Prediction of outcomes in patients with heart failure

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2 Depression and anxiety as predictors of mortality among HF patients: systematic review and meta-analysis

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ABSTRACT

Aims: Several studies suggest that psychological factors are associated with negative outcomes and in particular higher mortality rates among Heart Failure (HF) patients. We aimed to evaluate the effect sizes of depression and anxiety on all-cause mortality in HF patients.

Methods and results: We conducted a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology. We searched for studies on depression or anxiety effects on all-cause mortality among HF patients published up to June 2015. A number of 26 and 6 articles met inclusion criteria for depression (total 80627 patients) and anxiety (total 17214 patients) respectively. The effect estimates were pooled using random-effect meta-analysis.

Depression has significant and moderately heterogeneous effect on all-cause mortality (HR = 1.57; 95%CI 1.30 – 1.89, $P < 0.001$); adjustment for confounders led to a similar effect estimate (HR = 1.40; 95%CI 1.22 – 1.60; $p < 0.001$). Larger studies and higher study prevalence of depression were associated with smaller effect size. The effect of anxiety on mortality outcome was small and not conclusive given the low number of studies (n=6) (HR = 1.02; 95% CI 1.00 – 1.04, $P < 0.05$).

Conclusions: This systematic review and meta-analysis suggests that depression is an important and independent predictor of all-cause mortality among HF patients, while anxiety does not appear to have a strong effect. Further research is recommended towards the detection and treatment of depression.

INTRODUCTION

Heart Failure (HF) is defined as a clinical syndrome in which patients have typical symptoms such as breathlessness, ankle swelling, and fatigue and signs such as elevated jugular venous pressure, pulmonary crackles, and displaced apex beat, resulting from an abnormality of cardiac structure or function [1]. Approximately 1–2% of the adult population in developed countries has HF, with the prevalence rising to $\geq 10\%$ among persons 70 years of age or older [2]. HF is one of the most common causes of hospital readmission and mortality.

Psychological factors such as depression or anxiety are often reported with high prevalence and strong association with negative outcomes in patients with cardiovascular disease [3]. Many studies have reported high rates of depression among HF patients. A prior systematic review and meta-analysis published by Rutledge in 2006 [4] reported an overall aggregated depression prevalence rate of 21.6% among HF patients, while individual study prevalence estimates ranged from 9% to 60%. Moreover, in 2005 Konstam [5] reported that approximately 40% of HF patients may suffer from major anxiety, and overall anxiety levels are 60% higher than levels seen in the healthy population.

Depression has been linked to increased risk of negative outcomes, such as rehospitalization and mortality among HF patients. According to a previous meta-analysis, the aggregated risk estimate derived from 8 studies suggested a greater than 2-fold risk of death and secondary events for HF patients with heightened depressive symptoms or a depressive disorder [4]. A similar analysis was also published by Fan [6] in 2014 on 9 prospective studies, who reported a pooled Hazard Ratio of 1.51 for patients with depression compared to patients without depression. In both cases the result was strongly heterogeneous but no further analysis, such as meta-regression, was performed to examine the sources of this heterogeneity. On the other hand, there is, to the best of our knowledge, no meta-analysis published about the prevalence of anxiety among HF patients and the effect of anxiety on mortality outcome. Even though anxiety is usually correlated with depression, it has not extensively been studied among patients with HF.

Our aim is to provide an updated systematic review of prospective or retrospective studies and a meta-analysis of the effect of depression and the effect of anxiety on

mortality among HF patients. To reach this objective, we searched extensively for available studies investigating the impact of depression and anxiety on mortality of HF patients. Within these studies, we identified also the reported prevalence of depression or anxiety among HF patients.

METHODS

Search strategy and selection criteria

This systematic review and meta-analysis were conducted according to the guidelines introduced in the Preferred Reporting Items for Systematic reviews and Meta-analysis (the PRISMA Statement) [7]. The 27 checklist items of the PRISMA methodology followed are given in Appendix A. Three electronic databases (MEDLINE, BIOSIS and EMBASE) were searched for studies that investigated the relationship between depression or anxiety and mortality among Heart Failure (HF) patients. No publication time restriction was applied. All papers written in English and published before the 25th of June 2015 were included. Selected journals as well as the references of full-text papers were also hand-searched, when necessary, in order to identify studies that meet the inclusion criteria.

The database search string was created according to the PICO model (P, population/patient; I, intervention/indicator; C, comparator/control; and O, outcome). For the "P" in PICO the "HEART FAILURE" keyword was included. For the "I", the following keywords: "DEPRESS? OR STRESS OR ANXIETY OR PSYCHOLOG?". For the "C", no particular terms were used in our case. For "O", we used the following keywords: "MORTALITY OR DEATH". The complete query as used for the databases search is given in Appendix B.

Study selection

In our analysis, several inclusion and exclusion criteria were defined. All studies that met those criteria were included. The inclusion criteria were articles presenting studies focusing on the association between depression or anxiety and mortality in a HF adult population. All mortality outcomes such as all-cause or cardiac related mortality were included and studies focusing on inpatient, outpatient or both care settings were taken into account. On the other hand, publications analyzing data that had already been used before for the same purpose, studies introducing no quantitative assessment of the impact of depression or anxiety on the outcome or analyzing the use of antidepressants as primary focus were excluded from our analysis.

