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Heart failure and risk of dementia: a Danish nationwide population-based cohort study

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Abstract

Aims—The association between heart failure and dementia remains unclear. We assessed the risk of dementia among patients with heart failure and members of a general population comparison cohort.

Methods and results—Individual-level data from Danish medical registries were linked in this nationwide population-based cohort study comparing patients with a first-time hospitalization for heart failure between 1980 and 2012 and a year of birth-, sex- and calendar-year matched comparison cohort from the general population. Stratified Cox regression analysis was used to compute 1–35-year hazard ratios (HRs) for the risk of all-cause dementia and, secondarily, Alzheimer's disease, vascular dementia, and other dementias. Analyses included 324,418 heart failure patients and 1,622,079 individuals from the general population (median age = 77 years, 52% male). Compared with the general population cohort, risk of all-cause dementia was increased among heart failure patients, adjusted HR: 1.21, 95% confidence interval (CI), 1.18–1.24. The associations were stronger in men and in heart failure patients under age 70. Heart failure patients had higher risks of vascular dementia (adjusted HR: 1.49, 95% CI, 1.40–1.59) and other dementias (adjusted HR: 1.30, 95% CI, 1.26–1.34) than members of the general population cohort. Heart failure was not associated with Alzheimer's disease (adjusted HR: 1.00, 95% CI, 0.96–1.04).

Conclusion—Heart failure was associated with an increased risk of all-cause dementia. Heart failure may represent a risk factor for dementia, but not for Alzheimer's disease.

Keywords

Heart failure; dementia; morbidity; epidemiology

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Introduction

Dementia is one of the most burdensome health conditions in western countries (1–3). The prevalence of dementia is increasing globally, with 4.6 million incident cases every year (2). The societal and financial burdens are enormous. Identifying modifiable risk factors to prevent or delay dementia onset thus could have a major public health impact (2,4).

While dementia and heart failure often coexist, the relation between these two common conditions is unclear (5,6). A population-based Swedish cohort study found a 1.8-fold higher risk of dementia and Alzheimer's disease in heart failure patients aged 75 years and older compared with patients without heart failure (7). In another small cohort study, late-life heart failure was associated with a doubled risk of dementia and Alzheimer's disease (8). Putative mechanisms are unknown, but low cardiac output and neurohormonal effects of heart failure may lead to chronic cerebral hypoxia and potentially contribute directly to dementia pathogenesis (9) or may lower the threshold for the emergence of dementia symptoms in the presence of specific dementia pathologies (10).

To examine potential associations between heart failure and dementia and to examine factors that might mediate this association, we used nationwide population registries to examine the risk of dementia in heart failure patients and in a matched general population comparison cohort.

Methods

This nationwide cohort study was conducted between 1 January 1980 and 1 September 2012 within a cumulative population of 8,262,736 Danish residents (11). In Denmark all residents are assigned a unique personal identifier, which allows linkage of individual-level data across health care registries (11).

Heart failure

We identified a cohort of patients with a first-time inpatient hospitalization for heart failure recorded in the Danish National Patient Registry (DNPR) (12). This registry has coded hospital admissions and outpatient clinic visits according to the *International Classification of Diseases* since 1977 (*Eighth Revision* [ICD-8] until 1994 and *Tenth Revision* [ICD-10] starting in 1994) (12). Each hospital contact is registered in the DNPR with one main diagnosis (primary) and appropriate secondary diagnoses. We used both primary and secondary diagnoses to identify heart failure patients. The positive predictive value of the heart failure diagnosis in the DNPR is between 81% and 100% (12).

General population comparison cohort

We used the Danish Civil Registration System to construct a comparison cohort, consisting of up to five individuals randomly sampled from the general population for each heart failure patient, matched with replacement on year of birth, sex, and calendar year of heart failure diagnosis (11). The Danish Civil Registration System has provided daily updates on vital statistics, including dates of birth, emigration, and death since 1968 (11). Heart failure patients and persons in the matched comparison cohort who were diagnosed with dementia

before the index date were excluded. The index date was the date of heart failure diagnosis and the corresponding matching date for members of the general population cohort. If members of the general population cohort were diagnosed with heart failure after the index date, they were transferred to the heart failure group and new corresponding comparison cohort members were selected from the general population.

