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Title: Employment status at time of first hospitalization for heart failure is associated with death and rehospitalization for heart failure

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Abstract

Background: Employment status at time of first heart failure (HF) hospitalization may be an indicator of both self-perceived and objective health status. In this study, we examined the association between employment status and the risk of all-cause mortality and recurrent HF hospitalization in a nationwide cohort of patients with HF.

Methods and Results: We identified all patients of working age (18-60 years) with a first HF hospitalisation in the period 1997-2015 in Denmark, categorized according to whether or not they were part of the workforce at time of the index admission. The primary outcome was death from any cause and the secondary outcome was readmission for HF. Cumulative incidence curves, binomial regression and Cox regression models were used to assess outcomes. Of 25571 patients with a first hospitalization for HF, 15428 (60%) were part of the workforce at baseline. Patients in the workforce were significantly younger (53 vs. 55 years) more likely to be male (75% vs 64%) and less likely to have diabetes (13% vs 22%) and chronic obstructive pulmonary disease (5% vs 10%), all p-values <0.001. Not being part of the workforce was associated with a significantly higher risk of death (HR: 1.59 [95% CI 1.50–1.68]) and rehospitalisation for HF (HR: 1.09 [95% CI 1.05–1.14]), in analyses adjusted for age, sex, comorbidities, education level, calendar time, duration of first HF hospitalization.

Conclusion: Not being part of the workforce at time of first HF hospitalization was independently associated with increased mortality and recurrent HF hospitalization.

Keywords: Heart Failure, employment status, epidemiology

Introduction:

Heart failure (HF) is a common and costly disease associated with high risk of hospitalization and death.[1-4] Despite advances in treatment, HF is still associated with a reduced quality of life, and a prognosis comparable with some types of cancer.[5] The ability to work provides valuable information on patients' well-being and performance status. It might also have an impact on subsequent disease trajectory as employment status might be associated with better uptake of cardiac rehabilitation and adherence to evidence-based therapy. Contrarily, detachment from the workforce has been associated with increased risk of depression, mental health problems and even suicide.[6-8] Several parameters have been identified as independent predictors of morbidity and mortality in HF, including age, sex, ejection fraction, diabetes, renal function and New York Heart Association functional class (NYHA).[9, 10] Employment status could be a relevant additional predictive factor in younger patients with HF, but its importance for prognosis is unclear.[11-14] We hypothesized that employment status is correlated with prognosis in terms of morbidity and mortality for patients with HF. Information about the relationship between employment status and morbidity and mortality could help risk-stratify younger HF patients and identify individuals who might benefit from more intensive rehabilitation. Therefore, we examined the association between employment status and the risk of death from any cause and recurrent HF hospitalization in a nationwide cohort of HF patients.

Methods:

Data sources

Nationwide administrative registries were linked by use of unique personal identification numbers assigned to all Danish residents.[15] We were able to collect information on hospitalizations, prescribed medications, education level, public welfare payments, and vital status on an individual level.[16, 17]

Study population and baseline variables

Patients aged 18-60 years at time of first HF hospitalization in the period 1997-2015 were included in the study (Appendix 1). Employment status was determined during the 5 weeks prior to first hospitalization for HF. Patients who received public support due to reduced working capability in 3 or more of the 5 evaluated weeks were classified as detached from the workforce, as done previously.[18] Thus patients in the workforce also included patients who were unemployed. The evaluation period of 5 weeks was chosen so as not to include patients on short-term sick leave and misclassify them as detached from the workforce.

The following comorbidities were identified by discharge diagnoses during a 10 year period before first hospitalization with HF: ischemic heart disease, cancer, atrial fibrillation, chronic kidney disease, chronic obstructive pulmonary disease (COPD), diabetes mellitus, hypertension and stroke. Filled prescriptions for glucose lowering drugs 6 months prior to first HF hospitalization were used to identify additional patients with diabetes. Procedures for implantation of cardiac devices were identified and prior surgical procedures in the form of valve surgery and coronary artery bypass grafting were classified according to NOMESCO Classification of Surgical procedures.[19] Diagnose and procedure codes are listed in Appendix I. Baseline use of pharmacotherapy was defined by one or more filled in prescriptions 6 months prior to first HF hospitalization. Use of the following drugs was assessed: angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin-II receptor blockers (ARB), aspirin, calcium channel blockers, digoxin, clopidogrel, mineralocorticoid receptor antagonists (MRAs), statins, β blockers, loop-diuretics, antidepressants and antipsychotics. We did not account for treatment initiated during the index hospitalization for HF. Income was calculated as 5-year average family income prior to first HF hospitalization and further classified into quartiles.

Outcome measures

Our primary outcome was death from any cause. Recurrent hospitalization for HF was evaluated as the secondary outcome. Patients were followed from first hospitalization for HF until date of emigration, death, December 31, 2015 or a maximum of 5 years.