Review process and data collection

All titles and abstracts of studies identified by the electronic and hand search were screened by the reviewer (IS) to identify those meeting the inclusion/ exclusion criteria. Then, all the selected full texts were screened independently by two reviewers (IS, GJdV) to identify which articles should be included in the systematic review. Any disagreement between the reviewers was resolved by a third reviewer (SP). For each of the selected articles the reviewers extracted data about author, year of publication, follow-up period, outcome variable, location, study design, study population (size/ type), prevalence of depression or anxiety, assessment method of the psychological parameter, other parameters, statistical method and results.

Mendeley 1.13.8 software was used for organizing and managing of the articles.

Data analysis

All studies were categorized according to the psychological factor investigated (depression or anxiety). Information was extracted according to whether the analysis was adjusted for confounders such as age, gender, and clinical severity. For both groups the association between depression or anxiety and mortality was reported by collecting information of the hazard ratios/odds ratios, 95%CI and/or p-values.

Random-effects meta-analysis was applied to combine the results. We decided to pool not only the adjusted effect but also the unadjusted effects in order to avoid the bias of the different adjustments. For the few cases where Odds Ratios were reported, they were converted [8] into Hazard Ratios in order to be comparable with the other Hazard Ratios. In studies where results were presented for several periods of follow-up we selected the longest follow-up period to avoid bias of including multiple results on the same patient data.

Studies collected in our analysis were different with respect to patient population, locations and depression or anxiety assessment methods. The random-effects method allows for heterogeneity by assuming that the effects being estimated in the different studies are not identical, but follow a normal distribution. Heterogeneity across the studies was quantified by the I^2 statistic [9]. The I^2 statistic summarizes the fraction of the variation across studies due to heterogeneity relative to chance. Random-effect

meta-regression was used in an attempt to explain between-study heterogeneity and identify possible sources of bias. Meta-regression is a method to quantify the association between the estimated effect of depression and different study characteristics.

Meta analyses were presented in the form of forest plots created with the *metafor* package for R statistics version 3.0.3 (The R Foundation for Statistical Computing).

RESULTS

Search result

A total of 906 potentially relevant articles was identified from the electronic search and 5 from the hand search. After removing the duplicates and reviewing the titles and abstracts we ended up with 62 articles for a full text review. From these, 35 more articles were excluded, leaving 27 articles for the systematic review (Figure 2.1).

Characteristics of the selected studies

Depression and mortality

Among the identified studies, 26 reported on the effect of depression. The prevalence of depression varied from 10 to 79% in the identified literature studies. The unadjusted effect of depression is presented in Table 2.1, while the effect of depression after adjusting for several confounders in Table 2.2. The most common confounders, used in more than 10 studies, were age, gender, NYHA class and (left ventricular) ejection fraction. There were various techniques used among the studies to assess depression levels. We included all studies assessing for clinically significant depression. The most common scale used was the Beck Depression Inventory (BDI) [10], followed by the Patient Health Questionnaire (PHQ) [11].

FIGURE 2.1: Consort diagram

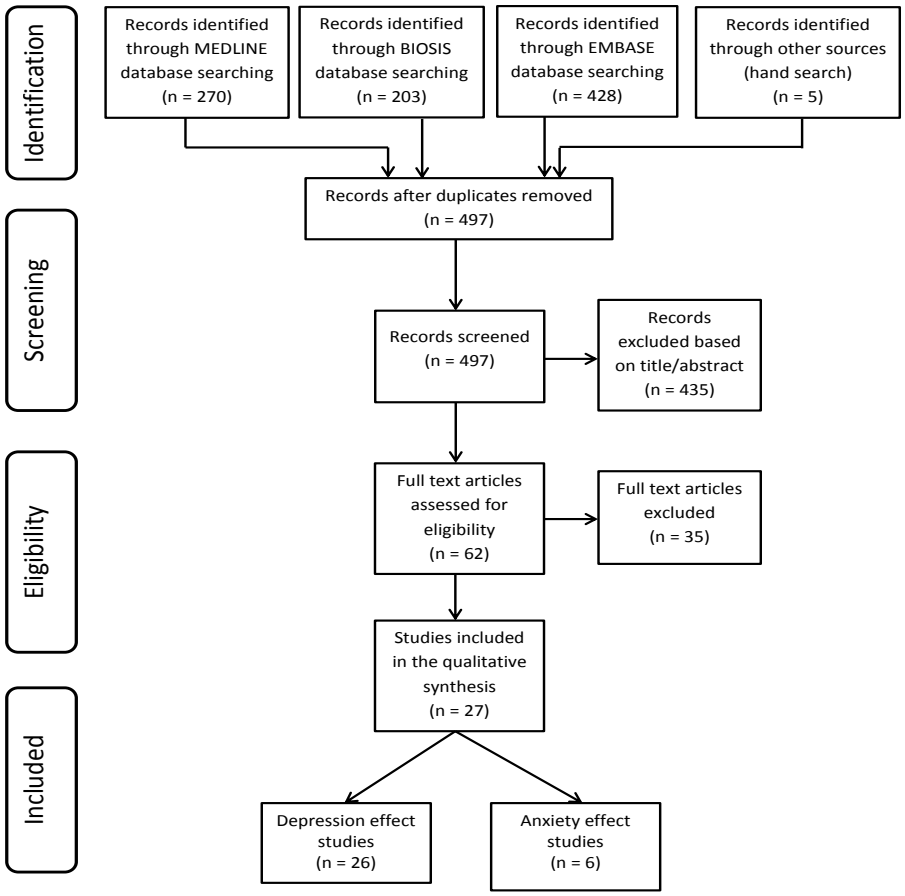

TABLE 2.1: Unadjusted effect of depression on all-cause mortality among HF patients

