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Mortality Risk Among Heart Failure Patients With Depression: A Nationwide Population-Based Cohort Study

Kasper Adelborg, MD; Morten Schmidt, PhD; Jens Sundbøll, MD; Lars Pedersen, PhD; Poul Videbech, DMSc; Hans Erik Bøtker, DMSc; Kenneth Egstrup, DMSc; Henrik Toft Sørensen, DMSc

Background—The prevalence of depression is 4- to 5-fold higher in heart failure patients than in the general population. We examined the influence of depression on all-cause mortality in patients with heart failure.

Methods and Results—Using Danish medical registries, this nationwide population-based cohort study included all patients with a first-time hospitalization for heart failure (1995–2014). All-cause mortality risks and 19-year mortality rate ratios were estimated based on Cox regression analysis, adjusting for age, sex, time period, comorbidity, and socioeconomic status. The analysis included 9636 patients with and 194 887 patients without a diagnosis of depression. Compared with patients without a history of depression, those with depression had higher 1-year (36% versus 33%) and 5-year (68% versus 63%) mortality risks. Overall, the adjusted mortality rate ratio was 1.03 (95% CI 1.01–1.06). Compared with no depression, the adjusted mortality rate ratios for mild, moderate, and severe depression, as defined by diagnostic codes, were 1.06 (95% CI 1.00–1.13), 1.03 (95% CI 0.99–1.08), and 1.02 (95% CI 0.96–1.09), respectively. In a subcohort of patients, the mortality rate ratios were modified by left ventricular ejection fraction, with adjusted mortality rate ratios of 1.17 (95% CI, 1.05–1.31) for ≤35%, 0.98 (95% CI 0.81–1.18) for 36% to 49%, and 0.96 (95% CI 0.74–1.25) for ≥50%. Results were consistent after adjustment for alcohol abuse and smoking.

Conclusions—A history of depression was an adverse prognostic factor for all-cause mortality in heart failure patients with left ventricular ejection fraction ≤35% but not for other heart failure patients. (***J Am Heart Assoc***. 2016;5:e004137 doi: 10.1161/JAHA.116.004137)

Key Words: cohort study • depression • heart failure • mortality

Heart failure is a major cause of hospitalization, morbidity, and mortality that affects >23 million people worldwide.[1] The prevalence of comorbid depression ranges between 9% and 60% and is highest among heart failure patients screened for depression, among women, and among those with advanced heart failure.[2]

Depression and heart failure share underlying biological mechanisms. Patients with depression have hyperactivity of the hypothalamic–pituitary–adrenal axis, higher levels of inflammatory markers, decreased heart rate variability, abnormalities in platelet function, lower compliance with medication and dietary guidelines, less social support, and a more sedentary lifestyle than patients without depression. These factors may aggravate cardiac dysfunction in heart failure patients.[3,4] Depressed heart failure patients appear to have a 1.5- to 2-fold higher risk of mortality than nondepressed heart failure patients.[2,5] Nevertheless, studies to date have been limited by inclusion of highly selected patients[6–11]; short follow-up periods (3 months to 3 years)[6,7,12–14]; use of self-reported symptoms or antidepressant prescriptions as proxies for depression[6,7,9,10,12–15]; limited control of confounding factors such as smoking, alcohol use, socioeconomic factors, and comorbidity[9,10,13–15]; and small sample size (<400 patients).[6,7,9,10,15]

Critical unanswered questions remain regarding the association between depression and mortality in subgroups of heart failure patients defined by sex, age group, left ventricular ejection fraction (LVEF) values, causes of heart failure, presence or absence of various comorbidities, and New York

Heart Association (NYHA) functional classes. We hypothesized that a history of depression is a prognostic factor for death in heart failure patients and examined long-term mortality among patients with and without a history of depression.

Methods

Setting and Design

This nationwide population-based cohort study, which used prospectively collected data, was conducted from July 1, 1995, to February 1, 2014. Using the unique personal identifiers assigned to all Danish residents at birth or at immigration, we linked individual-level data from Danish medical and administrative registries.[16] The Danish national health care system is government funded, ensuring equal and free access to all medical care services provided by hospitals and general practitioners.

Heart Failure Cohort

We identified all patients with a first-time hospitalization for heart failure (including primary and secondary diagnoses) from the Danish National Patient Registry (DNPR).[17] Admission date for the heart failure hospitalization defined the index date. The positive predictive value of heart failure diagnoses in the DNPR is 81% with clinical examination as the reference and 100% with information in medical records as the reference.[17]

Depression

Information on all recorded diagnoses of depression any time prior to the index date was obtained from the DNPR and the Danish Psychiatric Central Research Register (DPCR).[17,18] In addition, we retrieved information on severity of depression (mild, moderate, and severe) using codes from the *International Classification of Diseases, 10th Revision* (ICD-10). Patients with >1 depression diagnosis of any severity were classified as being in the group with the most severe depression. With an interview as the reference, the positive predictive value of a single severe or moderate depression episode in the DPCR is adequate (83% or 76%, respectively) but is lower for mild depression (65%).[19]

Because many patients receive treatment for depression in the primary care setting, depression may be underreported in Danish medical registries, which do not yet include primary care. To compensate for such underreporting, we obtained information on redeemed prescriptions for antidepressants. We divided patients into 6 categories: (1) no diagnosis of depression and ≤1 redeemed prescription for antidepressants before the index date (reference group); (2) no diagnosis of depression, >1 redeemed

prescription before the index date, and previous use of antidepressants; (3) no diagnosis of depression, >1 redeemed prescription for antidepressants before the index date, and current use of antidepressants; (4) a depression diagnosis and ≤1 redeemed prescription for antidepressants; (5) a depression diagnosis, >1 redeemed prescription before the index date, and previous use of antidepressants; and (6) a depression diagnosis, >1 redeemed prescription before the index date, and current antidepressant use. We defined "current users" as having redeemed a prescription for antidepressants within 90 days before the index date. "Former users" redeemed their last prescription >90 days before the index date. Data on redeemed prescriptions of antidepressants were obtained from the Danish Register of Medicinal Product Statistics, which has recorded all dispensed prescriptions according to the Anatomical Therapeutical Chemical (ATC) classification system since 1995.[20]

Outcome

The study outcome was all-cause mortality. We used the Danish Civil Registration System to ascertain mortality during the years following the index date.[16] This registry has recorded dates of death and emigration, with daily updates since 1968.[16] We also examined immediate causes of deaths using data from the Danish Register of Causes of Death[21] (data available through December 31, 2012). We estimated cardiovascular and noncardiovascular mortality in patients with and without depression. For this analysis, depression was defined as any diagnosis or >1 prescription of antidepressant before the index date. Patients registered with only an underlying and no immediate cause of death were considered not to have an immediate cause of death; however, the results did not change if the underlying cause of death was considered as the immediate cause of death in these patients (data not shown). Moreover, we specifically examined deaths caused by arrhythmia, venous thromboembolism, stroke, myocardial infarction, and heart failure.

Covariates

We collected information on a range of comorbidities diagnosed from 1977 until the index date. These included myocardial infarction, hypertension, atrial fibrillation or atrial flutter, stroke, cancer, obesity, diabetes mellitus, chronic pulmonary disease, chronic kidney disease, peptic ulcer, illicit drug/alcohol/smoking abuse, dementia, anemia, and peripheral artery disease. Data on these diagnoses were obtained from the DNPR and the DPCR using ICD-8 codes until 1994 and ICD-10 codes thereafter.[17,18] We used all available diagnoses other than emergency room diagnoses, given the assumed low positive predictive value of the latter.[17]

Data on the following comedications used ≤90 and >90 days before the index date were retrieved from the Danish Register of Medicinal Product Statistics: antidepressants, selective serotonin reuptake inhibitors, tricyclic antidepressants, anxiolytics or hypnotics, antipsychotics, statins, low-dose aspirin, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, beta blockers, diuretics, and nonsteroidal anti-inflammatory drugs.[20] Data on socioeconomic variables, including gross income, employment, and education, were obtained from the Integrated Database for Labor Market Research (for the index year or for previous years, depending on data availability).[22] For a subcohort of heart failure patients, we retrieved data from the Danish Heart Failure Registry on smoking status, alcohol habits, LVEF values, and NYHA functional class.[23] It has been mandatory for cardiologists to register all incident hospitalized heart failure cases in this nationwide registry since 2003. Patients with ICD-10 codes for heart failure are enrolled in the registry if they fulfill the European Society of Cardiology's definition of heart failure. Regular structured audits are conducted to ensure the high quality of the registry's data.[23] All ICD and ATC codes used in the study are provided in Table S1.