In a sensitivity analysis we further categorized patients not in the workforce at baseline according to whether their employment status 1 year before first HF hospitalization and examined the association with mortality and recurrent HF hospitalization. We also tentatively adjusted for prior outpatient clinic visit for heart failure. Furthermore we repeated our cox regression analyses on death including HF medication and cardiac devices.

Statistics

Differences in baseline characteristics among patients in and out of the workforce were tested by use of Wilcoxon's test for continuous variables and χ^2-test for categorical variables. Cumulative incidence curves were estimated for death and rehospitalization for HF, respectively. In analyses of rehospitalization, death was treated as a competing risk. Cumulative incidence curves were estimated by use of the Aalen-Johansen method.[20] Unadjusted differences were evaluated by use of Gray's test. Hazard ratios (HRs) for death and rehospitalization were calculated by use of cause specific Cox regression models. Cox regression analyses were adjusted for age, sex, level of education, calendar time, length of first HF hospitalization, antidepressants, antipsychotics and comorbidities i.e. ischemic heart disease, atrial fibrillation, chronic kidney disease, COPD, diabetes, hypertension, stroke and cancer. All factors were included in each of the presented adjusted models. Log (-log(survival)) curves was used to evaluate the proportional hazard assumption. Interactions between age, sex, comorbidities and employment status were tested for both outcomes and none were found to be significant. The rate of total hospitalizations for HF was compared by use of negative binomial regression with logarithm of the duration of follow-up as the offset.[21] Data management and statistical analyses were performed by use of SAS statistical software package, version 9.4 (SAS Institute, Cary, NC, USA) and R, version 3.3.2 (R development Core Team).

Results

Baseline characteristics of the study population

We identified 25571 patients with a first hospitalization for HF in the period 1997-2015. Of these, 15428 individuals (60%) were part of the workforce at baseline. Patients in the workforce were **significantly** younger (median age 53 years vs 55 years), more were men (75% vs 65%) and they had a higher level of education (higher education: 17% vs 10%); Table 1. All comorbidities were less prevalent among patients in the workforce group. Patients in the workforce were more often treated with β-blockers (56% vs 51%) and ACE-I/ARB (66% vs 63%) but were less likely to be on loop diuretics (49% vs 61%) and MRAs (21% vs 26%).

Mortality

The median follow-up of was 781 days; Q1-Q3 105-1825 days. During this period, 2205 (14%) died in the workforce group and 3213 (32%) in the non-workforce group (risk of death 14% [13%-16%] vs. 32% [31%-33%]; P<0.0001; Figure 1). The unadjusted HR for all-cause mortality was 2.15 (95% CI 2.03-2.27) for patients out of the workforce compared to patients in the workforce. In adjusted analyses, HF patients not part of the workforce at baseline remained at higher risk of death (HR 1.59 [1.50–1.68]; P<0.0001; figure 2). This risk was comparable to that of having diabetes (HR 1.41 [1.33-1.51]) and stroke (HR 1.36 [1.22-1.50]). Other factors associated with higher risk of death included older age, male sex, lower level of education, use of antidepressants and antipsychotics and all comorbidities; Figure 2.

In a sensitivity analysis, patients who were not in the workforce at baseline nor at 1 year before hospitalization (n=7718) had a mortality risk of HR 1.66 [1.56-1.77], compared to those in the workforce at baseline. Patients with recent detachment from the workforce (<1 year) had a mortality risk of HR 1.38 [1.25-1.51] compared patients in the workforce at baseline. There was a significant interaction between length of detachment (≥1year vs. <1year) and employment status in relation to mortality (P<0.0001). 3637 (14%) of the patients were seen in an outpatient clinic prior to first HF hospitalization adding this information to the main analyses did not change the results. In a cox regression analysis including cardiovascular medications and cardiac devices we found that HF patients not part of the workforce at baseline still had a higher risk of death. ARB, β blockers and Implantable cardiac defibrillators were associated with lower likelihood of death. Conversely, loop-diuretics and MRAs were associated with higher likelihood of Death (Supplementary figure 1).

Rehospitalization for heart failure

During follow-up, 6495 (42%) in the workforce group and 4739 (47%) in the non-workforce group were rehospitalized for HF (5-year risk of rehospitalization for HF 45% [44%-46%] vs. 47% [46%-48%]; P=0.03; figure 3). In Cox-regression analyses this yielded an unadjusted HR of 1.09 [1.05-1.13; P=0.0005] and an adjusted HR of 1.09 [1.05-1.14; P<0.0001]. Other factors associated with rehospitalization for HF included younger age, male sex, use of antidepressants, COPD, diabetes and cancer; Figure 4. In adjusted analyses the risk of rehospitalization for HF during the first year after discharge from first HF hospitalization was HR 1.05 [1.01-1.10; P=0.04]. Whereas the risk of rehospitalization was HR 1.20 [1.11-1.29; P<0.0001] from 1 to 5 years after first hospitalization for HF. The crude incidence rate of total HF hospitalizations was 354 hospitalizations per 1000 person years for patients out of the workforce and 302 hospitalizations per 1000 person years among patients in the workforce. This yielded an adjusted incidence rate-ratio of 1.30 [1.23-1.38; P<0.0001].