Author	Year	Assessment method	Population	Region	Study	Follow-up	Predicting period	Statistical method	HR/ OR	p-value	95% CI	Prevalence of depression
Adams [12]	2012	BDI ≥10	985 HF	US	Prospective cohort study	1792.3 days (mean)	–	Univariate Cox	1.35	<0.001	1.15– 1.57	30%
Albert [13]	2009	history of depression	48612 HF	US	OPTIMIZE-HF comprehensive registry	60-90 days	Inpatient	Univariate Cox proportional hazards model	1.36	0.027	1.04– 1.79	11%
Diez-Quevedo [14]	2013	GDS-4 ≥1	1017 HF	ES	Prospective cohort study	5.4 year (median)	Outpatient	Univariate Cox proportional-hazards model	1.39	0.001	1.15– 1.68	42%
Faller [15]	2007	PHQ-9	231 CHF	DE	Prospective cohort study	2.7 year (median)	Outpatient	Univariate Cox proportional-hazards model	3.3	<0.001	1.80– 6.10	13%
Faller [16]	2015	PHQ-9	863 HF	DE	Extended INH study	18 month	Outpatient	Univariate Cox proportional hazards model	1.07	<0.001	1.04– 1.09	-
Farisa [17]	2002	ICD-10	39 HF	UK	Retrospective cohort study	48 month (mean)	Outpatient	Univariate Cox proportional hazards model	2.1	0.0005	1.40– 3.20	21%
Friedmann [18]	2006	BDI-II	231 CHF	US	PFOS cohort study	23.6 month (mean)	Outpatient	Univariate Cox proportional hazards model	2.59	0.0177	0.23– 5.43	36%
Jiang [19]	2001	BDI ≥10	374 CHF	US	Prospective cohort study	1 year	Inpatient	Univariate logistic regression	2.26	0.04	1.04– 4.91	35%
Jiang [20]	2007	BDI ≥10	1006 HF	US	Cohort study	971 days (mean)	Inpatient	Univariate Cox proportional-hazards model	1.45	<0.001	1.19– 1.77	30%
Junger [21]	2005	HADS-D >6	209 CHF	DE	Prospective study	24.8 month (mean)	-	Univariate Cox proportional-hazards model	1.09	0.0071	1.02– 1.17	30%
Kato [22]	2009	CES-D ≥16	115 HF	JP	Prospective cohort study	2.1 year (median)	Outpatient	Univariate Cox proportional-hazards model	5.51	0.004	1.75– 17.39	23%

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Table 2.1 – *Continued from previous page*

Author	Year	Assessment method	Population	Region	Study	Follow-up	Predicting period	Statistical method	HR/ OR	p-value	95% CI	Prevalence of depression
Lesman-Leegte [23]	2009	CES-D $\geq$24	958 HF	NL	COACH prospective study	18 month	Inpatient	Univariate Cox proportional hazards model	1.18	0.172	0.93− 1.50	21%
Moraska [24]	2013	PHQ-9 $\geq$10	402 HF	US	Prospective cohort study	1.6 year (mean)	Inpatient/ outpatient	Univariate Cox proportional hazards model	3.37	<0.001	1.97− 5.75	15%
O'connor [25]	2008	history of depression	5791 HF	US	OPTIMIZE-HF Prospective cohort study	72.7 days (mean)	Inpatient	Univariate Cox proportional hazards model	1.56	0.0004	1.23− 1.97	14%
Sullivan [26]	2004	PRIME-MD interview/ HDRS/ SCL-20	142 HF	US	Prospective cohort study	3 year (mean)	Outpatient	Univariate Cox proportional hazards model	1.65	0.403	0.51− 5.28	29%

HR, hazard ratio; OR, odds ratio; CI, confidence interval; BDI, Beck depression inventory; GDS, geriatric depression scale; PHQ, patient health questionnaire; ICD, international classification of diseases; HADS-D, hospital anxiety and depression scale - depression; CES-D, center for epidemiological studies depression; HDRS, Hamilton rating scale for depression; SCL-20, Hopkins symptom checklist- 20-item depression scale; PRIME-MD, primary care evaluation of mental disorders; PFOS, psychosocial factors outcome study

TABLE 2.2: Adjusted effect of depression on all-cause mortality among HF patients