Incident dementia

The primary outcome was incident all-cause dementia diagnosed in hospital inpatient and outpatient settings. Secondary outcomes were dementia subtypes classified as Alzheimer's disease, vascular dementia, and other dementias (i.e., any specific or unspecified dementia other than Alzheimer's disease and vascular dementia). Information on dementia diagnoses was obtained from the DNPR and the Danish Central Psychiatric Registry (12). In the DNPR, dementia diagnoses are available for hospital admissions since 1977 and for hospital-based outpatient clinics since 1995 (12). In the Danish Central Psychiatric Registry, dementia has been registered in the psychiatric hospital system since 1969 (13). The positive predictive value of all-cause dementia diagnosis in the two registries is 86% and that of Alzheimer's disease is 81%. Positive predictive values for other dementia subtypes are lower, and the diagnostic sensitivity is unknown (14).

Covariates

We collected information on the following comorbidities to include as covariates in our analyses: myocardial infarction, angina pectoris, atrial fibrillation/atrial flutter, heart valve disease, hypercholesterolemia, hypertension, stroke, obesity, diabetes mellitus, chronic pulmonary disease (as an indicator of smoking exposure), myxedema, alcoholism-related diseases, head trauma, osteoarthritis (as an indicator for use of nonsteroidal anti-inflammatory drugs), anemia, chronic kidney disease, and a modified Charlson Comorbidity Index (CCI) score (excluding congestive heart failure, myocardial infarction, cerebrovascular disease, dementia, chronic pulmonary disease, diabetes, and chronic kidney disease) diagnosed up to the index date. Data on the above diagnoses (including all available primary and secondary diagnoses other than emergency room diagnoses) were retrieved from the DNPR from 1977 until the index date. ICD codes used in the study are provided in the Supplementary material online, Tables S1–S2.

Statistical analyses

All heart failure patients and members of the general population comparison cohort were followed from their index date until the date of an inpatient or outpatient hospital contact for any dementia diagnosis, emigration, death, or 1 September 2014, whichever came first. Descriptive data on sex, age groups (<60 years, 60–69 years, 70–79 years, and ≥80 years), index year calendar periods (1980–1989, 1990–1999, and 2000–2012), and comorbidities are presented in Table 1. We excluded the first year of follow-up, since dementia diagnosed in this period is unlikely to be a consequence of heart failure. Using the cumulative incidence (risk) function accounting for death as a competing risk, we calculated dementia risks during 1–35 years, 1–10 years, 11–20 years, and 21–35 years of follow-up. We calculated standardized incidence ratios as the observed number of dementia cases among heart failure patients divided by the number expected if heart failure patients had the same

dementia risk as the general population of Denmark. The expected number of dementia cases was calculated using national incidence rates for first-time dementia diagnoses, according to sex, age, and calendar 1-year intervals. The 95% confidence intervals (CIs) for the standardized incidence ratio estimates were computed assuming a Poisson distribution of the observed numbers of dementia cases in the different time periods.

Hazard ratios (HRs) and corresponding 95% CIs were computed with multivariable stratified Cox hazards regression models, comparing heart failure patients with members of the general population comparison cohort (15). In the multivariable analyses, we controlled for age, sex, and calendar year by the matched study design and adjusted for co-morbidities in Table 1 and the modified CCI score. We considered any potential interactions in stratified models, which we used to examine the risk of dementia by sex, age groups, and the following factors associated with heart failure: previous myocardial infarction, angina pectoris, atrial fibrillation/atrial flutter, valvular heart disease, myocarditis, hypertension, and cardiomyopathy. We also examined the risk of dementia in subgroups of heart failure patients with hypercholesterolemia, stroke, obesity, diabetes mellitus, chronic pulmonary disease, myxedema, alcoholism-related diseases, head trauma, osteoarthritis, anemia, chronic kidney disease, and different CCI levels as potential underlying conditions that might modify associations between heart failure and dementia. We assessed the proportionality of hazards graphically using log minus log plots and found the assumption to be fulfilled in the analyzed follow-up periods.

Sensitivity analyses

We performed three sensitivity analyses to assess the robustness of the study results: First, we redefined the cohort of heart failure patients to include patients diagnosed in outpatient as well as inpatient settings. Second, due to an assumed induction period in the development of dementia, we repeated the analyses sequentially excluding the initial two, three, five, and ten years of follow-up. Third, we reclassified Alzheimer's disease to include the ICD code for unspecified dementia in the Alzheimer's disease definition.

All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC). The study was approved by the Danish Data Protection Agency (record number: 1-16-02-268-14). No approval from an ethical committee or informed consent from patients is required for registry studies in Denmark.