Discussion

The present study examined the association between employment status and the risk of death and recurrent HF hospitalization in a nationwide cohort of 25571 HF patients. The main result of the study was that HF patients not in the workforce had a significant higher adjusted risk of death, and recurrent hospitalization for HF, although not as pronounced. This excess risk of death in patients not in the workforce was comparable to that associated with comorbidities such as diabetes or prior stroke.

Several prognostic factors for patients with HF have been identified and included in risk scores.[9, 10, 22-24] However, none of these models have included variables assessing functional performance in the community such as employment status. Evidently, employment status is only relevant in HF patients of working age, but in this subgroup of patients, it may be valuable when quantifying the overall prognosis of young HF patients. The exact mechanism of how employment status is related to mortality and recurrent HF hospitalization is complex and most likely multi-factorial. The ability to work can be seen as a measure of good performance status and may reflect that patients are able to meet the physical requirements of a full-time job. As performance status is closely associated with morbidity and mortality in HF this could, at least in part, explain the association we found. However, employment status is more than just another physical measurement as it also influences patients' quality of life and has been shown to be important for mental health and well-being.[6, 8] Quality of life is also associated with outcome in heart failure. There may be other more indirect mechanisms through which employment status influences outcome. For example, loss of income could lead to poorer nutrition and, through loss of self-esteem, adoption of unhealthy habits such as excessive alcohol consumption or resumption of smoking. Similarly, hopelessness or despair might reduce adherence to medical therapy and a healthy lifestyle. Thus both from a physical and psychological perspective, it makes sense to include employment status as part of the evaluation of young patients with HF. While it may not be surprising that employment status is related to prognosis, the strength of the association is. Employment status was associated with a risk of death comparable to that of comorbidities such as diabetes and stroke.[9, 25] For different reasons patients out of the workforce are not able to be part of the workforce. These reasons are likely to be associated with higher likelihood of death. We illustrate and adjust our analyses for some of the reasons i.e. higher age, male gender, lower level of education, length of first HF hospitalization, use of antidepressants and antipsychotics and history comorbidities in the form of chronic kidney disease, COPD, diabetes, stroke and cancer. But after adjusting for these factors, known to be associated with worse prognosis, the association of employment status and death is still highly significant. It is highly likely that not being part of the workforce captures some otherwise unmeasured covariates that influence prognosis in this population. Socio-economic characteristics have been shown to be related to the use of evidence based medication and cardiac devices. [26] Thus employment status might also have impact on use of medication and cardiac devices which in return could mediate some of the effect on mortality and rehospitalization related to employment status. Thus, further knowledge on which elements workforce exclusion covers could be valuable and might be target for intervention.[27] Thus so far employment status is an interesting and valuable factor to assess.

The main strength of this study is the use of nationwide registries with complete unselected information on all patients admitted to a hospital with HF as a discharge diagnosis. These registries made it possible for us to link weekly updated data on occupational status with data on hospitalization, pharmacotherapy use and vital status on a nationwide scale. We chose to look at workforce availability instead of employment and thus our results should not be affected by any fluctuations in the employment opportunities. The main limitation of the study is missing information on clinically important variables especially ejection fraction and NYHA status. It is highly likely that not being part of the workforce captures some otherwise unmeasured covariates that influence prognosis in this population and caution should be used when interpreting the finding that employment status is an independent predictor of mortality and rehospitalization among HF patients. The observational nature of the study means that the effect of unmeasured confounders cannot be excluded and that our findings reflect associations and not causal connections.

Workforce detachment at time of first HF hospitalization was associated with a higher subsequent risk of death and rehospitalization for HF. Patients outside the workforce had a risk of death comparable to that of patients with diabetes or stroke. Employment status could be a valuable factor in the evaluation of young HF patients' prognosis and a possible target for intervention.

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Table and figure legends

Table 1	Baseline characteristics according to employment status at time of first HF hospitalization.
Figure 1	Risk of death among patients in and out of the workforce at time of first HF hospitalization (n= 25571).
Figure 2	Results from one multivariable Cox regression model of factors associated with death among patients in and out of the workforce at time of first HF hospitalization (n=25571).
Figure 3	Risk of rehospitalization for HF with death as competing risk (i.e. death before HF rehospitalization) among patients in and out of the workforce (n=25571).
Figure 4	Results from one multivariable cause specific Cox regression model of factors associated with rehospitalization for HF among patients in and out of the workforce (n=25571).
Supplementary figure 1	Results from one multivariable Cox regression model of factors including HF medication and cardiac devices associated with death among patients in and out of the workforce at time of first HF hospitalization (n=25571).
Appendix 1	ICD-10 codes for heart failure and comorbidities and NOMESCO codes for surgical procedures.