Author	Year	Assessment method	Population	Region	Study	Follow-up	Predicting period	Statistical method	Other parameters	HR/ OR	p-value	95% CI	Prevalence
Adams [12]	2012	BDI $\geq$10	985 HF	US	Prospective Cohort study	1792.3 days (mean)	-	Multivariate Cox proportional-hazards model	age, sex, race, marital status, NYHA, ischemic etiology of HF, history of CABG, diagnosis of diabetes	1.4	$<$0.001	1.16$-$ 1.68	30%
Albert [13]	2009	interviews/ medical records	48612 HF	US	OPTIMIZE-HF comprehensive hospital-based registry	60-90 days	Inpatient	Multivariate Cox proportional-hazards model	age, race, history of: ischemic heart disease, hypertension, liver disease and diabetes, any mechanical ventilation, any revascularization procedure, discharge medication: ACE, aldosterone antagonists, digoxin and lipid-lowering agentl discharge vital signs: SBP, DBP, HR; admission laboratory: serum sodium; discharge laboratory: serum creatinine	1.46	0.025	1.05$-$ 2.03	11%
Alhurani [27]	2015	PHQ-9 $\geq$10	1260 HF	US	HF Health-Related QoL Collaborative Registry	12 month	Outpatient	Multivariate Cox proportional-hazards model	age, gender, ethnicity, NYHA, combined anxiety/ depression	1.06	0.012	1.01$-$ 1.11	33%
Coyne [28]	2011	CES-D $\geq$16	706 HF	NL	COACH study randomized control trial	18 month	Inpatient	Multivariate Cox proportional-hazards model	BNP, type D	1.01	0.066	0.10$-$ 1.03	34%

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Table 2.2 – *Continued from previous page*

Author	Year	Assessment method	Population	Region	Study	Follow-up	Predicting period	Statistical method	Other parameters	HR/ OR	p-value	95% CI	Prevalence
Cully [29]	2009	ICD-9	12028 HF	US	Retrospective cohort study	12 month	Outpatient	Multivariate logistic regression	age,gender,race, married,income, comorbidities,combined depression/ anxiety	0.93	ns	0.71–1.15	18%
Diez-Quevedo [14]	2013	GDS-4 $\geq$1	1017 HF	ES	Prospective cohort study	5.4 year (median)	Outpatient	Multivariate Cox proportional-hazards model	Sex, age, months since HF diagnosis, ischemic etiology, LVEF, NYHA, DM, COPD, peripheral vasculopathy, CrC, BMI, ACE or ARB, BB	1.31	0.008	1.07–1.60	42%
Faller [15]	2007	PHQ-9	231 CHF	DE	Prospective cohort study	2.7 year (median)	Outpatient	Multivariate Cox proportional-hazards model	Age, sex, aetiology, NYHA, EF, syst./ non-syst. LV dysfunction, interaction term b/w LVEF and LV dysfunction	2.4	0.008	1.3–4.6	13%
Faller [16]	2015	PHQ-9	863 HF	DE	extended INH study	18 month	Outpatient	Multivariate Cox proportional-hazards model	age, sex, randomization status, NYHA, LVEF 30%, amino-terminal pro-BNP, SBP, HR, coronary artery disease, renal dysfunction, anemia, diabetes, ACE, ARB, BB, diuretics, and statins	1.04	0.017	1.01–1.07	-
Farisa [17]	2002	ICD-10	396 HF	UK	Retrospective cohort study	48 month (mean)	Outpatient	Multivariate Cox proportional-hazards model	demographics, social, medical history, baseline functional status and clinical severity	3	0.004	1.4–6.4	21%

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Table 2.2 – *Continued from previous page*

Author	Year	Assessment method	Population	Region	Study	Follow-up	Predicting period	Statistical method	Other parameters	HR/ OR	p-value	95% CI	Prevalence
Friedmann [18]	2006	BDI-II	231 CHF	US	PFOS cohort study	23.6 month (mean)	Outpatient	Multivariate Cox proportional-hazards model	treatment:ICD, amiodarone, afib, EF, depression score, social support amount	2.35	0.0222	2.354–4.743	36%
Jiang [19]	2001	BDI≥10/ positive DIS result	374 CHF	US	Prospective cohort study	1 year	Inpatient	Multivariate logistic regression	age, LVEF, NYHA, ischemic aetiology of CHF	2.12	0.07	0.94–4.81	35%
Jiang [20]	2007	BDI ≥10	1006 HF	US	cohort study	971 days (mean)	Inpatient	Multivariate Cox proportional-hazards model	age, LVEF, NYHA, ischemic aetiology of CHF, history of diabetes, marital status	1.4	0.003	1.12–1.74	30%
Junger [21]	2005	HADS-D >6	209 CHF	DE	Prospective study	24.8 month (mean)	-	Multivariate Cox proportional-hazards model	peakVO2, LVEF	1.08	0.02	1.01–1.15	30%
Kato [22]	2009	CES-D ≥16	115 HF	JP	Prospective cohort study	2.1 year (median)	Outpatient	Multivariate Cox proportional-hazards model	age, ACE, BNP	5.52	0.006	1.65–18.46	24%
Konstam [30]	1996	HRQL	3375 HF	US	Randomized clinical trial	36.5 month (mean)	-	Multivariate Cox proportional-hazards model	EF, age, treatment, NYHA	1.07	0.023	1.01–1.12	-
Lesman-Leegte [23]	2009	CES-D ≥24	958 HF	NL	COACH Prospective study	18 month	Inpatient	Multivariate Cox proportional-hazards model	age, gender, BNP level	1.43	0.04	1.02–2.02	21%

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Table 2.2 – *Continued from previous page*

