis indicated that depressive symptoms were associated with poorer prognosis in HF. We extended Rutledge’s findings by reporting that depression increased all-cause, but not cardiovascular, mortality risk in HF patients. Subgroup analyses indicated that studies with shorter follow-up duration demonstrated larger effect sizes compared to studies with a longer follow-up. In addition, depression increased mortality risk in samples reporting multivariate HRs with a mean age 65, but not < 65 years. No additional moderating relationships emerged.

Depression adversely affected all-cause mortality risk in studies of short-, medium-, and long-term follow-up, with studies with a follow up of less than 2 years demonstrating the largest relationship between depression and mortality risk. This finding differs from Rutledge et al.'s⁷ report that study duration had no effect. The current analysis included more variability in study duration, which may account for this difference. Few individual reports have included HRs at multiple time points. In those that have, an inconsistent pattern of findings emerges. For example, Jiang and colleagues³⁹ found that depressive symptoms predicted mortality at 3 month follow-up, but not 1 year follow-up. Of note, Jiang et al.,³⁹ was not included in the present analysis due to differences in statistical analyses (i.e., reporting of odds ratios versus hazard ratios). Conversely, in a study of 209 HF patients, Junger and colleagues²⁵ found that mortality risk associated with depression was lowest during the first year of follow-up and increased over the course of the 30 month follow-up. At 6 months, the HR was 1.03 (95% CI: .44 – 2.39). At 30 months post-baseline, the HR increased to 8.22 (95% CI: 2.62 – 25.84). However, Junger's et al's²⁵ report did not extend substantially beyond the limits of the current meta-analyses definition of short-term studies, which makes the findings difficult to compare to longer follow-up durations. Over time, individuals are likely to experience worsening disease severity or develop additional medical comorbidities, which may attenuate the relationship between depression and mortality risk. Nonetheless, depression remains a prognostic marker of mortality risk in both the short- and long-term.

Subgroup analyses indicated that the pooled HR for studies reporting multivariate HRs with a mean age less than 65 years was non-significant. Conversely, subgroup analyses of univariate HRs revealed that both groups demonstrated significant effects which suggests that the association between depression and mortality risk may be consistent across ages. This discrepancy was surprising for multiple reasons. First, multivariate analyses typically control for age. Thus, the multivariate HRs convey the strength of the relationship beyond the influence of age. Additionally, the finding that depression predicted mortality in older, but not younger, samples was counterintuitive given that younger HF patients tend to endorse more depressive symptoms than older HF patients.⁴⁰ Significant heterogeneity was present within this subgroup, indicating that other factors, such as disease severity, race/ethnicity, gender, social support, or socioeconomic status, may play a role. For example, it remains possible that depression may serve as a marker of disease severity in older populations, while being more strongly related to functional limitations in younger populations. As older populations often present with other competing etiologies of mortality, and as studies often do not adjust for HF severity in a uniform way, it was impossible to examine this possibility in the present analysis. However, future work may consider exploration of these possibilities and provide clarity as to whether these findings may be influenced by Type 2 error when a systematic reporting style is consistent throughout the literature.

As opposed to the effects on all-cause mortality, pooled HRs suggested that depression does not lead to increased cardiovascular mortality risk in HF. Given that only three studies reported cardiovascular-specific outcomes, additional studies may lead to a different result. Alternatively, depression may not lead to cardiovascular-specific mortality in HF. HF patients represent a vulnerable clinical population with many medical comorbidities that

require significant self-monitoring and complicated treatment regimens. HF may lead to medical compromises that may increase likelihood of death when faced with onset of other illnesses or complications. Additionally, the presence of multiple comorbid conditions may make it difficult to determine a specific cause of death in some instances, which may lead to misclassification of death etiology.

Other potential moderators, such as recruitment setting and study location, did not demonstrate moderating effects. As limited explanation for the observed heterogeneity in effect sizes was ascertained in the current analysis, continued exploration of study and participant characteristics that explain differences in effect size is warranted. Thus, future research should increase efforts to include more female participants or to examine differences due to gender, racial/ethnic minority, SES, and social support, among others.