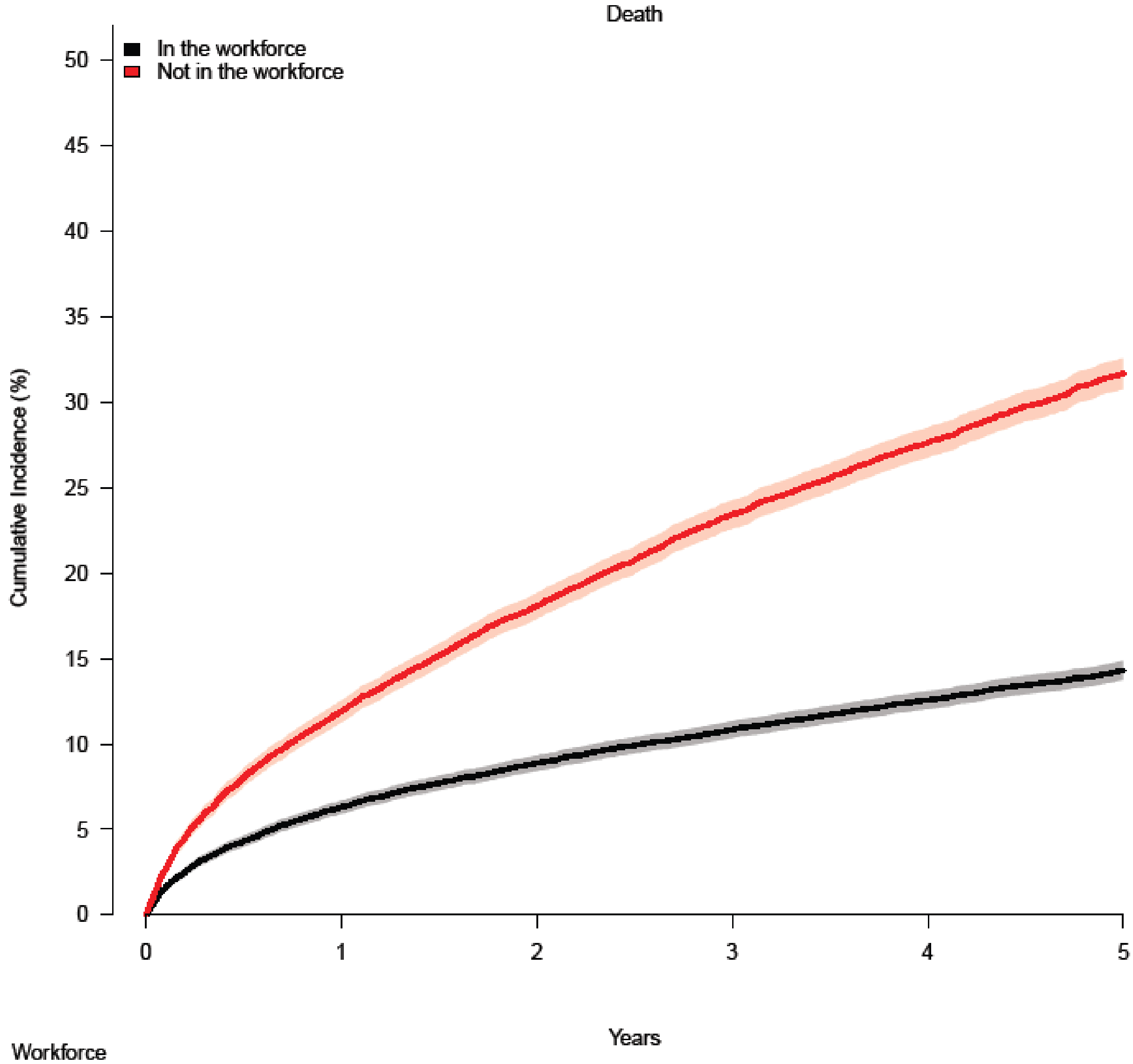
Table 1

Employment status	In the workforce	Out of the workforce
No. Patients	15428	10143
Age, median (IQR)	53 (47-57)	55 (50-58)
Male	11584 (75%)	6519 (64%)
Highest education Level		
Basic school <10 yrs	5095 (33%)	5055 (50%)
High school, +3yrs	647 (4%)	262 (3%)
Vocational Education	6062 (39%)	3411 (34%)
Short/medium higher, +2-4 yrs	2058 (13%)	858 (8%)
Long higher, +≥5 yrs	677 (4%)	157 (2%)
Unknown	889 (6%)	400 (4%)
Income group #		
Q1 (lowest)	3271 (21%)	3121 (31%)
Q4 (highest)	4939 (32%)	1454 (14%)
Length of first HF hospitalization		
0-2 days	5404 (35%)	3692 (36%)
3-7 days	5718 (37%)	3346 (33%)
> 7 days	4306 (28%)	3105 (31%)
Comorbidity (%)		
Ischemic heart disease	2993 (19%)	2379 (23%)
Atrial fibrillation	1459 (9%)	950 (9%)
Cancer	487 (3%)	643 (6%)
COPD	732 (5%)	998 (10%)