Statistical Analysis

All patients were followed from their admission date for heart failure (index date) until the date of death or emigration or September 1, 2014, whichever came first. We compiled descriptive data on the covariates described in the previous section. The Kaplan–Meier method was used to compute mortality risks at 1, 5, 10, and 15 years, and we generated survival curves for patients with and without previous depression. Crude and adjusted hazard ratios were computed using Cox proportional hazards regression analysis comparing heart failure patients with and without a history of depression. In multivariable analyses, we adjusted for age, sex, time periods, the comorbidities listed in Table 1, gross income, and employment.

In stratified analyses, we examined potential interactions on a relative scale according to time periods, age groups, sex, heart failure cause, LVEF, NYHA class, comorbidity, comedication use, and socioeconomic factors. The analyses stratified by LVEF group and NYHA class were restricted to patients with complete data on these variables. Because age was nonlinear, it was included in the models as the best-fitting second-degree fractional polynomial. We evaluated proportional hazards using log-log plots and found no violation of the assumption.

Sensitivity Analyses

To test the robustness of our estimates, we performed several sensitivity analyses. First, we analyzed patients whose first

Table 1. Characteristics of Heart Failure Patients With and Without Previous Depression

	No Depression	Previous Depression
Number	194 887 (95)	9636 (5)
Median age (25th to 75th percentiles), y	78 (68–84)	77 (67–84)
Women	89 671 (46)	6039 (63)
Time period		
1995–1999	49 498 (25)	1801 (19)
2000–2004	59 842 (31)	2850 (30)
2005–2009	48 796 (25)	2792 (29)
2010–2014	36 751 (19)	2193 (23)
Comorbidity		
Myocardial infarction	39 761 (20)	1770 (18)
Hypertension	50 303 (26)	3100 (32)
Atrial fibrillation/atrial flutter	38 175 (20)	1734 (18)
Stroke	21 968 (11)	1517 (16)
Cancer	31 198 (16)	1691 (18)
Obesity	10 728 (6)	827 (9)
Diabetes mellitus	26 724 (14)	1509 (16)
Chronic pulmonary disease	33 815 (17)	2369 (25)
Chronic kidney disease	9431 (5)	582 (6)
Peptic ulcer	17 751 (9)	1404 (15)
illicit drug/alcohol/ smoking abuse	9989 (5)	2358 (24)
Dementia	6483 (3)	1219 (13)
Anemia	17 345 (9)	1337 (14)
Peripheral artery disease	6077 (3)	369 (4)
Comedication in the prior 90 days		
Antidepressants	24 239 (12)	5814 (60)
SSRIs	16 358 (8)	3316 (34)
TCAs	4133 (2)	1104 (12)
Anxiolytics or hypnotics	50 070 (26)	4793 (50)
Antipsychotics	8238 (4)	2239 (23)
Statins	30 164 (15)	1578 (16)
Low-dose aspirin	60 214 (31)	3191 (33)
ACEI/ARB	55 582 (29)	2466 (26)
Beta blockers	46 395 (24)	2121 (22)
Diuretics	100 130 (51)	5143 (53)
NSAIDs	30 000 (15)	1586 (16)
Income		
Low	41 640 (21)	1654 (17)
Intermediate	52 031 (27)	2732 (28)
High	50 304 (26)	3082 (32)
Very high	50 912 (26)	2168 (23)

Table 1. Continued

	No Depression	Previous Depression
Employment		
Employed	25 618 (13)	557 (6)
Early retirement: receiving sickness, disability, or early retirement benefits	2649 (1)	145 (2)
Unemployed	20 163 (10)	1592 (17)
State pension	146 457 (75)	7342 (76)
Education		
Basic education, primary school	74 173 (38)	4288 (45)
Youth education, high school, or similar	43 145 (22)	2045 (22)
Higher education	15 199 (8)	827 (9)
Unknown	62 370 (32)	2476 (26)

Data are shown as number (percentage), except as otherwise indicated. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

diagnosis of depression was recorded in the DNPR separately from those whose first diagnosis was recorded in the DPCR. Second, we restricted our analysis to depression diagnoses occurring 1, 2, and 3 years before the index date. Third, we fitted 3 additional multivariable models, adjusted for education (omitted from the main model because data on education were missing for heart failure patients with a high age, and thus these data were missing not at random), use of anxiolytics or hypnotics, and use of antipsychotics. Fourth, we omitted myocardial infarction, stroke, hypertension, and diabetes mellitus because these covariates potentially could represent intermediate variables in the association between depression and all-cause mortality.[24–26] Finally, to increase the positive predictive value of the recorded diagnosis of heart failure, we repeated the main analysis restricted to patients included in the Danish Heart Failure Registry. In this subcohort, we also adjusted for smoking and alcohol habits as categorical variables in a complete-case analysis and used multiple imputation with chained equations to create 25 data sets with imputed values for smoking and alcohol.[27] We assumed that data were missing at random, and in the imputation model, we included the covariates from the main model and those presented in Table 1 (except for nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, and education), the outcome indicator, and the Nelson–Aalen cumulative baseline hazard. Finally, because depression can be difficult to assess in patients with illicit drug/alcohol/smoking abuse, or dementia, we repeated the analysis excluding these patients.

All analyses were performed using Stata version 14 (StataCorp LP). The study was approved by the Danish Data Protection Agency (record 1-16-02-268-14). No approval from an ethics committee or patient informed consent is required for registry-based studies conducted in Denmark.

Results

Overall, 205 719 patients with a first-time hospitalization for heart failure were eligible for analysis. We excluded 99 patients with negative follow-up time, 9 patients with missing data on age, and 1088 patients with missing data on gross income and employment. After these exclusions, 9636 heart failure patients with previous depression (5%) and 194 887 heart failure patients without depression (95%) were available for analysis. Median follow-up time was 844 days (25th to 75th percentiles: 164–2050 days) for patients without depression and 688 days (25th to 75th percentiles: 119–1737 days) for patients with previous depression. Median age was 78 years in patients without depression and 77 years in patients with depression. A higher proportion of patients with depression were women compared with patients without depression. Apart from hypertension, the groups were balanced in terms of cardiac comorbidities. Patients with a history of depression had a higher prevalence of noncardiac conditions than patients without depression (Table 1 and Table S2). We identified 29 854 heart failure patients from the Danish Heart Failure Registry. Descriptive data on these patients are provided in Table S3.

Mortality

Mortality risks among heart failure patients with depression were higher than among heart failure patients without depression (Table 2 and Figure S1). Compared with patients without depression, 19-year mortality rate ratios after multivariable adjustment were 1.03 (95% CI 1.01–1.06) overall, 1.06 (95% CI 1.00–1.13) for mild depression, 1.03 (95% CI 0.99–1.08) for moderate depression, and 1.02 (95% CI 0.96–1.09) for severe depression (Table 3). Slightly more positive associations were found with various combinations of depression diagnoses and antidepressant use (Table 4 and Table S2). Patients with previous depression had higher noncardiovascular mortality and slightly higher cardiovascular mortality than patients without previous depression (Table 5).

Age, Sex, Heart Failure Severity, Heart Failure Cause, and Comorbidity

No interactions were found by age, sex, NYHA class, and cause of heart failure (Figure and Figure S2). Among patients

Table 2. Mortality Risks (Percentage) Among Heart Failure Patients With and Without Previous Depression

	1 Year (95% CI)	5 Years (95% CI)	10 Years (95% CI)	15 Years (95% CI)
No depression	32.6 (32.4–32.9)	63.3 (63.0–63.5)	81.5 (81.3–81.8)	90.4 (90.2–90.6)
Depression	36.4 (35.4–37.3)	68.0 (67.0–69.0)	85.7 (84.8–86.5)	93.3 (92.3–94.1)

with LVEF values ≤35%, those with a history of depression had ≈20% higher mortality than those who never had depression (Figure). Stratified analyses among patients with various comorbidities and comedications and according to gross income, employment, and education showed no interactions (Figures S3 through S5).