The current meta-analysis also did not examine some factors which are likely important contributors to HF outcomes including the etiology of HF (i.e., ischemic vs. non-ischemic origin), presence or absence of systolic dysfunction, and differences in treatment. Many of the studies included patients with both systolic and diastolic HF, and did not report separate analyses. In addition, as future studies representing patients undergoing more current treatment options are published, it will be important for future analyses to consider temporal trends in mortality outcomes that may be influenced by changes in treatment. For example, the increased use of implantable cardioverter defibrillators (ICDs) over time may mitigate the effect of depression on arrhythmic death. However, the prevalence of ICDs commonly goes unreported. Finally, many individuals with HF have other cardiac diagnoses including history of MI, arrhythmia, and coronary artery disease. Future work may wish to examine more specifically whether there is a differential prognostic impact of depression in patient with HF with or without history of MI given the relationship between depression and mortality post-MI.

Limitations

Several limitations should be noted. Although adjusted HRs provide valuable estimates after controlling for potential confounding risk factors, most studies did not control for the same risk factors. Additionally, publication bias may be present and it remains possible that studies without significant effects have not been published. As a result, the results presented may be an overestimate of the true effect.

Several potentially relevant studies did not report sufficient information to be included in the meta-analysis. In addition, multiple studies included in the meta-analysis did not report sufficient detail regarding sample characteristics to be included in moderator analyses. It will be important for future studies to report more complete information. Other potential moderators were not included in the current analysis, but they may play a significant role in the relationship between depression and mortality. Future efforts to understand the impact of depressive symptoms on clinical outcomes in HF should also incorporate more thorough explorations of the impact of antidepressant use, the number and type of comorbidities, the impact of cognitive versus somatic symptoms, timing of depression onset, as well as the frequency and duration of recurrent hospitalizations in relation to the baseline and follow-up assessments.

Conclusions

Depression increases all-cause mortality risk in HF patients. Furthermore, all-cause mortality risk is increased in studies of short-, medium-, and long-term follow-up. These findings mirror the established association between depression and mortality in coronary heart disease and post-myocardial infarction. Depression was not related to cardiovascular mortality. However, given the small number of studies reporting cardiovascular-specific outcomes, additional research is warranted. Recruitment setting and study location did not impact effect size differences across studies. Other factors, such as disease severity, may be more important contributors. However, additional studies with increased more female and minority participants are needed. The relationship between depression and HF may reflect behavioral and psychosocial factors or underlying changes in pathophysiology, or a combination. No treatment studies have effectively improved HF outcomes by treating depression. Nonetheless, depression treatment effectively addresses symptoms and improves quality of life in depressed HF patients. Screening of depression in HF patients and attention to persistent depressive symptoms remains important to identify patients in need of increased clinical management and support.

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Highlights

- An updated meta-analysis of depression and mortality in HF is presented.
- Depression is a predictor of all-cause mortality in HF.
- Stronger effects were found in samples of older adults and with shorter follow-up.
- Future work should continue to explore depression and cardiac mortality.

Figure 1.
Flow diagram of study selection.

Figure 2.
Forest plot of the univariate association between depression and all-cause mortality in HF.

Figure 3.
Forest plot of the multivariate association between depression and all-cause mortality in HF.

Figure 4.
Forest plot of association between depression and cardiovascular mortality in HF.

Table 1

Summary of studies included in the meta-analysis.