Diabetes	1950 (13%)	2267 (22%)
Hypertension	2584 (17%)	2061 (20%)
Chronic kidney disease	422 (3%)	584 (6%)
Stroke	439 (3%)	696 (7%)
Surgical procedures		
Valve surgery	287 (2%)	254 (3%)
CABG	471 (3%)	610 (6%)
Pharmacotherapy* (%)		
Loop diuretics	7598 (49%)	6192 (61%)
Antiplatelets, any	6002 (39%)	4559 (45%)
β-blockers	8702 (56%)	5223 (51%)
ACE-I/ARB	10188 (66%)	6372 (63%)
Statins	4827 (31%)	3711 (37%)
Thiazides	1783 (12%)	1581 (16%)
Ca^{2+} channel blockers	2342 (15%)	2240 (22%)
Digoxin	2646 (17%)	1636 (16%)
MRAs	3182 (21%)	2598 (26%)
Antidepressants	1410 (9%)	2287 (23%)
Antipsychotics	436 (3%)	1199 (12%)

CABG- coronary artery bypass grafting; COPD - chronic obstructive pulmonary disease;
MRAs - mineralocorticoid receptor antagonists;
ACE-I angiotensin-converting enzyme inhibitors, ARB- angiotensin-II receptor blockers;
*Filled in prescriptions 180 days prior to admission;
#Average 5-year family income prior to event, in quartiles;

Figure 1



Workforce						
In:	15428	13201	11544	10478	9490	8556
Out:	10143	8937	8311	7305	6437	5638