Results

In total, 324,418 heart failure patients (median age: 77, male: 52%) and 1,622,079 individuals from the general population (median age: 77, male: 52%) were included in the analysis. Median follow-up time was 2 years (interquartile range: 0.2–5.3 years) for patients with heart failure and 6.5 years (interquartile range: 3.1–11.6 years) for members of the comparison cohort, due primarily to higher mortality in the heart failure cohort. Heart failure patients had a higher prevalence of comorbidity than members of the general population cohort (Table 1).

Risk of dementia

During the 35-year follow-up period, 148,541 were diagnosed with dementia (51,412 with Alzheimer's disease, 18,624 with vascular dementia, and 78,505 with other dementias) (Table 2). Because of competing mortality, the absolute 1–35 year risk of all-cause dementia was substantially lower among heart failure patients (7.22%; 95% CI, 7.08%–7.36%) than among members of the general population comparison cohort (14.95%; 95% CI, 14.84%–15.06%) (Table 2). After adjustment for comorbid diseases, the risk of all-cause dementia among heart failure patients was higher than that among the general population (1–35-year HR: 1.21, 95% CI, 1.18–1.24). There was no association with Alzheimer's disease (1–35-year HR: 1.00, 95% CI: 0.96–1.04), but the relative risks of vascular dementia (1–35-year HR: 1.49, 95% CI: 1.40–1.59) and other dementias (1–35-year HR: 1.30, 95% CI, 1.26–1.34) were higher in heart failure patients than in members of the general population (Table 2). The dementia incidence ratios standardized to the Danish population agreed with the unadjusted HRs (Table 2).

Age, sex, heart failure causes, and comorbidity

Age-stratified analyses revealed that the magnitude of association between heart failure and all-cause dementia was higher in patients under age 70 than in patients above 70 (Table 3). The 1–35 year HRs were higher for men than women (Table 3). For men, the 1–35-year HR was 1.31 (95% CI: 1.26–1.36), and for women it was 1.15 (95% CI: 1.11–1.18). HRs for all-cause dementia were similar for heart failure patients with or without previous myocardial infarction, angina pectoris, atrial fibrillation/atrial flutter, heart valve disease, and hypertension (Table 4). Results of analyses stratified by other comorbidities are reported in Supplementary material online, Table S3. The association between heart failure and all-cause dementia applied to patients in 190–1994 as well as for patients in 1995–2012 (Supplementary material online, Table S4).

Sensitivity analyses

Redefining the cohort to include both inpatient and outpatient diagnoses of heart failure did not change the overall results (Supplementary material online, Table S4). Excluding the first year of follow-up decreased the overall risk estimates of dementia, but HRs did not change by excluding more than the initial year of follow-up (Supplementary material online, Table S5). When ICD codes for unspecified dementia were reclassified as Alzheimer's disease, heart failure patients now had a higher risk of this diagnosis than members of the general population comparison cohort: 1–35-year adjusted HR of 1.16, 95% CI, 1.14–1.20, with similar hazards for 1–10, 11–20, and 21–35 year categories (Supplementary material online, Table S7).

Discussion

In this nationwide cohort study, we found a clear association between heart failure and risk of all-cause dementia, driven by higher risks of vascular and other dementias, compared with members of the general population cohort over 35 years of follow up. Dementia risk was increased for both men and women but was somewhat greater for men. Although causes and outcomes of heart failure can differ between men and women (16), the basis of the sex

difference in dementia risk is unclear. Heart failure was a less strong relative risk factor for dementia in elderly than in young patients.

Two small studies have examined the risk of dementia in heart failure patients (7,8). A Finnish cohort study of 55 heart failure patients showed no association between midlife heart failure and dementia (25 year HR =0.84 [95% CI, 0.33–2.13]), but in 86 patients with late-life heart failure the risk of dementia was doubled (25 year HR =2.06 [95% CI, 1.00–4.27]) (8). A Swedish population-based cohort study of 205 heart failure patients aged 75 years or more reported an adjusted 9-year HR of 1.84 (95% CI, 1.35–2.51) for dementia (7). In the Framingham Offspring Cohort Study, subjects with an impaired cardiac index (n=269) had higher risks of all-cause dementia (adjusted HR=2.07, 95% CI, 1.02–4.19) and Alzheimer's disease (adjusted HR=2.10, 95% CI, 0.96–4.61) than patients with a normal cardiac index, after 7.7 years of follow-up (17). Supporting a weak association between heart failure and dementia, the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study of 931 subjects showed an increased risk of mild cognitive impairment or dementia for each 10% decrease in left ventricle ejection fraction (odds ratio=1.02, 95% CI, 0.75–1.38), 10 mL decrease in left ventricular stroke volume (odds ratio=1.24, 95% CI, 0.99–1.57), and 1 L/min decrease in cardiac output (odds ratio=1.40, 95% CI, 0.99–2.00) (18). Our results extend these findings within a large, nationwide cohort, indicating that heart failure is associated with about 20% elevated risk of all-cause dementia among patients surviving at least one year after their heart failure diagnosis.

