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ORIGINAL RESEARCH

Incidence, Clinical Correlates, and Prognostic Impact of Dementia in Heart Failure

A Population-Based Cohort Study

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ABSTRACT

BACKGROUND Heart failure (HF) may increase the risk of dementia via shared risk factors.

OBJECTIVES The authors investigated the incidence, types, clinical correlates, and prognostic impact of dementia in a population-based cohort of patients with index HF.

METHODS The previously territory-wide database was interrogated to identify eligible patients with HF (N = 202,121) from 1995 to 2018. Clinical correlates of incident dementia and their associations with all-cause mortality were assessed using multivariable Cox/competing risk regression models where appropriate.

RESULTS Among a total cohort aged ≥18 years with HF (mean age 75.3 ± 13.0 years, 51.3% women, median follow-up 4.1 [IQR: 1.2-10.2] years), new-onset dementia occurred in 22,145 (11.0%), with age-standardized incidence rate of 1,297 (95% CI: 1,276-1,318) per 10,000 in women and 744 (723-765) per 10,000 in men. Types of dementia were Alzheimer's disease (26.8%), vascular dementia (18.1%), and unspecified dementia (55.1%). Independent predictors of dementia included: older age (≥75 years, subdistribution hazard ratio [SHR]: 2.22), female sex (SHR: 1.31), Parkinson's disease (SHR: 1.28), peripheral vascular disease (SHR: 1.46), stroke (SHR: 1.24), anemia (SHR: 1.11), and hypertension (SHR: 1.21). The population attributable risk was highest for age ≥75 years (17.4%) and female sex (10.2%). New-onset dementia was independently associated with increased risk of all-cause mortality (adjusted SHR: 4.51; $P < 0.001$).

CONCLUSIONS New-onset dementia affected more than 1 in 10 patients with index HF over the follow-up, and portended a worse prognosis in these patients. Older women were at highest risk and should be targeted for screening and preventive strategies. (JACC: Asia 2023;3:108–119) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Heart failure (HF) and dementia commonly coexist in old age, with shared pathological processes and risk factors, such as hypertension, anemia, and cardiovascular risk factors.[1] As a major risk factor for HF, diabetes has been linked to cognitive impairment,[2-4] suggesting a potential mechanism underlying the association between HF and dementia. Some reports suggested that HF is associated with an increased risk of dementia or cognitive impairment independent of vascular disorders.[5,6] The presence of dementia or cognitive decline in HF not only portends poorer outcomes, but further complicates patient selfcare.[1] Both conditions are associated with enormous health care and societal costs. Globally, 57.4 million individuals lived with dementia in 2019, with a projected increase to 152.8 (number of cases) (95% CI: 130.8-175.9) million cases in 2050.[7] On the other hand, more than 64 million people had been afflicted with HF,[8] with its prevalence increasing rapidly, accounting for an estimated $31 billion USD in health care expenditure in 2012.[9] Advances in the treatment of HF and better management of cardiovascular diseases have contributed to longer survival, albeit at the expense of increasing absolute prevalence of HF globally.[10] In Asia, the prevalence of dementia is expected to increase dramatically in tandem with the rapidly ageing population.[11] During the last decade, dementia was expected to affect 2.0% to 13.0 % of the elderly in China, which was relatively higher than that of the European country.[12] Earlier studies have suggested that HF afflicts Asian patients at least a decade earlier than their Western counterparts.[13] Currently, there is a paucity of data relating to dementia, its prevalence, types, clinical correlates, and its prognostic impact in HF, particularly among Asian patients.

The aim of the study is to examine the incidence, clinical correlates, and the association of dementia with all-cause mortality among patients with HF. Interactions by sex, age group, and education status are further explored. Identification of the clinical correlates of new-onset dementia and their associated population-attributable fractions (PAF) can inform preventive measures and target high-risk population for intensive cognitive surveillance.

METHODS

DATA SOURCES. This is a retrospective cohort study using data derived from the Clinical Data Analysis and Reporting System (CDARS), a territory-wide database developed by the Hong Kong Hospital Authority. As the statutory body and the singular provider of public health care services in Hong Kong, the Hospital Authority provides over 80% of in-patient services with a population of 7.5 million.[14] Patient information including, but not limited to, demographic data, diagnoses, drug prescriptions, procedures, laboratory tests, and episodes of hospital visits since 1993 were prospectively collected into the CDARS.[15] Prior studies have demonstrated a high percentage of coding accuracy in CDARS data.[15,16] Diagnostic data, specifically, were determined using the International Classification of Diseases-9th Revision (ICD-9) and -10th Revision (ICD-10), which have also shown a high degree of coding accuracy.[15,16] Patient data (name and Hong Kong identification number) were deidentified in CDARS and unique personal reference numbers were generated. The study was approved by the institutional review board of the University of Hong Kong and the West Cluster of the Hong Kong Hospital Authority.