Study	Location	Sample	Mean Age of Sample	Gender (% Male)	Follow-up Duration	Depression Measure	Analysis	Outcome
Adams et al., 2012 ²²	United States	985 HF inpatients	69.07	62.22	Mean 4.9 years	BDI	Univariate & Multivariate	All-Cause Mortality
Diez-Quezveredo et al., 2013 ²³	Spain	1,017 HF outpatients	68.0 (median)	73.0	Median 5.4 years	GDS-4	Univariate & Multivariate	All-Cause & Cardiovascular Mortality
Faller et al., 2007 ⁸	Germany	231 HF patients [‡]	64.00	70.6	Median 986 days	PHQ-9	Univariate & Multivariate	All-Cause Mortality
Jiang et al., 2007 ²⁴	United States	1006 inpatients	69.12 [±]	62.39 [±]	Mean 971 days	BDI	Univariate & Multivariate	All-Cause
Junger et al., 2005 ²⁵	Germany	209 HF patients [‡]	54.00	86.1	Mean 24.8 months	HADS-D	Univariate & Multivariate	All-Cause Mortality
Kato, 2009 ²⁶	Japan	115 HF outpatients	64.7 [±]	73.9 [±]	Median 756 days	CES-D	Univariate & Multivariate	All-Cause Mortality
Monmersteeg, 2016 ²⁷	Netherlands	104 HF outpatients	66 [±]	85 [±]	6.1 years	BDI	Multivariate	All-Cause Mortality
Moraska et al., 2013 ²⁸	United States	402 HF inpatients and outpatients	73.3	57.7	Mean 1.6 years	PHQ-9	Univariate & Multivariate	All-Cause Mortality
Murad et al., 2013 ²⁹	United States	1,082 HF outpatients	79.2	52	4.3 years	CES-D	Multivariate	All-Cause Mortality
Murberg et al., 1999 ³⁰	Norway	119 HF outpatients	65.7	71.4	2 years	SDS	Multivariate	All-Cause Mortality
Rollman et al., 2012 ³¹	United States	471 HF inpatients	69.57 [±]	64.5 [±]	1 year	PHQ-2	Multivariate	All-Cause & Cardiovascular Mortality
Schiffer et al., 2009 ³²	Netherlands	366 HF outpatients	65.22 [±]	71.58 [±]	Mean 37.2 months	BDI	Univariate	All-Cause Mortality
Sherwood et al., 2007 ³³	United States	204 HF outpatients	56.8	68.1	Median 3 years	BDI	Multivariate	All-Cause Mortality
Sullivan et al., 2004 ³⁴	United States	142 HF outpatients	53.2	77.5	Mean 3 years	PRIME-MD; HDRS; SCL-20	Univariate	All-Cause Mortality
Testa et al., 2011 ³⁵	Italy	125 HF outpatients and 1,143 healthy controls	75.9	39.7	12 years	GDS	Multivariate	All-Cause Mortality
van den Broek et al., 2011 ³⁶	United States	208 HF outpatients	72.9	49	Median 11 years	CES-D	Multivariate	All-Cause & Cardiovascular Mortality
Volz et al., 2011 ³⁷	Switzerland	111 HF outpatients	57	82	Mean 2.8 years	HADS	Multivariate	All-Cause Mortality
Zuluaga et al., 2010 ³⁸	Spain	433 HF inpatients	77.54 [±]	43.65 [±]	Mean 5.7 years	GDS	Multivariate	All-Cause Mortality

Note. SD = standard deviation; HF = heart failure; BDI = Beck Depression Inventory; GDS = Geriatric Depression Scale; PHQ = Patient Health Questionnaire; HADS-D = Hospital Anxiety and Depression Scale- Depression; CES-D = Center for Epidemiologic Studies Depression Scale; SDS = Zung Self-rating Depression Scale.

[‡]Information calculated based on reported information.

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Information unclear or not reported in manuscript.
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Table 2

Subgroup analyses examining the impact of covariates on the effect size of the relationship between depression and all-cause mortality risk in HF.

Variable	Number of Studies	Effect Size	95% CI	Q within
<i>Univariate</i>				
Mean Age				
< 65	4	1.95	1.17 – 3.25	20.43 *** }p = .71
65	4	1.72	1.13 – 2.62	9.83 *
Study Location				
United States	3	1.94	1.18 – 3.17	8.84 *
Not United States	5	1.69	1.18 – 2.40	26.63 }p = .65
<i>Multivariate</i>				
Mean Age				
< 65	5	1.15	.97 – 1.37	14.07 **
65	9	1.26	1.12 – 1.42	41.59 *** }p = .41
Recruitment Setting				
Inpatient	3	1.33	1.09 – 1.62	6.07 *
Outpatient	8	1.11	1.03 – 1.20	17.65 *
Length of Follow-up				
24 months	3	3.24	2.21 – 4.74	1.43
> 24 – < 60 months	7	1.13	1.03 – 1.24	18.77 ** }p = .00
60 months	5	1.13	1.03 – 1.24	6.79
Study Location				
United States	5	1.31	1.11 – 1.54	35.14 ***
Not United States	9	1.19	1.05 – 1.35	22.26 ** }p = .36

Note. Hazard Ratios presented as effect size for categorical moderators. 95% CI = 95% Confidence Interval;

Q = Q-statistic for heterogeneity.

* p < .05,

** p < .01,

*** p < .001