Low cardiac output may directly reduce cerebral blood flow, contributing to cerebral hypoperfusion, impaired vascular autoregulation, and white matter injury. Moreover, neurohormonal activation related to heart failure may cause inflammation and cerebral microvascular dysfunction (9). These mechanisms may lead to chronic cerebral hypoxia and contribute directly to dementia pathogenesis (9) or lower the threshold for the emergence of dementia symptoms in the presence of dementia pathology (10).

Dementia risk was elevated for vascular dementia and other dementias, but heart failure was not associated with registry diagnoses of Alzheimer's disease. However, relatively large numbers of patients were classified as having unspecified dementia (ICD-10), suggesting substantial misclassification of specific dementia subtypes into this less specific categories. Patients with heart failure have multiple vascular risk factors that may explain their observed increased risk of vascular dementia (19,20). Heart failure has been suggested to increase the risk of stroke (21). Similarly, heart failure is associated with atrial fibrillation, diabetes, and hypertension, all of which are strongly associated with stroke or vascular dementia (22), but also with Alzheimer's disease (23). Although heart failure was unassociated with Alzheimer's disease per se, our sensitivity analysis, in which unspecified dementia was reclassified as Alzheimer's disease implied that heart failure patients might in fact be at higher risk of Alzheimer's disease than members of the general population comparison cohort.

Due to the dramatic increase in ageing populations of Western countries in the coming years, the number of patients with dementia is expected to increase (2). More assiduous management of heart failure might reduce the burden of dementia. Since cognitive

impairment and dementia in heart failure patients predicts mortality (24), clinicians should remain vigilant to these conditions, and more research on prevention and intervention strategies are warranted.

Strengths and limitations

This is the largest cohort study to date on the association between heart failure and dementia. Study strengths include its nationwide population coverage and complete long-term follow-up, virtually eliminating the risk of selection bias. However, our study is subject to the limitations inherent to dementia registration in the Danish medical registries. The diagnosis of dementia has a high positive predictive value (14), but the sensitivity of this diagnosis is unknown. Low sensitivity would be expected to underestimate associations with dementia. Heart failure patients are more frequently in contact with the health care system than members of the general population. Therefore, registration of dementia may be higher for heart failure patients than for members of the general population, and surveillance bias could have overestimated the associations observed with dementia (25). We lacked results of diagnostic brain imaging, data on drug treatment, socioeconomic status, marital status, and other potential confounders; and objective measures of cognitive function. Also, due to vascular risk factors in heart failure patients, diagnostic bias may contribute to findings on our initial analysis of increased risk of vascular dementia but the null association with Alzheimer's disease. In addition, while we adjusted for previous cardiovascular comorbidities, we did not include incident cardiovascular conditions occurring during follow-up, because these conditions could represent factors that mediate the association between heart failure and dementia. Because data on heart failure severity is not registered in the DNPR, we could not investigate the risk of dementia in subgroups of patients with more advanced heart failure. However, dementia risks were similar in heart failure patients with shorter and longer follow-up intervals. The Danish population is relatively homogenous, consisting mostly of Caucasians, and the generalizability of our study results to other populations is unknown.

Conclusion

Heart failure was associated with an increased risk of all-cause dementia, with stronger associations for men than for women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of patients hospitalized with a first-time diagnosis of heart failure during 1980–2012 and members of the general population comparison cohort