Figure 2

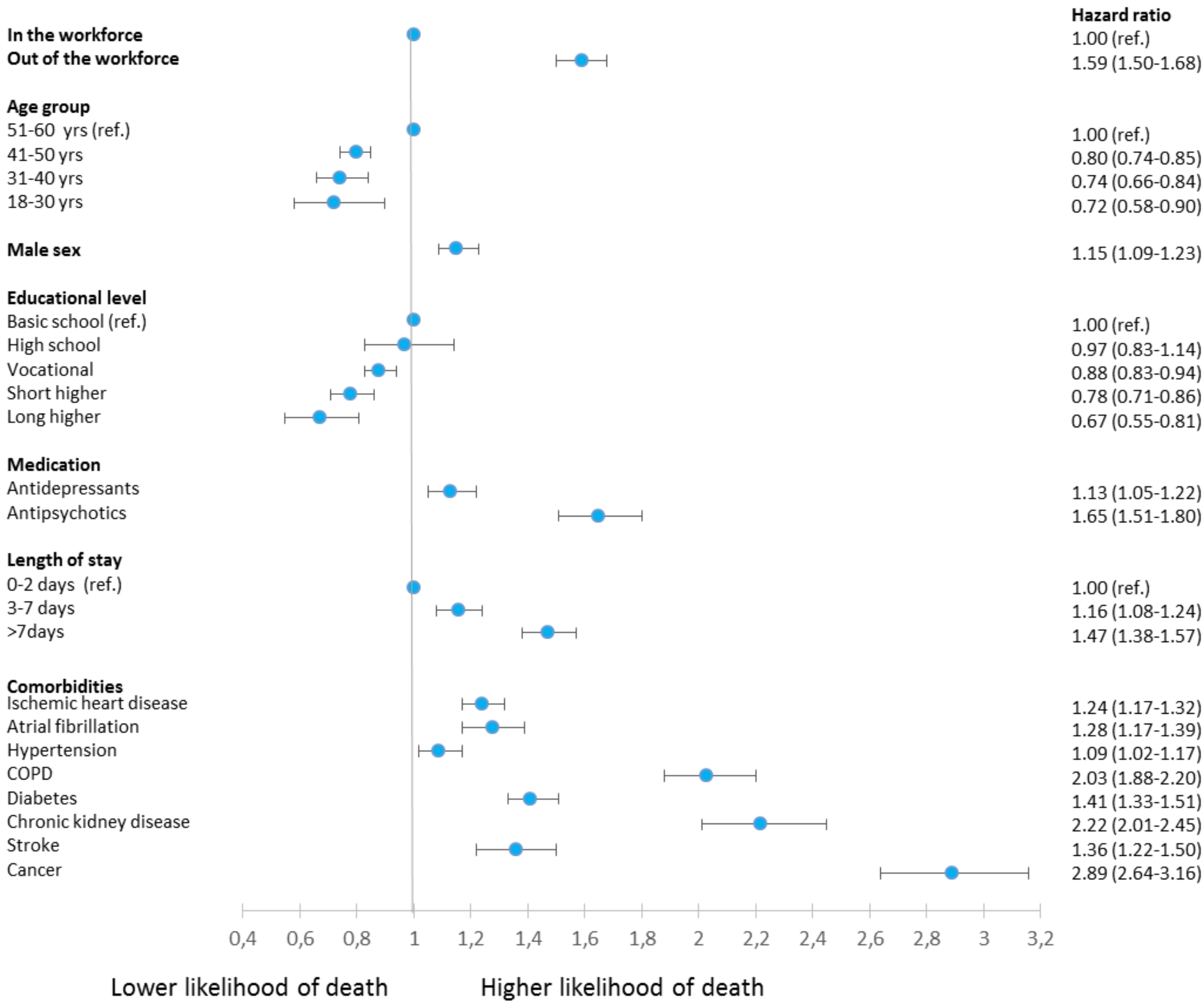
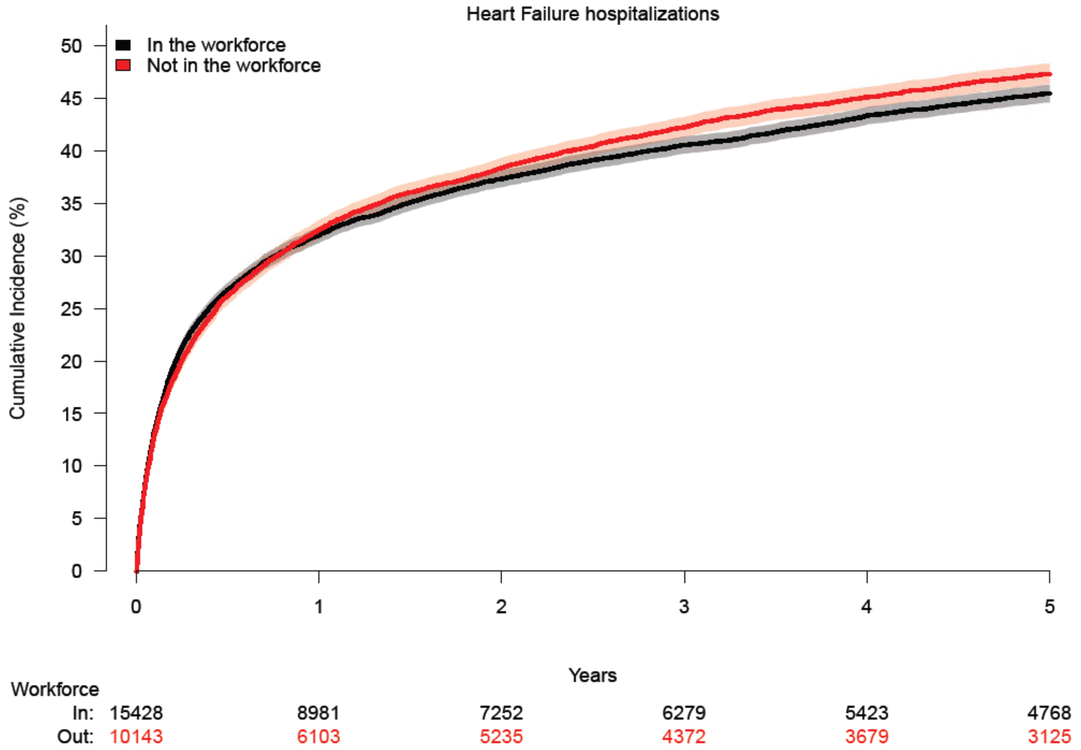

Hazard ratio
In the workforce
1.00 (ref.)
Out of the workforce
1.59 (1.50-1.68)
Age group
51-60 yrs (ref.)
1.00 (ref.)
41-50 yrs
0.80 (0.74-0.85)
31-40 yrs
0.74 (0.66-0.84)
18-30 yrs
0.72 (0.58-0.90)
Male sex
1.15 (1.09-1.23)
Educational level
Basic school (ref.)
1.00 (ref.)
High school
0.97 (0.83-1.14)
Vocational
0.88 (0.83-0.94)
Short higher
0.78 (0.71-0.86)
Long higher
0.67 (0.55-0.81)
Medication
Antidepressants
1.13 (1.05-1.22)
Antipsychotics
1.65 (1.51-1.80)
Length of stay
0-2 days (ref.)
1.00 (ref.)
3-7 days
1.16 (1.08-1.24)
>7days
1.47 (1.38-1.57)
Comorbidities
Ischemic heart disease
1.24 (1.17-1.32)
Atrial fibrillation
1.28 (1.17-1.39)
Hypertension
1.09 (1.02-1.17)
COPD
2.03 (1.88-2.20)
Diabetes
1.41 (1.33-1.51)
Chronic kidney disease
2.22 (2.01-2.45)
Stroke
1.36 (1.22-1.50)
Cancer
2.89 (2.64-3.16)
0,4
0,6
0,8
1
1,2
1,4
1,6
1,8
2
2,2
2,4
2,6
2,8
3
3,2
Lower likelihood of death
Higher likelihood of death