Sensitivity Analyses

Separate analyses of the prognostic impact of depression based on cases registered in the DNPR and the DPCR agreed with the main results (all sensitivity analyses are reported in Table S4). When patients with depression diagnosed within 1, 2, and 3 years before the index date were excluded, the results remained similar to the overall estimates. Repeating the analyses restricted to heart failure patients included in the Danish Heart Failure Registry also did not change the overall estimates. The estimates remained unchanged among patients included in this subcohort when we extended the Cox model by adjusting for education, use of anxiolytics or hypnotics, and use of antipsychotics, as well as for smoking and alcohol use (in a complete case analysis and using multiple imputation). Similarly, the main results were unchanged when myocardial infarction, stroke, hypertension,

Table 3. The 19-Year MRRs in Heart Failure Patients With and Without Depression, Overall and by Depression Severity

	Crude MRR (95% CI)	Adjusted MRR (95% CI)*
No depression	Reference	Reference
Depression overall[†] (n=9636)	1.14 (1.12–1.17)	1.03 (1.01–1.06)
Mild depression[‡] (n=1379)	1.27 (1.20–1.35)	1.06 (1.00–1.13)
Moderate depression[‡] (n=2914)	1.16 (1.11–1.21)	1.03 (0.99–1.08)
Severe depression[‡] (n=1305)	1.05 (0.99–1.12)	1.02 (0.96–1.09)

ICD indicates *International Classification of Diseases*; MRR, mortality rate ratio.
*Adjusted for age, sex, time period, myocardial infarction, hypertension, atrial fibrillation or atrial flutter, stroke, cancer, obesity, diabetes mellitus, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking abuse, dementia, anemia, peripheral artery disease, gross income, and employment.
[†]Including all ICD codes for depression.
[‡]Specific ICD-10 codes are provided in Table S1.

and diabetes mellitus were omitted from the multivariable model and when we repeated the analysis excluding patients with illicit drug/alcohol/smoking abuse, or dementia from the cohort. Analyses stratified by time periods did not change the results appreciably (Table S5).

Discussion

In this cohort study of patients with a first-time hospitalization for heart failure, depression was a prognostic factor for all-cause mortality in patients with LVEF ≤35%; however, in other heart failure patients, a history of depression was not associated with all-cause mortality. The prognostic effect of depression showed no interaction with age, sex, heart failure causes, NYHA class, cardiac comorbidities, and noncardiac comorbidities.

A meta-analysis of 8 studies demonstrated that comorbid depression was an adverse prognostic factor for all-cause mortality in heart failure patients (overall adjusted relative risk 2.10, 95% CI 1.71–2.58).[2] Consistent with this result, another meta-analysis of 9 studies including 4012 heart failure patients reported adjusted relative risk of all-cause mortality of 1.51 (95% CI 1.19–1.91) and adjusted relative risk of cardiovascular mortality of 2.19 (95% CI 1.46–3.29).[5] Severe depression was associated with increased mortality (relative risk 1.98, 95% CI 1.23–3.19) but not with mild depression (overall adjusted relative risk 1.04, 95% CI 0.75–1.45).[5]

The disparity between our results and those of the meta-analyses may have several explanations. Unlike our study, studies in the meta-analyses used self-reported symptoms to diagnose depression. Self-reported depression likely mimics somatic symptoms and could reflect increasing heart failure severity, which, if not sufficiently accounted for in the analyses, could explain the poor prognosis of patients with depression reported in previous studies.[2,5] In addition, some studies were not able to account for confounding factors such as socioeconomic factors, smoking, and alcohol use, which could have led to overestimation of the impact of depression on mortality.[9,10,13–15]

In contrast to previous studies investigating the prevalence of comorbid depression, we retrieved data on at least 15 years of depression history. Even so, the prevalence of depression was lower in our cohort (5%) than reported previously.[2] This may be attributed to our strict definition of

Table 4. The 19-Year MRRs in Heart Failure Patients According to Depression Diagnosis and Use of Antidepressants Before the Index Date

	Use of Antidepressants	Crude MRR (95% CI)	Adjusted MRR (95% CI)*
No depression	No use (n=156 168)	Reference	Reference
	Former use (n=16 457)	1.08 (1.06–1.10)	1.07 (1.05–1.09)
	Current use (n=22 262)	1.37 (1.34–1.39)	1.21 (1.19–1.23)
Depression	No use (n=1912)	1.07 (1.02–1.13)	1.00 (0.95–1.06)
	Former use (n=2007)	1.07 (1.01–1.13)	1.00 (0.95–1.06)
	Current use (n=5717)	1.28 (1.25–1.32)	1.10 (1.06–1.13)

MRR indicates mortality rate ratio.

*Adjusted for age, sex, time period, myocardial infarction, hypertension, atrial fibrillation or atrial flutter, stroke, cancer, obesity, diabetes mellitus, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking abuse, dementia, anemia, peripheral arterial disease, gross income, and employment.

depression history, use of ICD codes, and restriction to patients with incident heart failure. When we defined previous depression using both diagnosed depression and use of antidepressants, the prevalence increased to 24% (Table 4), which is in accordance with the existing literature.[2]

Our results extend the results of previous studies. Supporting our findings, the US Cardiovascular Health Study demonstrated that patients with depression and elevated NT-proBNP had substantially increased all-cause mortality (hazard ratio 3.72, 95% CI 2.20–6.37) and cardiovascular mortality (hazard ratio 5.42, 95% CI 2.38–12.36) compared with patients without depression and with low NT-proBNP levels.[15] The prevalence of depression has been found to increase with severity of heart failure symptoms, from 11% among patients in NYHA class 1 to 20% in NYHA class 2, 38% in NYHA class 3, and 42% in NYHA class 4[2]; however, we did not find that depression was an adverse prognostic factor in different NYHA classes. Nevertheless, standardized diagnostic

measures of depression could be particularly important for patients with LVEF ≤35%.

Several pathophysiological and psychosocial mechanisms in patients with depression and heart failure may underlie the higher mortality observed for patients with LVEF ≤35%.[3,4] Evidence suggests that patients with ongoing or remitted depression have disturbances in the hypothalamic–pituitary–adrenal axis, including higher cortisol levels than persons without depression. This may augment the sympathetic hyperactivity observed in advanced heart failure.[28] Cortisol has negative cardiovascular side effects, such as elevation of blood pressure, truncal obesity, hyperinsulinemia, hyperglycemia, insulin resistance, dyslipidemia, and increased plasma volume, which could worsen the prognosis of advanced heart failure patients.[29] Inflammatory cytokines such as tumor necrosis factor, interleukin 1, and interleukin 6 also are elevated in patients with heart failure, and these cytokines may be implicated in disease progression.[3] Elevation of these cytokines is also characteristic of depression

Table 5. Cardiovascular and Noncardiovascular Mortality in Patients With and Without Previous Depression, 1995–2012

	Rate Per 1000 Person-Years (95% CI)		Adjusted MRR (95% CI)*
	No Depression (n=149 235)	Depression (n=45 224)	
All-cause mortality	194.1 (193.0–195.2)	255.7 (253.1–258.3)	1.14 (1.12–1.15)
Cardiovascular mortality	70.3 (69.6–71.0)	86.0 (84.4–87.7)	1.09 (1.06–1.11)
Arrhythmia	7.6 (7.4–7.9)	8.9 (8.4–9.5)	1.08 (1.01–1.16)
Venous thromboembolism	1.7 (1.6–1.8)	2.3 (2.1–2.6)	1.15 (1.00–1.32)
Myocardial infarction	9.3 (9.0–9.6)	11.6 (11.0–12.3)	1.02 (0.97–1.09)
Stroke	6.5 (6.3–6.7)	9.2 (8.7–9.8)	1.12 (1.05–1.21)
Heart failure	23.4 (23.0–23.8)	29.8 (28.9–30.8)	1.08 (1.04–1.13)
Noncardiovascular mortality	108.9 (108.0–109.8)	160.2 (158.0–162.5)	1.19 (1.17–1.21)

MRR indicates mortality rate ratio.