Author	Year	Assessment method	Population	Region	Study	Follow-up	Predicting period	Statistical method	Other parameters	HR/ OR	p-value	95% CI	Prevalence
Moraska [24]	2013	PHQ-9 $\geq$10	402 HF	US	Prospective cohort study	1.6 year (mean)	In/ out-patient	Multivariate Cox proportional-hazards model	age, gender, CCI, incident vs. prevalent HF status	4.06	<0.001	2.35-7.01	15%
Murberg and Bru [31]	2001	SDS	119 CHF	NO	Prospective study	2 year	Outpatient	Multivariate Cox proportional-hazards model	age, NYHA, depressive symptoms, functional status	1.05	0.116	0.99–1.11	-
O'connor [25]	2008	history of depression	5791 HF	US	OPTIMIZE-HF prospective cohort study	72.7 days (mean)	Inpatient	Multivariate step-wise Cox proportional-hazards model	SBP, age, weight, reactive airway disease, sodium, SCr, liver disease, lower extremity edema, statin at discharge, BB at discharge	1.48	0.0034	1.14–1.93	14%
Rollman [32]	2012	PHQ-2	471 HF	US	Prospective study	up to 12 months	Inpatient	Multivariate Cox proportional-hazards model	sex,age$\geq$65, EF$\leq$30%, NYHA 3/4, anxiety, COPD, renal insufficiency, ACE-I or ARB, BB, Coumadin, hemoglobin<10, sodium<136, DBP, SBP	3.1	0.003	1.40–6.70	79%
Sherwood [33]	2007	BDI $\geq$10	204 HF	US	Prospective study	median 3 years	Outpatient	Multivariate Cox proportional-hazards model	NT-proBNP, antidepressant, age, HF etiology, and LVEF	1.05	0.06	1.00-1.10	46%

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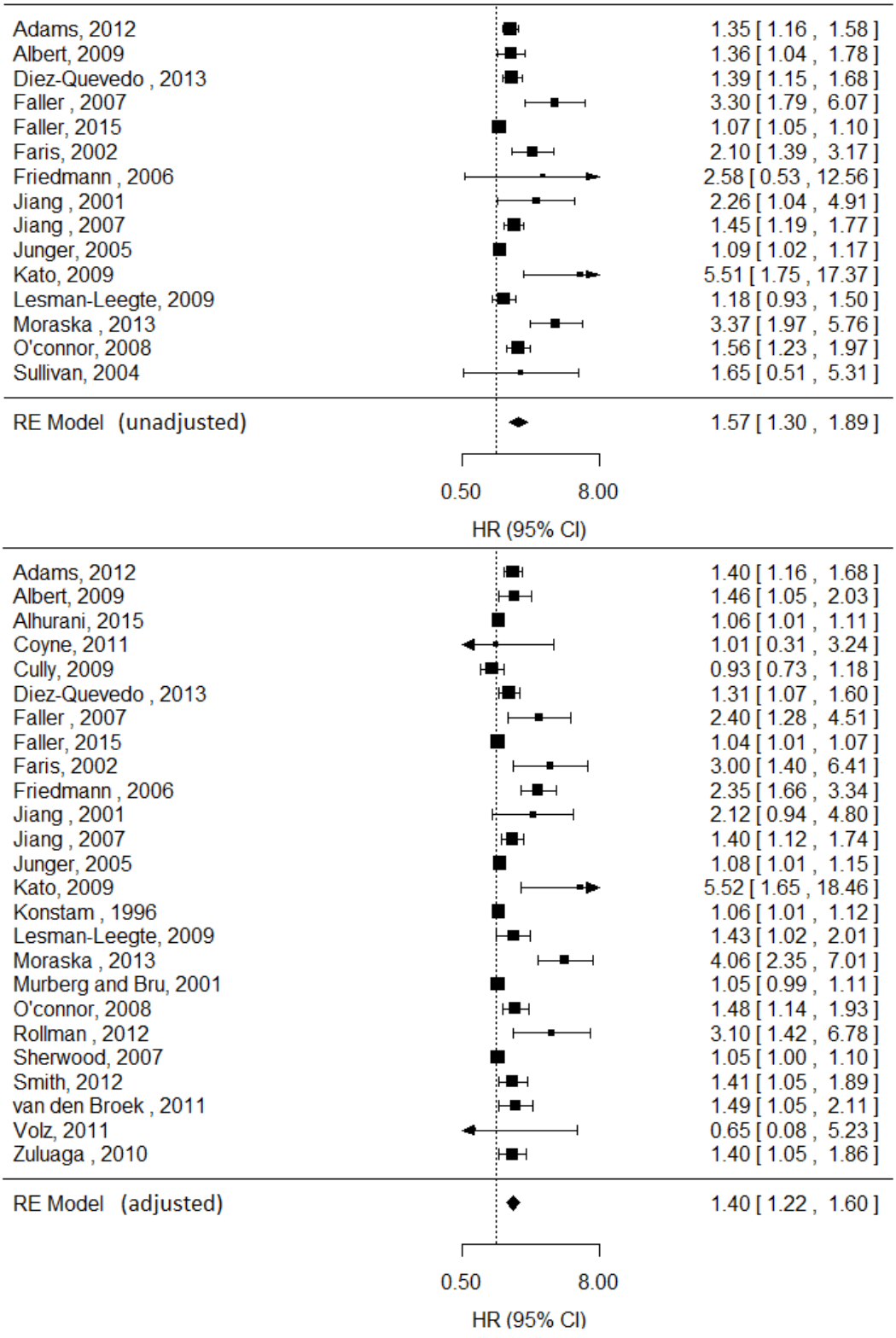
Table 2.2 – *Continued from previous page*