Figure 3


Heart Failure hospitalizations
In the workforce
Not in the workforce
Cumulative Incidence (%)
0 5 10 15 20 25 30 35 40 45 50
0 1 2 3 4 5
Years
Workforce
In: 15428 8981 7252 6279 5423 4768
Out: 10143 6103 5235 4372 3679 3125

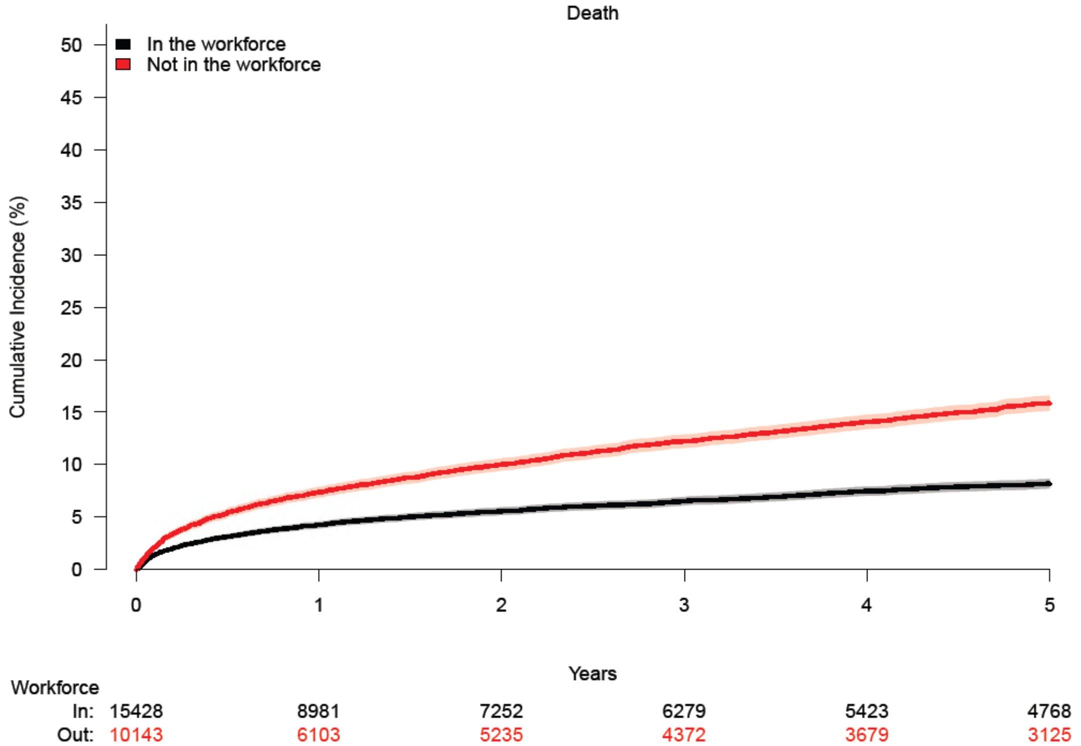
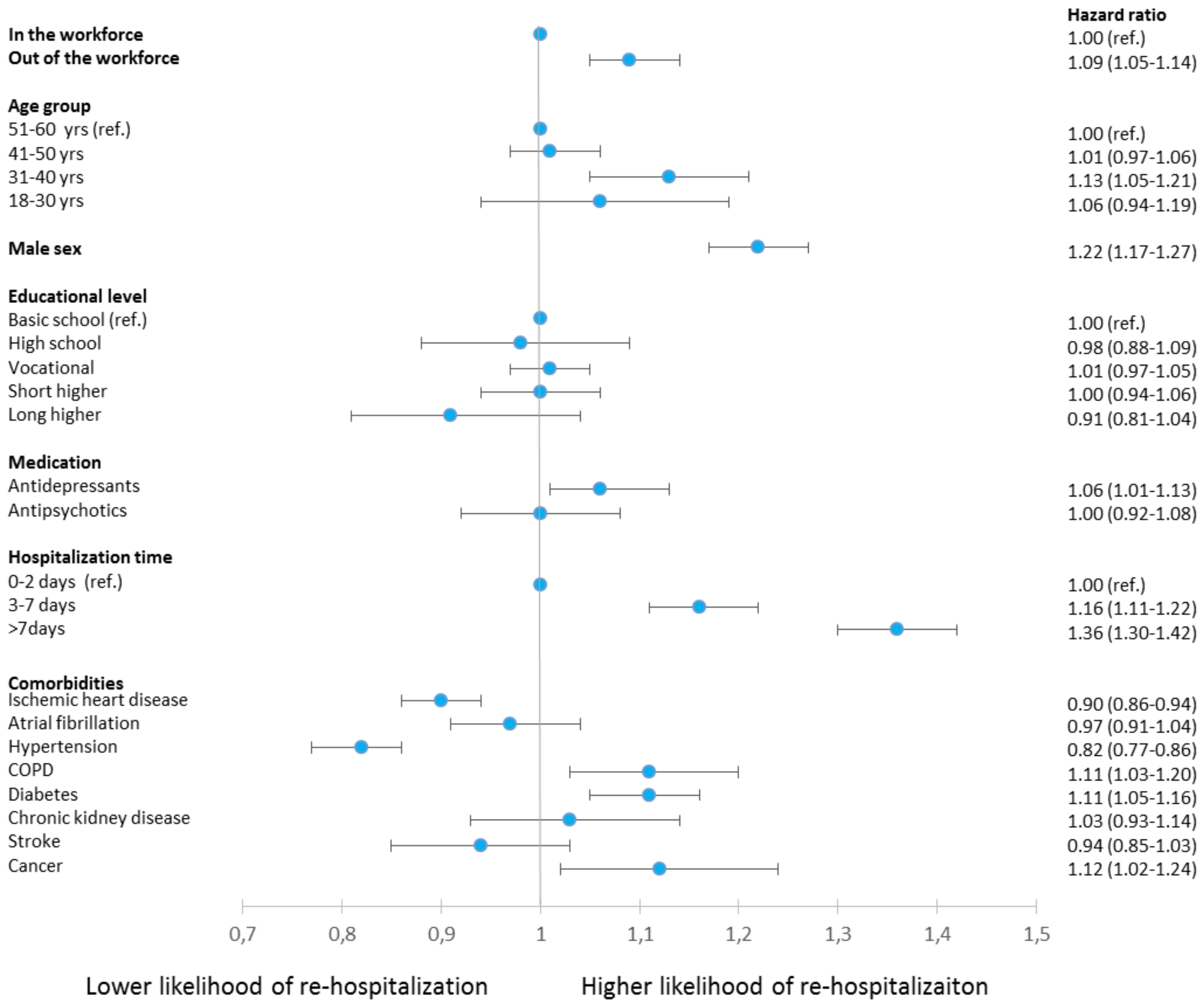