*Adjusted for age, sex, time period, myocardial infarction, hypertension, atrial fibrillation or atrial flutter, stroke, cancer, obesity, diabetes mellitus, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking abuse, dementia, anemia, peripheral artery disease, gross income, and employment.
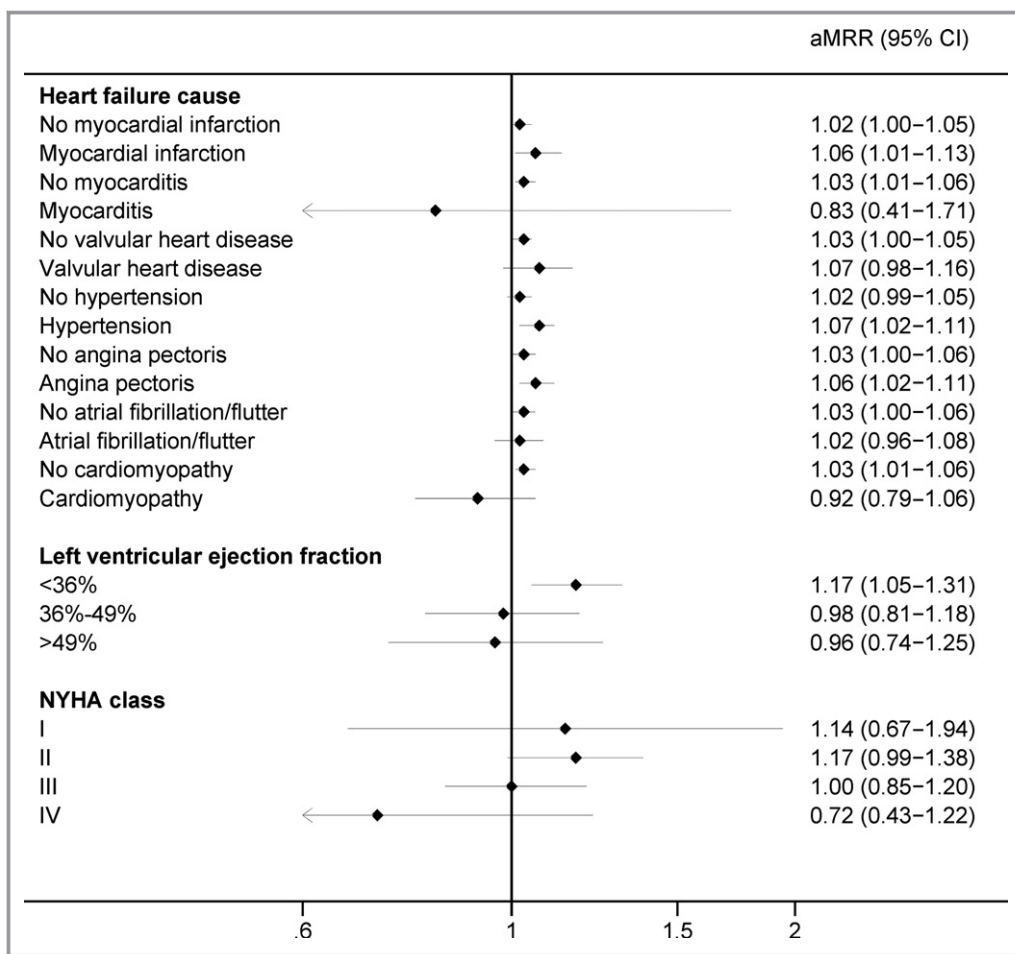
Figure. The aMRRs with 95% CIs in subgroups of heart failure patients with and without depression. The aMRRs were adjusted for age, sex, time period, myocardial infarction, hypertension, atrial fibrillation or atrial flutter, stroke, cancer, obesity, diabetes mellitus, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking abuse, dementia, anemia, peripheral artery disease, gross income, and employment (except for the stratifying variable). aMRR indicates adjusted mortality rate ratio; NYHA, New York Heart Association.

and may further adversely affect prognosis of heart failure patients with depression.[3] Studies to date, however, have found no association between depression severity and cytokine response, indicating that these cytokines may be trait markers for depression rather than markers of current depression.[3] Patients with depression also have decreased heart rate variability, which is a predictor of increased mortality and a prognostic factor for arrhythmias.[3] Finally, platelet abnormalities, noncompliance, poor social support, and suicide have been proposed as other mechanisms responsible for the adverse prognostic effect of depression in heart failure patients with low LVEF.[3]

Our study is the first nationwide population-based study to address the association between depression and all-cause mortality among heart failure patients. Strengths distinguishing this study from previous studies include the nationwide coverage and a sample size exceeding the combined number

of patients included in the previous 2 meta-analyses.[2,5] This enabled us to study the prognostic impact of depression in several subgroups. We had no loss to follow-up, largely avoiding selection bias. Our study also has limitations. Because the validity of depression in the DNPR is unknown, misclassification of depression cannot be ruled out. We sought to address this potential limitation by showing that results were consistent when analyzed separately for cases identified in the DNPR and in the DPCR and by reclassifying depression using both diagnoses and antidepressant use; however, we had only a few years of prescription history for patients identified early in the study period. In addition, antidepressants are used for indications other than depression, a fact that we were unable to take into account. Consequently, some of the patients using an antidepressant without being diagnosed with depression may be misclassified as surrogates for a history of depression. Moreover, we had

data on depression severity for only about half of the patients, and positive predictive values for codes for mild, moderate, and severe depression were only moderate (65–83%). Another concern is that the observational nature of the study design did not permit us to exclude the risk of unmeasured confounding. Nevertheless, we were able to adjust for known prognostic comorbid conditions (anemia, chronic kidney disease, peripheral artery disease, atrial fibrillation, and diabetes mellitus).[30,31] Furthermore, we were able to adjust for smoking, alcohol use, and socioeconomic status.

Conclusions

We found that depression was an adverse prognostic factor for death in patients with LVEF ≤35%, but not in other heart failure patients. Consequently, clinical attention to depression seems particularly warranted for patients with advanced heart failure.

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Disclosures

None.

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Mortality Risk among Heart Failure Patients with Depression: A Nationwide Population-Based Cohort Study

SUPPLEMENTAL MATERIAL

Table S1. *International Classification of Diseases* codes and Anatomical Therapeutic Classification codes used in the study.

	ICD-8	ICD-10	ATC codes
Heart failure	42709, 42710, 42711, 42719, 42899, 78249	I110, I130, I132, I420, I426, I427, I428, I429, I500, I501, I502, I503, I508, I509	N/A
Depression	29609, 29629, 29809, 30049	F32-F33	N/A
Mild depression	N/A	F320, F3200, F3201, F330, F3300, F3301	N/A
Moderate depression	N/A	F321, F3210, F3211, F331, F3310, F3311	N/A
Severe depression	N/A	F322, F323, F3230, F3231, F332, F333, F3330, F3331	N/A
Cardiac comorbidity			
Myocardial infarction	410	I21	N/A
Heart valve disease	394-397	I05-I08, I098, I34-I37	N/A
Myocarditis	422, 39129	I40-I41, I090, I514	N/A
Hypertension	400-404	I10-I15	N/A
Angina pectoris	411, 413	I20, I251, I259	N/A
Atrial fibrillation/atrial flutter	42793, 42794	I48	N/A
Cardiomyopathy	425	I42-I43	N/A
Non-cardiac comorbidities			
Stroke	430-434	I60-I61, I63-I64	N/A
Cancer	140-209	C00-C96	N/A
Obesity	277	E65-E66	N/A
Diabetes	24900-24909 (excluding 24902), 25000-25009 (excluding 25002)	E10 (excluding E102), E11 (excluding E112), E14 (excluding E142)	N/A
Chronic pulmonary disease	490-493, 515-518	J40-J47, J60-J67, J684, J701, J703, J841, J920, J961, J982-J983	N/A
Chronic kidney disease	24902, 25002, 75310-75319, 582-584, 59009, 59320, 792	E102, E112, E142, N03, N05, N110, N14, N16, N18-N19, N269, Q611-Q614	N/A
Peptic ulcer	53091, 53098, 531-534	K221, K25-K28	N/A
Illicit drug/alcohol/smoking abuse*	303-304	F10-F19	N/A
Dementia*	29009-29019, 29309	F00-F03, G30	N/A
Anaemia	280-281, 283-285	D50-55, D59, D61-D64	N/A
Peripheral arterial disease	44389-44399	I739	N/A
Comedication prescription <90 days			
Antidepressants	N/A	N/A	N06A
SSRIs	N/A	N/A	N06AB
TCAs	N/A	N/A	N06AA
Anxiolytics/hypnotics	N/A	N/A	N05B, N05C
Antipsychotics	N/A	N/A	N05A
Statins	N/A	N/A	C10AA, C10B
Low-dose aspirin	N/A	N/A	B01AC06, N02BA01
ACEI/ARBs	N/A	N/A	C09A, C09B, C09C, C09D
Betablockers	N/A	N/A	C07