	Heart failure cohort (n=324,418)	Comparison cohort cohort (n=1,622,079)
Gender		
Male	168,564 (52)	842,810 (52)
Age, years		
<60	31,848 (10)	159,659 (10)
60–69	57,446 (18)	287,942 (18)
70–79	109,496 (34)	546,989 (34)
≥80	125,628 (39)	627,489 (39)
Median (interquartile range)	77 (69–84)	77 (69–84)
Decade of diagnosis		
1980–1989	96,020 (30)	480,096 (30)
1990–1999	109,866 (34)	549,327 (34)
2000–2012	118,532 (37)	592,656 (37)
Comorbidities		
Myocardial infarction	51,802 (16)	69,041 (4)
Angina pectoris	53,484 (17)	89,915 (6)
Atrial fibrillation or flutter	39,005 (12)	61,464 (4)
Valvular heart disease	14,329 (4)	14,878 (0.9)
Hypercholesterolemia	9,066 (3)	18,136 (1)
Hypertension	52,564 (16)	119,823 (7)
Stroke	20,625 (6)	57,244 (4)
Obesity	14,292 (4)	20,342 (1)
Diabetes mellitus	36,143 (11)	60,980 (4)
Chronic pulmonary disease	46,660 (14)	76,580 (5)
Myxedema	4,995 (2)	12,458 (0.8)
Alcoholism-related diseases	8,480 (3)	16,852 (1)
Head trauma	43,632 (13)	183,321 (11)
Osteoartrhitis	38,387 (12)	146,389 (9)
Anemia	19,575 (6)	42,714 (3)
Chronic kidney disease	10,095 (3)	12,900 (0.8)
Charlson Comorbidity Index *		
Normal	235,534 (73)	1,350,105 (83)
Moderate	45,406 (14)	118,649 (7)
Severe	31,105 (10)	123,189 (8)
Very severe	12373 (4)	30,136 (2)

Values are given as n (%).

* Categories of comorbidity were based on scores on the modified Charlson Comorbidity Index of 0 (normal), 1 (moderate), 2 (severe), and ≥3 (very severe)

Table 2

Cumulative incidence risks and hazard ratios of dementia in heart failure patients and members of the general population cohort

	Comparison Cohort		Heart Failure Patients				
Years since diagnosis	**Events /No. at risk**	**Cumulative incidence risk, % (95% CI)**	**Events /No. at risk**	**Cumulative incidence risk, % (95% CI)**	**Standardized incidence ratio (95% CI)**	**Hazard ratio controlled for matching factors* (95% CI)**	**Adjusted hazard ratio (95% CI)†**
All-cause dementia							
1–10	92,228/1,492,102	7.18 (7.13 – 7.22)	9,808/198,038	5.39 (5.29 – 5.49)	1.13 (1.10–1.15)	1.28 (1.25–1.31)	1.21 (1.18–1.24)
11–20	37,332/511,213	9.82 (9.72 – 9.92)	1,534/29,655	6.96 (6.62 – 7.31)	1.13 (1.07–1.18)	1.26 (1.17–1.35)	1.19 (1.11–1.28)
21–35	7,497/99,527	13.42 (13.00 – 13.86)	142/2,906	7.60 (6.27 – 9.09)	1.20 (1.01–1.41)	1.47 (1.14–1.88)	1.38 (1.07–1.79)
1–35	137,057/1,492,102	14.95 (14.84 – 15.06)	11,484/198,038	7.22 (7.08 – 7.36)	1.13 (1.11–1.15)	1.28 (1.25–1.30)	1.21 (1.18–1.24)
Alzheimer's disease							
1–10	34,454/1,492,102	2.67 (2.65 – 2.70)	2,921/198,038	1.59 (1.54 – 1.65)	0.90 (0.87–0.93)	1.02 (0.98–1.06)	1.02 (0.97–1.06)
11–20	11,170/511,213	2.95 (2.89 – 3.00)	356/29,655	1.62 (1.45 – 1.80)	0.82 (0.74–0.91)	0.79 (0.69–0.90)	0.80 (0.70–0.92)
21–35	2,469/99,527	4.62 (4.37 – 4.88)	42/2,906	2.61 (1.74 – 3.75)	1.02 (0.74–1.38)	1.37 (0.88–2.12)	1.31 (0.83–2.07)
1–35	48,093/1,492,102	5.18 (5.11 – 5.25)	3,319/198,038	2.07 (1.98 – 2.15)	0.89 (0.86–0.92)	1.00 (0.96–1.04)	1.00 (0.96–1.04)
Vascular dementia							
1–10	11,168/1,492,102	0.87 (0.86 – 0.89)	1,546/198,038	0.85 (0.81 – 0.90)	1.43 (1.36–1.50)	1.66 (1.56–1.77)	1.47 (1.38–1.57)
11–20	4,710/511,213	1.25 (1.22 – 1.29)	248/29,655	1.12 (0.98 – 1.27)	1.44 (1.26–1.63)	1.84 (1.54–2.20)	1.59 (1.32–1.93)
21–35	922/99,527	1.71 (1.56 – 1.87)	30/2,906	1.53 (1.03 – 2.21)	2.04 (1.37–2.91)	2.64 (1.44–4.85)	2.29 (1.18–4.45)
1–35	16,800/1,492,102	1.90 (1.85 – 1.94)	1,824/198,038	1.17 (1.11 – 1.23)	1.44 (1.37–1.50)	1.69 (1.59–1.79)	1.49 (1.40–1.59)
Other dementias							
1–10	46,606/1,492,102	3.67 (3.63 – 3.70)	5,341/198,038	2.96 (2.88 – 3.03)	1.22 (1.19–1.25)	1.38 (1.33–1.43)	1.29 (1.25–1.34)
11–20	21,452/511,213	5.71 (5.63 – 5.79)	930/29,655	4.26 (3.99 – 4.54)	1.23 (1.15–1.31)	1.46 (1.33–1.60)	1.37 (1.24–1.51)
21–35	4,106/99,527	7.37 (7.03 – 7.72)	70/2,906	3.52 (2.71 – 4.49)	1.11 (0.87–1.41)	1.26 (0.89–1.79)	1.18 (0.82–1.70)
1–35	72,164/1,492,102	8.17 (8.08 – 8.26)	6,341/198,038	4.03 (3.92 – 4.14)	1.22 (1.19–1.25)	1.39 (1.35–1.43)	1.30 (1.26–1.34)