Author	Year	Assessment method	Population	Region	Study	Follow-up	Predicting period	Statistical method	Other parameters	HR/ OR	p-value	95% CI	Prevalence
Smith [34]	2012	BDI	380 CHF	NL	-	2.3 year (median)	Outpatient	Multivariate Cox proportional-hazards model	male, age, LVEF, NYHA, smoking, exertion fatigue	1.41	0.02	1.05−1.88	-
van den Broek [35]	2011	CES-D ≥8	208 HF	NL	Prospective community based study	11 year (median)	Outpatient	Multivariate Cox proportional-hazards model	age, gender, race, SBP, cholesterol, DM, BMI, smoking, reduced physical activity, CHD at baseline, LVEF, left ventricular hypertrophy, NT-proBNP	1.49	-	1.05−2.11	36%
Volz [36]	2011	HADS >10	111 HF	CH	Prospective cohort study	2.8 year (mean)	Outpatient	Multivariate Cox proportional-hazards model	LVEF, peak oxygen uptake	0.65	0.7	0.08−5.17	10%
Zuluaga [37]	2010	GDS-10 ≥5	433 HF	ES	Prospective study	5.7 year (mean)	Outpatient	Multivariate Cox proportional-hazards model	age, gender, race, COPD, CCI, serum creatinine level, LVEF, NYHA, HF hospitalization in last year, ischemic cardiopathy, heart valve disease	1.4	<0 .01	1.05−1.86	24%

HR, hazard ratio; OR, odds ratio; CI, confidence interval; BDI, Beck depression inventory; PHQ, patient health questionnaire; CES-D, center for epidemiological studies depression; ICD, international classification of diseases; GDS, geriatric depression scale; HADS-D, hospital anxiety and depression scale - depression; HDRS, Hamilton rating scale for depression; SCL-20, Hopkins symptom checklist- 20-item depression scale; PRIME-MD, primary care evaluation of mental disorders; PFOS, psychosocial factors outcome study; NYHA, New York heart association; CABG, coronary artery mypass grafting; ACE, angiotensin converting enzyme; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; BNP, b-type natriuretic peptide; LVEF, left ventricular ejection fraction; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; CrC, creatinine clearance by Cockcroft formula; BMI, body mass index; ARB, angiotensin receptor blocker; BB, beta-blockers; CHD, coronary heart disease; CCI, Charlson comorbidity index

The pooled hazard ratio for the unadjusted effect of depression on mortality was strongly significant across 15 studies (HR = 1.57; 95%CI 1.30 – 1.89; $p < 0.001$). The pooled estimation was strongly heterogeneous as reflected by the I^2 statistic (I^2 = 94%, heterogeneity $p < 0.001$). The pooled adjusted Hazard Ratio was also significant (HR = 1.40; 95%CI 1.22 – 1.60; $p < 0.001$) and again heterogeneous (heterogeneity $p < 0.001$; I^2 = 97%, Figure 2.2).

FIGURE 2.2: Meta-analysis – Forest plot calculating the effect of depression (a) unadjusted effect, (b) adjusted effect



A random-effect meta-regression was performed to understand the sources of the higher than 90% observed heterogeneity between the studies. The potential study-level covariates analyzed were the study characteristics introduced in Tables 2.1, 2.2. There was no association found between heterogeneity and the depression assessment method, the adjusted or univariate analysis, the location where the study was conducted, the inpatient or outpatient predictive period, the year of the study, the type of the study and the follow-up period. On the other hand, significant heterogeneity was associated with the total population size (smaller effect in larger studies $p < 0.01$) and the prevalence of the depression in the study (smaller effect for prevalence $>29\%$; $p < 0.01$, Table 2.3).

Anxiety and mortality

Only 6 studies analyzing the effect of anxiety on mortality among HF patients were identified with a prevalence of anxiety varying from 9 to 53%. Table 2.4 shows the unadjusted effects reported in the studies and Table 2.5 the reported effects on mortality after adjusting for a group of confounders. Age, NYHA class and (left ventricular) ejection fraction were the most common confounders in the identified studies.

TABLE 2.3: Random-effect meta-regression; Univariate Analysis

	Estimated coefficient (SE)	**p-value**
Year	-0.0016 (0.0124)	0.8957
Assessment method		
BDI	0.0349 (0.1287)	0.7863
PHQ	0.2096 (0.1433)	0.1434
Other	-0.1571 (0.1117)	0.1596
Population size	**-0.0004 (0.0002)**	**<0.05**
Region		
EU	-0.1119 (0.1134)	0.3241
US	0.04355 (0.1140)	0.7555
Follow-up period	0.0014 (0.0269)	0.9599
Statistical method		
Unadjusted	0.1066 (0.1159)	0.3573
Adjusted	Reference	Reference
Study type		
Prospective	0.1453 (0.1134)	0.2003
Retrospective	0.0667 (0.2217)	0.7637
Other	-0.1756 (0.1178)	0.1359
Depression prevalence	**-0.0108 (0.0059)**	**<0.1**
Predicting period		
Inpatient	-0.1641 (0.1156)	0.1156
Outpatient	Reference	Reference

In order to estimate the unadjusted effect of each study-level factor, the studies with missing values were excluded in each case