Diuretics	N/A	N/A	C03
NSAIDs	N/A	N/A	M01A
Causes of death			
Cardiovascular mortality	N/A	I00-I99	N/A
Venous thromboembolism	N/A	I26, I80	N/A
Myocardial infarction	N/A	I21-I23	N/A
Stroke	N/A	I61, I63-I64	N/A
Heart failure	N/A	I50, I110, I130, I132	N/A
Arrhytmia	N/A	I44-I49	N/A
Non-cardiovascular mortality	N/A	All other codes than I00-I99	N/A

Abbreviations: SSRIs, Selective serotonin inhibitors; TCAs: Tricyclic antidepressants; ACEI/ARBs: Angiotensin-converting enzyme inhibitors/Angiotensin II receptor blockers; NSAIDs, Nonsteroidal anti-inflammatory drugs

*Data from the Danish National Patient Registry and the Danish Psychiatric Central Research Register.

Table S2. Descriptive data for patients with and without depression combining diagnoses and use of antidepressants.

	No depression			Depression		
	No use of antidepressants	**Former use of antidepressants**	**Current use of antidepressants**	**No use of antidepressants**	**Former use of antidepressants**	**Current use of antidepressants**
Median age (25th-75th percentiles)	77 (68-84)	77 (67-84)	79 (70-85)	75 (66-81)	74 (64-83)	78 (69-85)
Women	67,806 (43)	8954 (54)	12,911 (58)	1057 (55)	1166 (58)	3816 (67)
Time period						
1995-1999	43,912 (28)	1,820 (11)	3,766 (17)	649 (34)	239 (12)	913 (16)
2000-2004	48,178 (31)	4,606 (28)	7,058 (32)	603 (32)	551 (27)	1,696 (30)
2005-2009	37,111 (24)	5,181 (31)	6,504 (29)	427 (22)	626 (31)	1,739 (30)
2010-2014	26,967 (17)	4,850 (30)	4,934 (22)	233 (12)	591 (30)	1,369 (24)
Comorbidity						
Myocardial infarction	31,945 (21)	3524 (21)	4292 (19)	387 (20)	411 (21)	972 (17)
Hypertension	37,061 (24)	5869 (36)	7373 (33)	474 (25)	679 (34)	1947 (34)
Atrial fibrillation/atrial flutter	29,868 (19)	3623 (22)	4684 (21)	283 (15)	396 (20)	1055 (19)
Stroke	14,787 (9)	2681 (16)	4500 (20)	238 (12)	322 (16)	957 (16)
Cancer	24,083 (16)	3015 (18)	4100 (18)	275 (14)	366 (18)	1050 (18)
Obesity	7675 (5)	1383 (9)	1670 (8)	157 (8)	213 (11)	467 (8)
Diabetes	20,052 (13)	2883 (18)	3789 (17)	278 (15)	361 (18)	870 (15)
Chronic pulmonary disease	24,696 (16)	3845 (23)	5274 (24)	429 (22)	500 (25)	1440 (25)
Chronic kidney disease	7018 (4)	1094 (7)	1319 (6)	116 (6)	140 (7)	326 (6)
Peptic ulcer	12,868 (8)	1980 (12)	2903 (13)	271 (14)	306 (15)	827 (14)
Illicit drug/alcohol abuse	6147 (4)	1723 (11)	2119 (10)	509 (27)	570 (28)	1279 (22)
Dementia	3383 (2)	888 (5)	2212 (10)	136 (7)	244 (12)	839 (15)
Anaemia	12,437 (8)	1982 (12)	2926 (13)	190 (10)	287 (14)	860 (15)
Peripheral arterial disease	4267 (3)	862 (5)	948 (4)	59 (3)	94 (5)	216 (4)
Comedication < 90 days						
Antidepressants	1977 (1)	0 (0)	22,262 (100)	97 (5)	0 (0)	5717 (100)
SSRIs	1325 (0.9)	0 (0)	15,033 (68)	72 (4)	0 (0)	3244 (57)
TCAs	253 (0.2)	0 (0)	3880 (17)	6 (0.3)	0 (0)	1098 (19)
Anxiolytics/hypnotics	33,771 (22)	6281 (38)	10,018 (45)	705 (37)	887 (44)	3201 (56)

Antipsychotics	4599 (3)	1072 (7)	2567 (12)	338 (18)	347 (17)	1554 (27)
Statins	22,634 (14)	3362 (20)	4168 (19)	217 (11)	347 (17)	1014 (18)
Low-dose aspirin	46,153 (30)	5602 (34)	8459 (38)	536 (28)	620 (31)	2035 (36)
ACEI/ARBs	43,925 (28)	5167 (31)	6490 (29)	443 (23)	531 (26)	1492 (26)
Betablockers	36,578 (23)	4403 (27)	5414 (24)	361 (19)	477 (24)	1283 (23)
Diuretics	78,477 (50)	8401 (51)	13,252 (60)	914 (48)	888 (44)	3341 (58)
NSAIDs	23,122 (15)	2744 (17)	4134 (19)	296 (15)	308 (15)	982 (17)
Income						
Low	35,301 (23)	2345 (14)	3994 (18)	493 (26)	270 (13)	891 (16)
Intermediate	41,426 (27)	4209 (26)	6396 (29)	614 (32)	530 (26)	1588 (28)
High	38,271 (25)	5266 (32)	6767 (30)	497 (26)	689 (34)	1896 (33)
Very high	41,170 (26)	4637 (28)	5105 (23)	308 (16)	518 (26)	1342 (24)
Employment						
Employed	22,497 (14)	1601 (10)	1520 (7)	134 (7)	142 (7)	281 (5)
Early retirement, receiving sickness/incapacity/early retirement	2197 (1)	238 (1)	214 (1)	24 (1)	40 (2)	81 (1)
Unemployed	15,154 (10)	2426 (15)	2583 (12)	336 (18)	447 (22)	809 (14)
State pensioner	116,320 (75)	12,192 (74)	17,945 (81)	1418 (74)	1378 (69)	4546 (80)
Education						
Basic education, primary school	57,997 (37)	6916 (42)	9260 (42)	899 (47)	878 (44)	2511 (44)
Youth education, high school or similar	34,551 (22)	4042 (25)	4552 (21)	396 (21)	511 (25)	1138 (20)
Higher education	11,989 (8)	1548 (9)	1662 (7)	113 (6)	210 (11)	504 (9)
Missing	51,631 (33)	3951 (24)	6788 (30)	504 (26)	408 (20)	1564 (27)

Data are numbers (%).

Abbreviations: SSRIs, Selective serotonin inhibitors; TCAs, Tricyclic antidepressants; ACEI/ARBs: Angiotensin-converting enzyme inhibitors/Angiotensin II receptor blockers; NSAIDs, Nonsteroidal anti-inflammatory drugs

Table S3. Characteristics of heart failure patients with and without depression registered in the Danish Heart Failure Registry (1 January 2003–1 February 2014).

	No depression	Depression
Number of patients	28,602 (96)	1252 (4)
Left Ventricular Ejection Fraction		
>49%	1842 (6)	93 (7)
36%-49%	5509 (19)	270 (22)
<36%	17,948 (63)	714 (57)
Missing	3303 (12)	175 (14)
New York Heart Association (NYHA) classification		
NYHA Class I	2359 (8)	63 (5)
NYHA Class II	10,838 (38)	425 (34)
NYHA Class III	5798 (20)	299 (24)
NYHA Class IV	649 (2)	28 (2)
Missing	8958 (31)	437 (35)
Alcohol intake		
Maximum 14 drinks for women and 21 for men per week	20,491 (72)	827 (66)
More than 14 drinks for women and 21 for men per week	2075 (7)	125 (10)
Missing	6036 (21)	300 (24)
Smoking habits		
Smoker	7987 (28)	448 (36)
Former smoker	9741 (34)	376 (30)
Never smoker	6448 (23)	230 (18)
Missing	4426 (15)	198 (16)

Data are numbers (%).