CI, confidence interval

*Age, sex, and calendar year

†Controlled for matching factors by study design and adjusted for stroke, atrial fibrillation/atrial flutter, hypertension, hypercholesterolemia, myocardial infarction, stable angina pectoris, valvular heart disease, diabetes, chronic obstructive pulmonary disease, obesity, myxedema, alcoholism-related disease, head trauma, osteoarthritis, anemia, chronic kidney disease, and a modified CCI score.

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Table 3

Age- and sex-stratified analyses and cumulative incidence risks, %, and hazard ratio of dementia in heart failure patients and members of the general population

	1–10 years		11–35 years		1–35 years	
	Cumulative incidence risk, % (95% CI)	Adjusted hazard ratio (95% CI)*	Cumulative incidence risk, % (95% CI)	Adjusted hazard ratio (95% CI)*	Cumulative incidence risk, % (95% CI)	Adjusted hazard ratio (95% CI)*
All-cause dementia						
Male	4.60 (4.46 – 4.73)	1.31 (1.27–1.37)	7.69 (7.07 – 8.34)	1.26 (1.13–1.40)	6.29 (6.10 – 6.49)	1.31 (1.26–1.36)
Female	6.22 (6.07 – 6.39)	1.14 (1.11–1.18)	9.79 (9.07 – 10.54)	1.18 (1.07–1.29)	8.17 (7.95 – 8.38)	1.15 (1.11–1.18)
<60 y	1.05 (0.92 – 1.19)	2.50 (2.02–3.08)	4.90 (4.15 – 5.73)	1.56 (1.29–1.89)	3.77 (3.33 – 4.25)	1.93 (1.68–2.23)
60–69 y	3.03 (2.86 – 3.22)	1.71 (1.57–1.86)	10.77 (9.87 – 11.72)	1.31 (1.17–1.46)	6.52 (6.18 – 6.88)	1.56 (1.46–1.66)
70–79 y	6.25 (6.07 – 6.45)	1.24 (1.20–1.29)	10.88 (10.12 – 11.67)	1.06 (0.95–1.18)	8.13 (7.90 – 8.36)	1.22 (1.18–1.27)
80+ y	7.51 (7.31 – 7.73)	1.06 (1.03–1.10)	6.33 (5.33 – 7.43)	0.80 (0.57–1.12)	7.85 (7.64 – 8.07)	1.06 (1.02–1.10)
Alzheimer's disease						
Male	1.32 (1.24 – 1.39)	1.13 (1.06–1.21)	1.82 (1.50 – 2.19)	0.80 (0.65–1.00)	1.72 (1.62 – 1.83)	1.09 (1.02–1.16)
Female	1.89 (1.80 – 1.98)	0.95 (0.90–1.01)	2.69 (2.20 – 3.24)	0.86 (0.73–1.02)	2.43 (2.29 – 2.57)	0.94 (0.89–0.99)
<60 y	0.13 (0.09 – 0.18)	2.73 (1.51–4.92)	1.40 (0.98 – 1.94)	1.07 (0.74–1.56)	0.90 (0.67 – 1.21)	1.35 (1.00–1.84)
60–69 y	0.76 (0.67 – 0.85)	1.22 (1.05–1.42)	2.78 (2.29 – 3.35)	0.98 (0.79–1.20)	1.66 (1.48 – 1.87)	1.14 (1.01–1.28)
70–79 y	2.05 (1.94 – 2.16)	1.05 (0.98–1.12)	2.68 (2.30 – 3.11)	0.69 (0.56–0.85)	2.52 (2.39 – 2.65)	1.01 (0.94–1.07)
80+ y	2.17 (2.06 – 2.29)	0.94 (0.88–1.00)	0.86 (0.52 – 1.35)	0.35 (0.13–0.92)	2.22 (2.10 – 2.34)	0.93 (0.87–0.99)
Vascular dementia						
Male	0.83 (0.77 – 0.89)	1.47 (1.34–1.62)	1.47 (1.22 – 1.76)	1.70 (1.31–2.21)	1.16 (1.07 – 1.24)	1.50 (1.37–1.64)
Female	0.88 (0.82 – 0.94)	1.48 (1.35–1.62)	1.50 (1.23 – 1.81)	1.64 (1.28–2.11)	1.18 (1.10 – 1.27)	1.50 (1.38–1.64)
<60 y	0.25 (0.19 – 0.33)	4.43 (2.65–7.41)	1.11 (0.79 – 1.53)	2.41 (1.54–3.76)	0.87 (0.68 – 1.11)	3.27 (2.36–4.53)
60–69 y	0.71 (0.62 – 0.80)	2.48 (2.05–3.01)	2.21 (1.80 – 2.68)	1.91 (1.46–2.50)	1.43 (1.27 – 1.60)	2.24 (1.92–2.62)
70–79 y	1.07 (0.99 – 1.15)	1.54 (1.39–1.70)	1.36 (1.09 – 1.67)	1.23 (0.89–1.68)	1.31 (1.22 – 1.41)	1.50 (1.36–1.66)
80+ y	0.94 (0.86 – 1.01)	1.13 (1.02–1.26)	0.62 (0.34 – 1.04)	0.53 (0.16–1.80)	0.97 (0.89 – 1.05)	1.13 (1.01–1.25)
Other dementias						
Male	2.46 (2.36 – 2.56)	1.41 (1.33–1.48)	4.47 (3.99 – 4.98)	1.43 (1.24–1.66)	3.45 (3.31 – 3.60)	1.41 (1.34–1.48)
Female	3.47 (3.35 – 3.60)	1.22 (1.17–1.28)	5.72 (5.25 – 6.22)	1.30 (1.15–1.47)	4.62 (4.47 – 4.78)	1.23 (1.18–1.29)
<60 y	0.67 (0.57 – 0.79)	2.24 (1.72–2.93)	2.44 (1.94 – 3.03)	1.63 (1.24–2.15)	2.02 (1.72 – 2.37)	1.93 (1.60–2.33)