Death
In the workforce
Not in the workforce
Cumulative Incidence (%)
0 5 10 15 20 25 30 35 40 45 50
0 1 2 3 4 5
Years
Workforce
In: 15428 8981 7252 6279 5423 4768
Out: 10143 6103 5235 4372 3679 3125

Figure 4


Hazard ratio
In the workforce
1.00 (ref.)
Out of the workforce
1.09 (1.05-1.14)
Age group
51-60 yrs (ref.)
1.00 (ref.)
41-50 yrs
1.01 (0.97-1.06)
31-40 yrs
1.13 (1.05-1.21)
18-30 yrs
1.06 (0.94-1.19)
Male sex
1.22 (1.17-1.27)
Educational level
Basic school (ref.)
1.00 (ref.)
High school
0.98 (0.88-1.09)
Vocational
1.01 (0.97-1.05)
Short higher
1.00 (0.94-1.06)
Long higher
0.91 (0.81-1.04)
Medication
Antidepressants
1.06 (1.01-1.13)
Antipsychotics
1.00 (0.92-1.08)
Hospitalization time
0-2 days (ref.)
1.00 (ref.)
3-7 days
1.16 (1.11-1.22)
>7days
1.36 (1.30-1.42)
Comorbidities
Ischemic heart disease
0.90 (0.86-0.94)
Atrial fibrillation
0.97 (0.91-1.04)
Hypertension
0.82 (0.77-0.86)
COPD
1.11 (1.03-1.20)
Diabetes
1.11 (1.05-1.16)
Chronic kidney disease
1.03 (0.93-1.14)
Stroke
0.94 (0.85-1.03)
Cancer
1.12 (1.02-1.24)
0,7
0,8
0,9
1
1,1
1,2
1,3
1,4
1,5
Lower likelihood of re-hospitalization
Higher likelihood of re-hospitalizaiton

Appendix 1

Heart failure	I11.0, I13.0, I13.2, I42, I50
Renal disease	N03, N04, N17-N19, R34, I12, I13
Hypertension	I10-I15
Stroke	I60-I61, I63-I64
Diabetes mellitus	E10-E14
Ischemic heart disease	I20-I25
Atrial fibrillation	I48
Myocardial infarction	I21, I22
Cancer	C00-C99
COPD	J42, J44

CABG	KFNA-E
Valve surgery	KFG, KFK, KFM, KFJE-F