Table S4. Sensitivity analyses: Mortality rate ratios comparing heart failure patients with and without depression. The number of patients with depression is reported in parentheses.

	Crude mortality rate ratio (95% confidence intervals)	Adjusted mortality rate ratio[*] (95% confidence intervals)
Registry with first diagnosis of depression		
National Patient Registry (n=2325)	1.28 (1.23-1.34)	1.01 (0.97-1.06)
Psychiatric Central Research Register (n=7311)	1.10 (1.07-1.13)	1.04 (1.01-1.06)
Years since first depression diagnosis		
Within 1 year (n=1253)	1.26 (1.19-1.34)	1.05 (0.99-1.12)
Within 2 years (n=1991)	1.23 (1.17-1.29)	1.05 (1.00-1.10)
Within 3 years (n=2578)	1.23 (1.18-1.29)	1.05 (1.00-1.10)
Danish Heart Failure Registry cohort		
Depression *vs.* no depression (n=1252)	1.24 (1.15-1.35)	1.07 (0.99-1.16)
+ adjustment for smoking[†] (n=1054)	1.24 (1.14-1.35)	1.07 (0.97-1.17)[‡]
+ adjustment for alcohol[†] (n=952)	1.20 (1.09-1.31)	1.06 (0.96-1.16)[‡]
Additional adjustments[*]		
+ education[†] (n=7160)	1.25 (1.22-1.29)	1.04 (1.01-1.07)
+ anxiolytics/hypnotics (n=9636)	1.14 (1.12-1.17)	1.00 (0.98-1.03)
+ antipsychotics (n=9636)	1.14 (1.12-1.17)	0.99 (0.96-1.01)
No adjustment for myocardial infarction, stroke, hypertension, and diabetes (n=9636)	1.14 (1.12-1.17)	1.04 (1.01-1.06)
Excluding patients with illicit drug/alcohol/smoking abuse or dementia		
Depression *vs.* no depression (n=6,331)	1.12 (1.09-1.16)	1.08 (1.05-1.11)

[*]Adjusted for age, sex, time period, myocardial infarction, hypertension, atrial fibrillation/atrial flutter, stroke, cancer, obesity, diabetes, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking abuse, dementia, anaemia, peripheral arterial disease, gross income, and employment.

[†]Analyses restricted to patients with complete data on all variables.

[‡]Using multiple imputation, the adjusted mortality rate ratio, including adjustment for smoking, was 1.09 (95% confidence interval: 1.00-1.18) and the adjusted mortality rate ratio, including adjustment for alcohol, was 1.09 (95% confidence interval: 1.01-1.18)
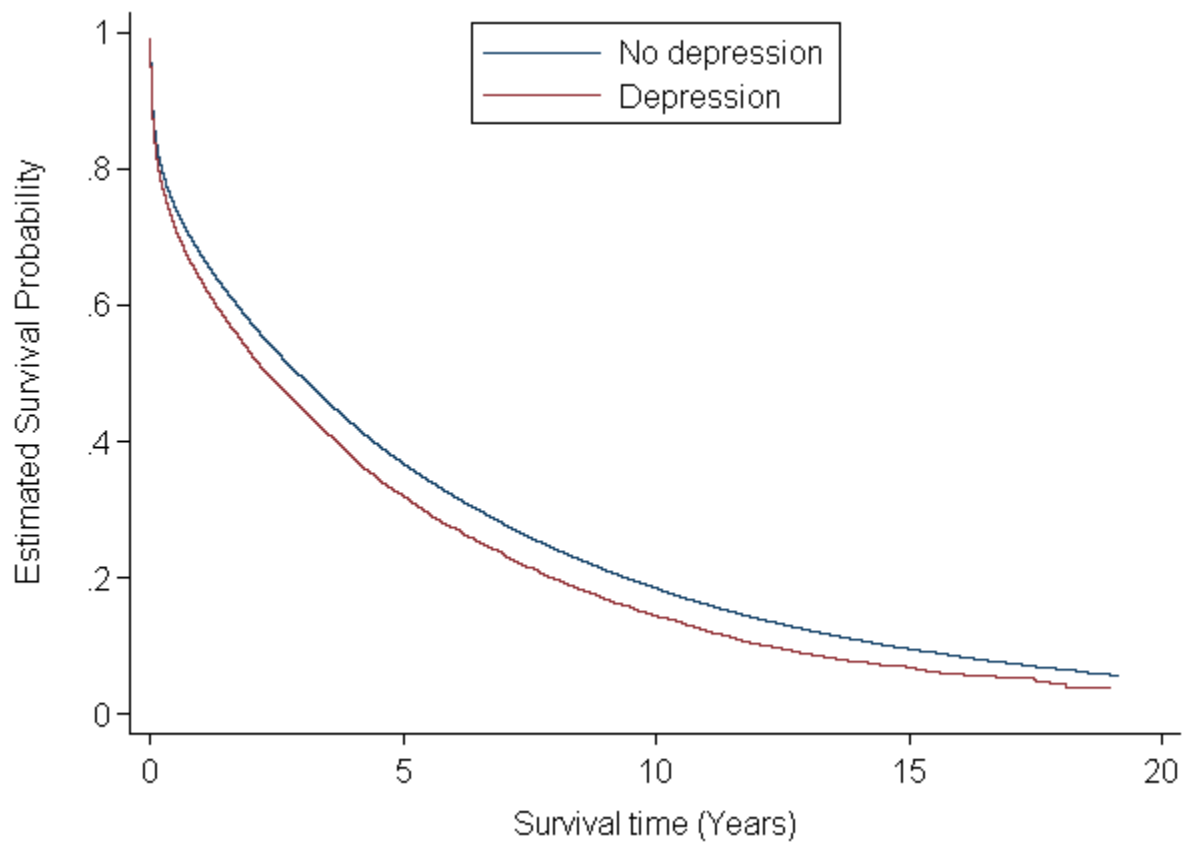
Table S5. Mortality rate ratios in heart failure patients according to depression diagnosis and use of antidepressants before the index date, by time periods.

Diagnosis	Use of antidepressants	Crude mortality rate ratio (95% confidence intervals)	Adjusted mortality ratio (95% confidence intervals)[*]
1995-1999			
No depression	-	Reference	Reference
Depression	-	1.13 (1.08-1.19)	1.07 (1.02-1.13)
	No use	Reference	Reference
No depression	Former use	1.17 (1.11-1.22)	1.09 (1.04-1.14)
	Current use	1.28 (1.24-1.33)	1.20 (1.16-1.24)
	No use	1.14 (1.05-1.23)	1.07 (0.99-1.16)
Depression	Former use	1.33 (1.17-1.52)	1.27 (1.11-1.44)
	Current use	1.14 (1.06-1.22)	1.06 (0-99-1.14)
2000-2004			
No depression	-	Reference	Reference
Depression	-	1.12 (1.08-1.17)	0.99 (0.95-1.03)
	No use	Reference	Reference
No depression	Former use	1.18 (1.14-1.22)	1.09 (1.06-1.13)
	Current use	1.37 (1.34-1.41)	1.18 (1.15-1.22)
	No use	1.00 (0.91-1.09)	0.96 (0.88-1.05)
Depression	Former use	1.13 (1.03-1.24)	0.94 (0.86-1.03)
	Current use	1.27 (1.21-1.34)	1.06 (1.01-1.12)
2005-2009			
No depression	-	Reference	Reference
Depression	-	1.19 (1.14-1.25)	1.02 (0.97-1.07)
	No use	Reference	Reference
No depression	Former use	1.14 (1.10-1.18)	1.05 (1.02-1.09)
	Current use	1.50 (1.45-1.54)	1.22 (1.18-1.26)
	No use	1.02 (0.90-1.14)	0.92 (0.82-1.04)
Depression	Former use	1.09 (0.99-1.20)	0.93 (0.85-1.03)
	Current use	1.43 (1.36-1.51)	1.11 (1.05-1.18)
2010-2014			
No depression	-	Reference	Reference
Depression	-	1.26 (1.19-1.34)	1.07 (1.00-1.14)
No depression	No use	Reference	Reference
	Former use	1.07 (1.02-1.12)	1.02 (0.97-1.07)
	Current use	1.52 (1.46-1.59)	1.22 (1.17-1.28)
Depression	No use	1.12 (0.92-1.36)	1.03 (0.85-1.26)
	Former use	1.06 (0.93-1.20)	1.02 (0.89-1.16)
	Current use	1.54 (1.43-1.66)	1.14 (1.06-1.24)

[*]Adjusted for age, sex, time period, myocardial infarction, hypertension, atrial fibrillation/atrial flutter, stroke, cancer, obesity, diabetes, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking abuse, dementia, anaemia, peripheral arterial disease, gross income, and employment.