	1–10 years		11–35 years		1–35 years	
	Cumulative incidence risk, % (95% CI)	**Adjusted hazard ratio (95% CI)***	**Cumulative incidence risk, % (95% CI)**	**Adjusted hazard ratio (95% CI)***	**Cumulative incidence risk, % (95% CI)**	**Adjusted hazard ratio (95% CI)***
60–69 y	1.58 (1.45 – 1.71)	1.92 (1.70–2.16)	5.94 (5.26 – 6.68)	1.39 (1.19–1.63)	3.51 (3.26 – 3.79)	1.70 (1.55–1.87)
70–79 y	3.15 (3.02 – 3.29)	1.34 (1.26–1.42)	6.95 (6.33 – 7.60)	1.29 (1.13–1.48)	4.36 (4.19 – 4.54)	1.33 (1.26–1.41)
80+ y	4.43 (4.27 – 4.60)	1.14 (1.08–1.19)	4.87 (4.00 – 5.86)	0.95 (0.63–1.42)	4.69 (4.52 – 4.87)	1.13 (1.08–1.19)

CI, confidence interval.

*Controlled for matching factors by study design and adjusted for stroke, atrial fibrillation/atrial flutter, hypertension, hypercholesterolemia, myocardial infarction, stable angina pectoris, valvular heart disease, diabetes, chronic obstructive pulmonary disease, obesity, myxedema, alcoholism-related disease, head trauma, osteoarthritis, anemia, chronic kidney disease, and a modified CCI score.