TABLE 2.4: Unadjusted effect of anxiety on all-cause mortality among HF patients

Author	Year	Assessment method	Population	Region	Study	Follow-up	Predicting period	Statistical method	HR/ OR	p-value	95% CI	Prevalence of anxiety
Friedmann [18]	2006	STAI	149 CHF	US	PFOS cohort study	23.6 month	Outpatient	Univariate Cox proportional-hazards model	1.037	0.06	0.998-1.078	45%
Jiang [38]	2004	STAI	291 CHF	US	Prospective cohort study	1 year	Inpatient	Univariate Cox proportional-hazards model	State-A:1.017; Trait-A:1.010	State-A:0.12; Trait-A: 0.44	State-A:0.996 -1.039; Trait-A:0.98-1.03	29%

HR, hazard ratio; OR, odds ratio; CI, confidence interval; STAI, State-Trait anxiety inventor; PFOS, psychosocial factors outcome study

TABLE 2.5: Adjusted effect of anxiety on all-cause mortality among HF patients

Author	Year	Assessment method	Population	Region	Study	Follow-up	Predicting period	Statistical method	Other parameters	HR/ OR	p-value	95% CI	Prevalence of anxiety
Alhurani [27]	2015	BSI	1260 HF	US	Registry	12 month	Outpatient	Multivariate Cox proportional-hazards model	age, gender, ethnicity, NYHA, depression	1.07	0.652	0.79-1.45	-
Cully [29]	2009	ICD-9	12028 HF	US	Retrospective cohort study	12 month	Outpatient	Multivariate logistic regression	age, gender, race, married, income, comorbidities, combined depression/anxiety	1.01	ns	0.76 - 1.54	9%
Friedmann [18]	2006	STAI	149 CHF	US	PFOS cohort study	23.6 month	Outpatient	Multivariate Cox proportional-hazards model	NYHA, atrial fibrillation/ flutter, treatment group	1.03	0.12	0.989 - 1.072	45%
Jiang [38]	2004	STAI ≥ 40	291 CHF	US	Prospective cohort study	1 year	Inpatient	Multivariate Cox proportional-hazards model	BDI, age, LVEF, NYHA, ischemic CHF origin	State-A: 1.01; Trait-A: 1.00	State-A: 0.30; Trait-A: 0.97	State-A: 0.988-1.040; Trait-A: 0.971-1.031	-
Konstam [30]	1996	HRQL	3375 HF	US	Randomized clinical trial	36.5 month (mean)	-	Multivariate Cox proportional-hazards model	EF, age, treatment, NYHA	1.02	ns	-	-
Volz [36]	2011	HADS-A >10	111 HF	CH	Prospective cohort study	2.8 year (mean)	Outpatient	Multivariate Cox proportional-hazards model	LVEF, peak oxygen uptake	1.75	0.47	0.37-8.21	9%

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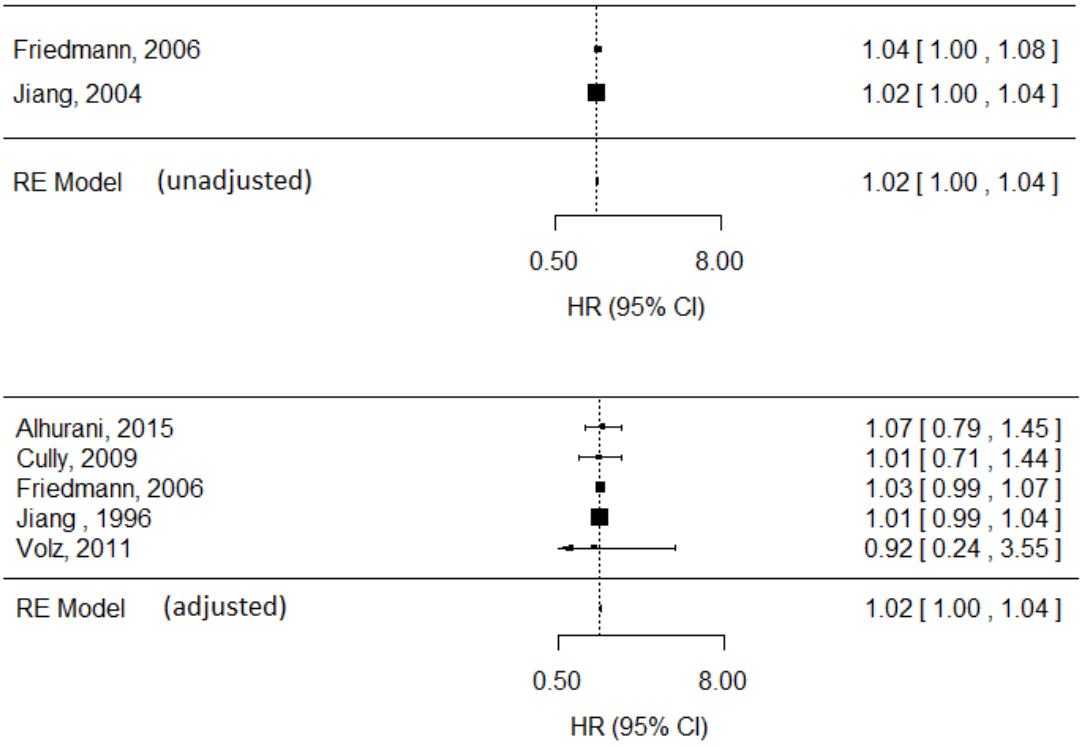
Table 2.5 – *Continued from previous page*

Author	Year	Assessment method	Population	Region	Study	Follow-up	Predicting period	Statistical method	Other parameters	HR/ OR	p-value	95% CI	Prevalence of anxiety