Figure S1. Kaplan-Meier survival curve for heart failure patients with and without depression.

Figure S2. Adjusted mortality rate ratios with 95% confidence intervals by age and sex comparing heart failure patients with and without depression.

aMRR (95% CI)

Age group		
<40 years		0.86 (0.56, 1.31)
40-59 years		0.98 (0.90, 1.08)
60-79 years		1.04 (1.01, 1.08)
80 years		1.02 (0.98, 1.06)
Sex		
Male		1.04 (1.00, 1.08)
Female		1.03 (1.00, 1.06)

.6   1   1.5   2

Adjusted for age, sex, time period, myocardial infarction, hypertension, atrial fibrillation/atrial flutter, stroke, cancer, obesity, diabetes, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking abuse, dementia, anaemia, peripheral arterial disease, gross income, and employment.

Abbreviations: aMRR, adjusted mortality rate ratio; CI, confidence interval

Figure S3. Comorbidity-stratified adjusted mortality rate ratios comparing heart failure patients with and without depression.

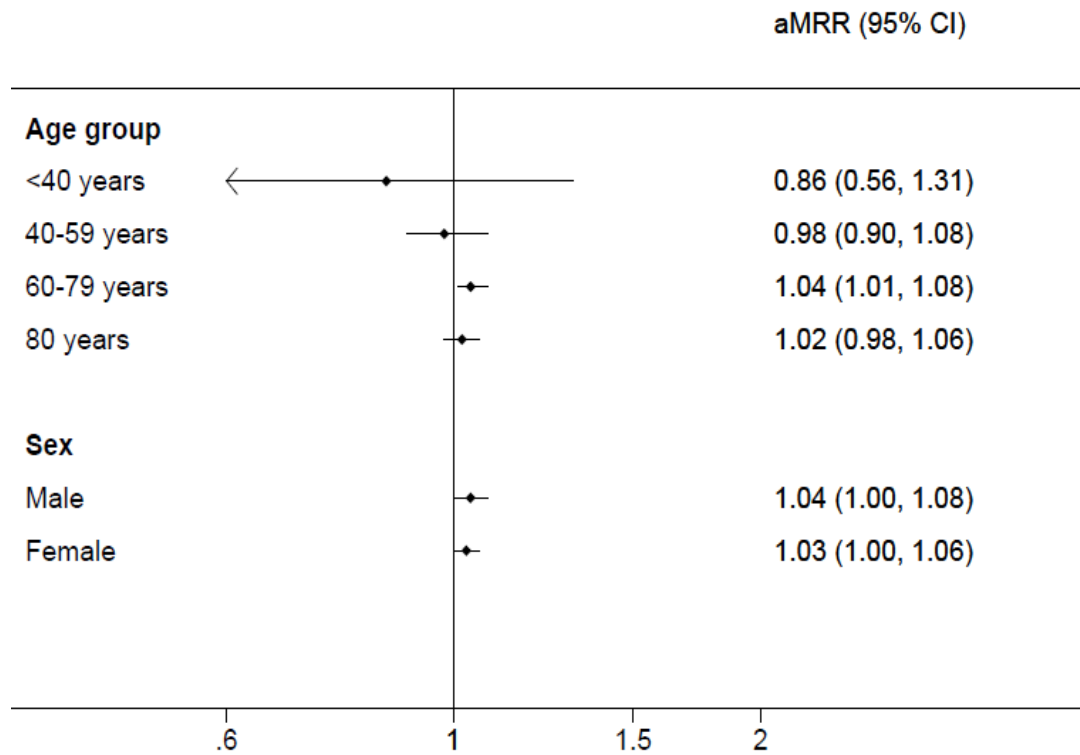|	aMRR (95% CI)
No Stroke	1.03 (1.01, 1.06)
Stroke	1.02 (0.96, 1.08)
No Cancer	1.03 (1.01, 1.06)
Cancer	1.03 (0.97, 1.08)
No obesity	1.03 (1.01, 1.06)
Obesity	1.03 (0.95, 1.13)
No diabetes	1.03 (1.00, 1.06)
Diabetes	1.05 (0.99, 1.12)
No chronic pulmonary disease	1.05 (1.02, 1.08)
Chronic pulmonary disease	0.98 (0.94, 1.03)
No chronic kidney disease	1.02 (1.00, 1.05)
Chronic kidney disease	1.11 (1.01, 1.22)
No peptic ulcer	1.04 (1.01, 1.07)
Peptic ulcer	0.97 (0.91, 1.03)
No illicit drug use	1.06 (1.03, 1.09)
Illicit drug use	0.95 (0.90, 1.00)
No dementia	1.05 (1.03, 1.08)
Dementia	0.91 (0.85, 0.97)
No anemia	1.05 (1.02, 1.07)
Anemia	0.95 (0.89, 1.01)
No peripheral arterial disease	1.03 (1.01, 1.06)
Peripheral arterial disease	0.95 (0.84, 1.08)