Table 4

Risk of dementia in selected subgroups of heart failure patients: adjusted hazard ratios (reference group general population)

	1–10 year adjusted hazard ratio (95% CI)*				11–35 year adjusted hazard ratio (95% CI)*			
	Alzheimer's disease	**Vascular dementia**	**Other dementias**	**All-cause dementia**	**Alzheimer's disease**	**Vascular dementia**	**Other dementias**	**All-cause dementia**
Myocardial infarction								
Yes	1.01 (0.90–1.15)	1.23 (1.05–1.44)	1.14 (1.04–1.24)	1.11 (1.04–1.19)	0.88 (0.65–1.20)	1.15 (0.79–1.69)	1.18 (0.95–1.46)	1.08 (0.92–1.27)
No	0.99 (0.95–1.03)	1.39 (1.31–1.48)	1.26 (1.22–1.30)	1.18 (1.15–1.20)	0.85 (0.76–0.95)	1.43 (1.25–1.64)	1.24 (1.15–1.33)	1.14 (1.08–1.21)
Angina pectoris								
Yes	0.77 (0.69–0.86)	1.35 (1.18–1.54)	1.17 (1.09–1.26)	1.07 (1.01–1.13)	0.74 (0.55–1.00)	1.47 (1.01–2.14)	1.03 (0.84–1.26)	0.99 (0.86–1.16)
No	1.02 (0.98–1.07)	1.36 (1.28–1.45)	1.26 (1.22–1.30)	1.19 (1.16–1.22)	0.87 (0.78–0.97)	1.38 (1.20–1.58)	1.26 (1.18–1.35)	1.16 (1.10–1.22)
Atrial fibrillation or flutter								
Yes	0.94 (0.83–1.06)	1.12 (0.96–1.31)	1.18 (1.08–1.28)	1.10 (1.03–1.17)	0.94 (0.61–1.43)	1.07 (0.66–1.72)	1.10 (0.84–1.43)	1.05 (0.86–1.30)
No	0.99 (0.95–1.03)	1.40 (1.32–1.49)	1.25 (1.22–1.29)	1.18 (1.15–1.20)	0.84 (0.75–0.93)	1.42 (1.25–1.62)	1.24 (1.16–1.33)	1.14 (1.08–1.20)
Valvular heart disease								
Yes	0.78 (0.62–0.98)	1.17 (0.86–1.61)	1.29 (1.09–1.53)	1.08 (0.96–1.22)	1.01 (0.46–2.23)	2.24 (0.79–6.37)	2.04 (1.21–3.46)	1.71 (1.14–2.54)
No	1.00 (0.96–1.04)	1.37 (1.30–1.45)	1.25 (1.21–1.28)	1.17 (1.15–1.20)	0.85 (0.76–0.94)	1.38 (1.22–1.57)	1.22 (1.14–1.31)	1.13 (1.07–1.19)
Hypertension								
Yes	0.96 (0.86–1.06)	1.27 (1.12–1.44)	1.31 (1.22–1.40)	1.19 (1.13–1.26)	0.63 (0.42–0.93)	1.39 (0.90–2.16)	1.13 (0.89–1.44)	1.01 (0.84–1.22)
No	0.99 (0.95–1.03)	1.38 (1.29–1.47)	1.23 (1.19–1.27)	1.16 (1.13–1.19)	0.86 (0.78–0.96)	1.39 (1.22–1.59)	1.24 (1.15–1.32)	1.14 (1.08–1.20)
Myocarditis								
Yes	(.–.)	(.–.)	3.72 (1.02–13.59)	0.99 (0.37–2.67)	(.–.)	(.–.)	(.–.)	(.–.)
No	0.99 (0.95–1.03)	1.37 (1.30–1.45)	1.25 (1.21–1.29)	1.17 (1.15–1.20)	0.85 (0.76–0.94)	1.39 (1.23–1.58)	1.23 (1.15–1.31)	1.13 (1.08–1.19)
Cardiomyopathy								
Yes	0.86 (0.41–1.78)	1.47 (0.63–3.46)	1.18 (0.73–1.93)	1.15 (0.80–1.65)	1.12 (0.07–18.41)	(.–.)	1.06 (0.15–7.30)	1.85 (0.51–6.70)
No	0.99 (0.95–1.03)	1.37 (1.29–1.45)	1.25 (1.21–1.29)	1.17 (1.15–1.20)	0.85 (0.76–0.94)	1.39 (1.23–1.58)	1.23 (1.15–1.32)	1.13 (1.08–1.19)

CI, confidence interval.

(.–.) Insufficient for estimates.

*Adjusted for age, sex, calendar year, stroke, atrial fibrillation/atrial flutter, hypertension, hypercholesterolemia, myocardial infarction, stable angina pectoris, valvular heart disease, diabetes, chronic obstructive pulmonary disease, obesity, myxedema, alcoholism-related disease, head trauma, osteoarthritis, anemia, chronic kidney disease, and a modified CCI score (except the stratified variable).