HR, hazard ratio; OR, odds ratio; CI, confidence interval; BSI, Brief symptom inventory; ICD, international classification of diseases; STAI, State-Trait anxiety inventor; HRQL, health related quality of life; HADS-A, hospital anxiety and depression scale - anxiety; PFOS, psychosocial factors outcome study; NYHA, New York heart association; BDI, Beck depression inventory; LVEF, left ventricular ejection fraction; EF, ejection fraction

There was no evidence found for anxiety as an independent predictor of mortality. The pooled hazard ratio for the unadjusted effect of anxiety on mortality, which was based on 2 studies, was 1.02 (95% CI 1.00 – 1.04; p = 0.24, heterogeneity p = 0.38; I^2 = 0%). The pooled hazard ratio for the adjusted effect of anxiety on mortality could be based on 5 studies and was identical (HR = 1.02; 95% CI 1.00 – 1.04; p = 0.09) and reasonably homogenous (heterogeneity p = 0.97; I^2 = 0%, Figure 2.3)).

FIGURE 2.3: Meta-analysis – Forest plot calculating the effect of anxiety (a) unadjusted effect, (b) adjusted effect



DISCUSSION

This systematic review was conducted according to the PRISMA guidelines to assess the evidence on the effect of depression (26 studies) and anxiety (6 studies) on all-cause mortality outcome among Heart Failure (HF) patients. <Key results: 1.6 for depression but very heterogeneous across studies; no effect for anxiety>. In contrast to other reviews, our study was not limited on follow-up duration or only in prospective studies reporting adjusted effects of the two parameters. We reviewed all studies published quantifying the effect of depression or anxiety.

The prevalence of depression varied among the 26 different studies with an average of approximately 29% ranging from 10 to 79%. The meta-analysis showed that the unadjusted risk of death among HF patients facing depression was 1.57 times higher than the risk among HF patients without depression and the pooled estimate of the adjusted Hazard Ratio was 1.40. In both univatiate and adjusted analysis, strong heterogeneity among the studies was found. Our findings are more conservative than previous reviews published [4, 6]. Rutledge et al reported a 2.10 higher adjusted risk of mortality and secondary events based on 8 studies and Fun et al reported a pooled adjusted Hazard Ratio of 1.51 based on 9 studies, both with substantial heterogeneity. From our attempt to explain heterogeneity we found that the effect of depression is weaker in larger studies; this suggests publication bias: small studies were published if they found relatively large effect estimates, while small studies with modest effect estimates were not. The weaker effect in studies with higher prevalence of depression may relate to the use of different cut-offs on an underlying, latent, scale for depression. If a more liberal cut-off was used, those labeled as depressed actually were milder than with a more strict definition of depression.

Our results for anxiety do not have the same weight as the results with respect to depression since anxiety was less studied in the literature. Anxiety had a similar prevalence to depression among the six identified studies (average 29%, range $9 - 45\%$), but patients with anxiety had no increased risk of death compared to those without anxiety. However, since anxiety is usually correlated with other factors such as depression, further research of anxiety as a covariate to other factors is recommended.

One limitation of our study is related to the variation in follow-up times. Follow-up

times varied from 30 days to a number of years; furthermore, there were studies covering different follow-up periods but in these cases we always selected the longest follow-up. Further analysis such as subgroup analysis would be recommended to investigate the effect variation in different follow-up periods, however limited information in some of the literature publications is restrictive towards this direction.

Moreover, we focused only on mortality. Nevertheless, there is evidence that depression and anxiety are also associated to other adverse events such as readmission. Further investigation in needed also towards this direction. One limitation of the meta-regression is that even though we tried to cover a broad selection of study-level covariates there are more that might also be related to the heterogeneity. Further research on different factors' interactions would be recommended.

The "gold standard" test of causality of a putative risk factor is a randomized clinical trial. Such a trial minimizes concerns about confounders [39, 40, 41]. To the best of our knowledge, there is no randomized clinical trial conducted for depression among a HF population. Based on our findings we strongly recommend such a trial in order to evaluate the causality of depression.

Finally, according to our findings from the meta-regression, depression should not be underestimated in clinical practice within HF population groups where prevalence is low. Furthermore, based on our overall findings on the effect of depression, we recommend further research on the recognition and management of depression in clinical practice which might improve patient outcomes. Further analysis such as subgroup analysis and interventional studies are required for stronger evidence towards this direction.

APPENDIX A: PRISMA CHECKLIST

TABLE 2.6: PRISMA checklist

Section/ topic	N	Checklist item	Page
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	15
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	17
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	18-19
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	20
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Appendix A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	20
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	20
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix B
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	20
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	21
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	20-22
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	21
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	21
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	21

Continued on next page

Table 2.6 – *Continued from previous page*

Section/ topic	N	Checklist item	Page
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	21
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	21
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Fig. 2.1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Tables 2.1,2.2,2.4, 2.5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	/
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Tables 2.1,2.2,2.4,2.5; Fig. 2.2 - 2.3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Fig. 2.2 - 2.3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	34/ Table 2.3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	34/ Table 2.3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	40-41
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	40-41
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	40-41
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	/

APPENDIX B: DATABASE SEARCH QUERY

S (HEART(W)FAILURE)/TI AND ((DEPRESS? OR STRESS? OR ANXIETY OR PSYCHOLOG?) (S)(MORTALITY OR DEATH))/TI,AB.

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