Adjusted for age, sex, time period, myocardial infarction, hypertension, atrial fibrillation/atrial flutter, stroke, cancer, obesity, diabetes, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking abuse, dementia, anaemia, peripheral arterial disease, gross income, and employment (except for the stratifying variable).
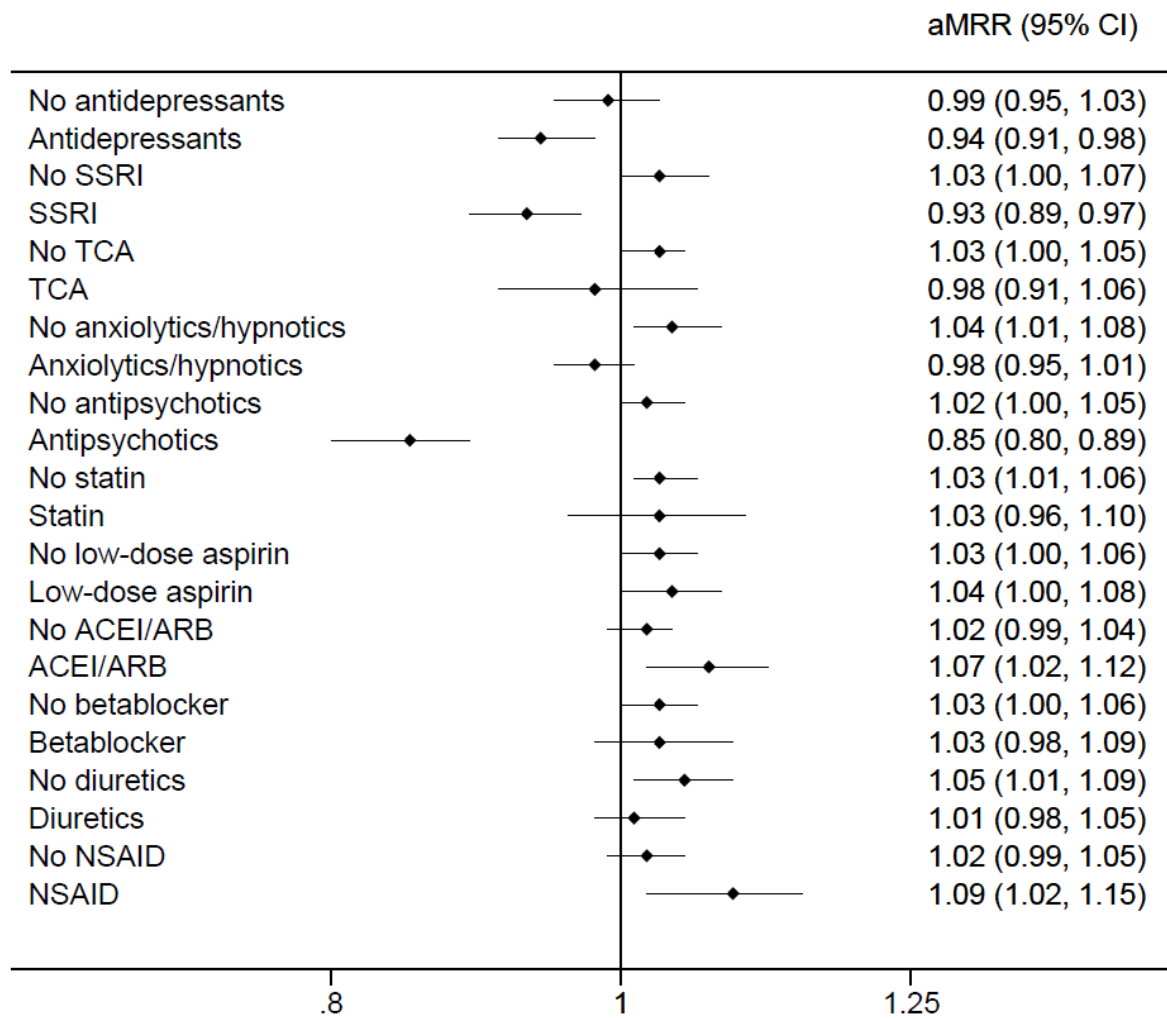Abbreviations: aMRR, adjusted mortality rate ratio; CI, confidence interval
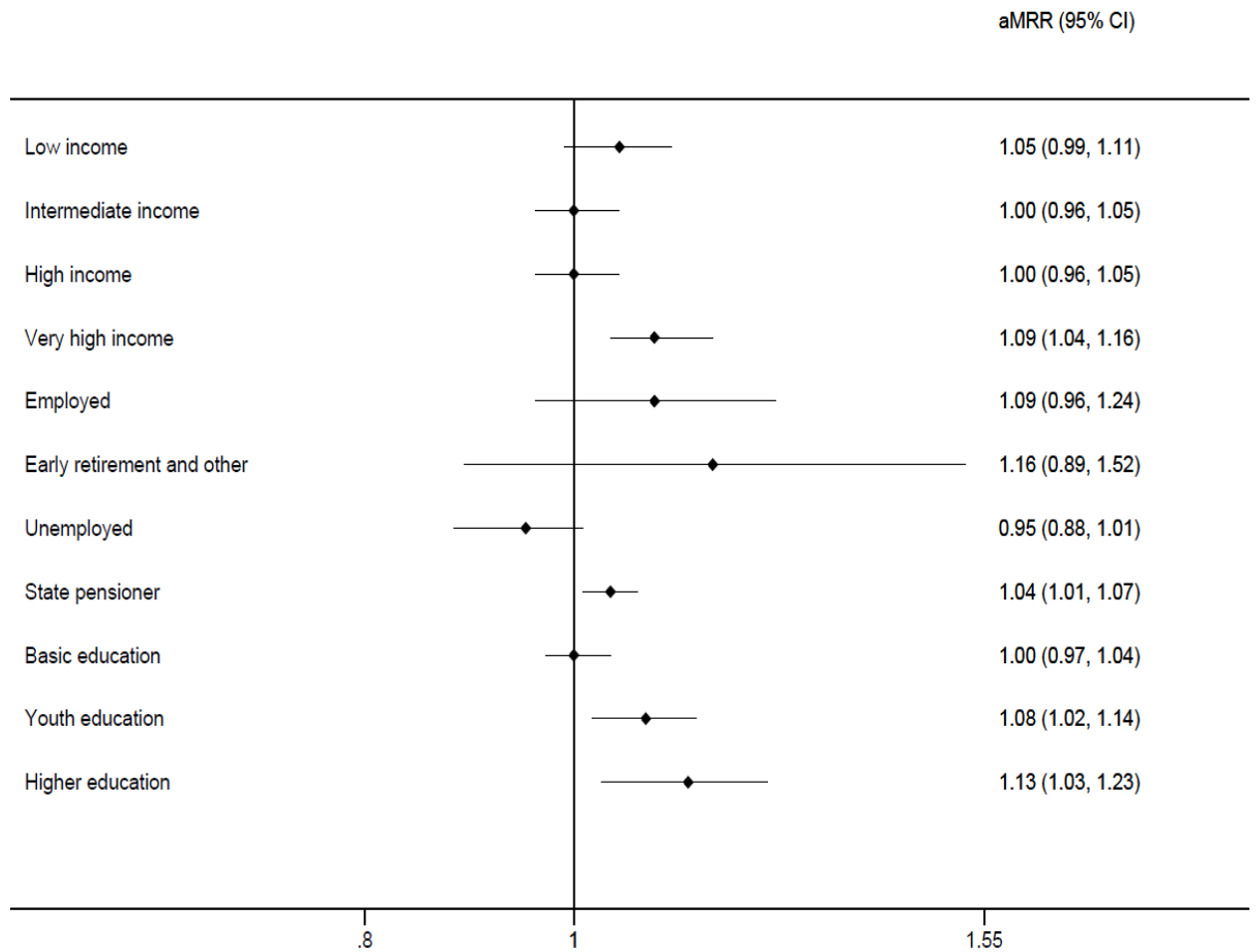
Figure S4. Adjusted mortality rate ratios comparing heart failure patients with and without depression according to use of comedications within 90 days prior to the index date.

	aMRR (95% CI)
No antidepressants	0.99 (0.95, 1.03)
Antidepressants	0.94 (0.91, 0.98)
No SSRI	1.03 (1.00, 1.07)
SSRI	0.93 (0.89, 0.97)
No TCA	1.03 (1.00, 1.05)
TCA	0.98 (0.91, 1.06)
No anxiolytics/hypnotics	1.04 (1.01, 1.08)
Anxiolytics/hypnotics	0.98 (0.95, 1.01)
No antipsychotics	1.02 (1.00, 1.05)
Antipsychotics	0.85 (0.80, 0.89)
No statin	1.03 (1.01, 1.06)
Statin	1.03 (0.96, 1.10)
No low-dose aspirin	1.03 (1.00, 1.06)
Low-dose aspirin	1.04 (1.00, 1.08)
No ACEI/ARB	1.02 (0.99, 1.04)
ACEI/ARB	1.07 (1.02, 1.12)
No betablocker	1.03 (1.00, 1.06)
Betablocker	1.03 (0.98, 1.09)
No diuretics	1.05 (1.01, 1.09)
Diuretics	1.01 (0.98, 1.05)
No NSAID	1.02 (0.99, 1.05)
NSAID	1.09 (1.02, 1.15)

Adjusted for age, sex, time period, myocardial infarction, hypertension, atrial fibrillation/atrial flutter, stroke, cancer, obesity, diabetes, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking abuse, dementia, anaemia, peripheral arterial disease, gross income, and employment.

Abbreviations: aMRR, adjusted mortality rate ratio; CI, confidence interval; SSRIs, Selective serotonin inhibitors; TCAs, Tricyclic antidepressants; ACEI/ARB, Angiotensin-converting enzyme inhibitors/Angiotensin II receptor blockers; NSAIDs, Nonsteroidal anti-inflammatory drugs

Figure S5. Adjusted mortality rate ratios comparing heart failure patients with and without depression according to socioeconomic status.

aMRR (95% CI)

Low income	1.05 (0.99, 1.11)
Intermediate income	1.00 (0.96, 1.05)
High income	1.00 (0.96, 1.05)
Very high income	1.09 (1.04, 1.16)
Employed	1.09 (0.96, 1.24)
Early retirement and other	1.16 (0.89, 1.52)
Unemployed	0.95 (0.88, 1.01)
State pensioner	1.04 (1.01, 1.07)
Basic education	1.00 (0.97, 1.04)
Youth education	1.08 (1.02, 1.14)
Higher education	1.13 (1.03, 1.23)

Adjusted for age, sex, time period, myocardial infarction, hypertension, atrial fibrillation/atrial flutter, stroke, cancer, obesity, diabetes, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking abuse, dementia, anaemia, peripheral arterial disease, gross income, and employment (except for the stratifying variable).
Abbreviations: aMRR, adjusted mortality rate ratio; CI, confidence interval