STUDY SUBJECTS AND OUTCOME DEFINITION. We searched for all patients age 18 years old or above with HF (ICD-9: 398.91, 402, 404, 425, 428; ICD-10: I11, I13, I50, I42, I43) as a primary cause of hospitalization between January 1, 1995, and December 31, 2018 (N = 228,938). The index date was defined as the date of first diagnosis of HF. We also excluded patients who were diagnosed with HF before January 1, 1995 (N = 9,715) to identify incident HF. Further, patients who had any history of dementia diagnosis and human immunodeficiency disease were excluded (**Figure 1**).

The primary outcome of the study was incident dementia after the diagnosis of HF. The secondary outcomes were cardiovascular death (CVD), non-CVD, or all-cause mortality. Patients were followed up until death, or December 31, 2020.

ABBREVIATIONS AND ACRONYMS

AD = Alzheimer's disease

CDARS = Clinical Data Analysis and Reporting System

CVD = cardiovascular death

HF = heart failure

ICD = International Classification of Diseases

PAF = population attributable fractions

SHR = subdistribution hazard ratio

VD = vascular dementia

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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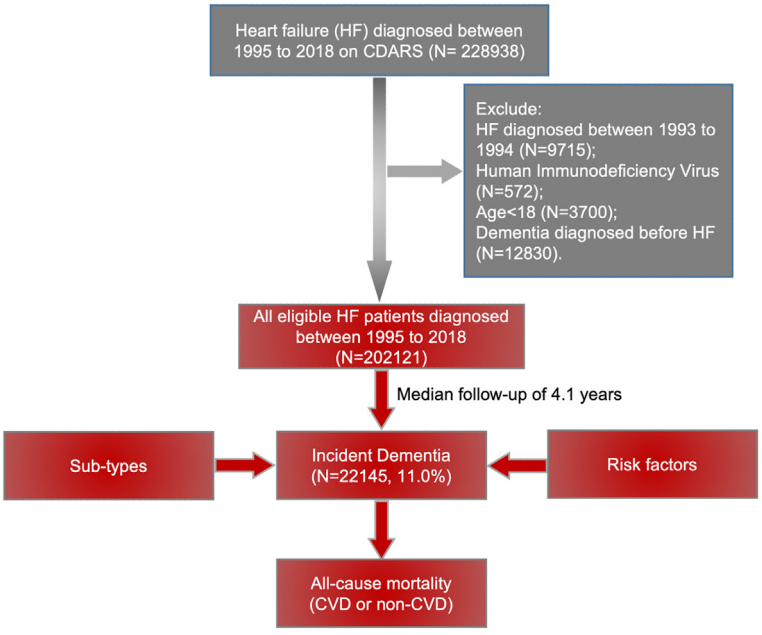
FIGURE 1 Flow Chart of Study Cohort



Among 228,928 heart failure (HF) patients derived from Clinical Data Analysis and Reporting System (CDARS) between 1995 and 2018, 26,817 patents were excluded. A total of 22,145 patients developed incident dementia during a median follow-up of 4.1 years. The subtypes of dementia were counted, and the risk factors attributed to dementia were analyzed. Further, we evaluated the impact of dementia on all-cause mortality, cardiovascular disease (CVD), or non-CVD, respectively.

STUDY COVARIATES. We traced patient records to 2 years before index date (of HF) and collected data including age at baseline, sex, comorbidities (hypertension, diabetes, obesity, stroke, anemia, coronary artery disease, peripheral vascular disease, dyslipidemia, atrial fibrillation, other arrhythmias, cirrhosis, chronic renal failure, other chronic kidney diseases, hearing loss, head injury, cancer, Parkinson's disease, depression, sleep apnea, rheumatism), and drug history (baseline use of aspirin, other antiplatelet agents, antihypertensive agents, antidiabetic drugs, beta-blockers, statins, diuretic agents), and lifestyle factors (smoking, alcohol), as well as education level (as proxy for socioeconomic status).[17] Baseline drug exposure was defined as ≥90 days consecutive use of the drug within 2 years before the index date.[18,19] Details of ICD-9 and ICD-10 codes used are listed in Supplemental Table 1.

STATISTICAL ANALYSIS. Baseline characteristics of participants were categorized into types of dementia: Alzheimer's disease (AD), vascular dementia (VD), and unspecified dementia. Sex difference by age stratification (years): women and men in each age stratum (age ≤65, 66-70, 71-75, 76-80, 81-85, age >85 years) were used for statistical adjustment. Continuous variables were summarized as mean ± SD, and categorical variables were presented as count (percentage). Baseline characteristics were compared by study groups, which were estimated using independent *t*-test, analysis of variance, or chi-square test, as appropriate.

Relative risks and PAF were calculated to estimate the proportion of risk of incident dementia that is attributable to a specific risk factor. Patients might have several risk factors and individual PAFs, therefore they cannot be summed to get the total PAF. Thus, it is important to calculate a weighted PAF, taking communality into account as described in previous studies.[17] Incidence rates were directly standardized by age groups (≤55, 56-65, 66-75, 76-85, 86-95, >95 years) to the HF population of 2019 in Hong Kong.

Cox proportional hazards modeling was performed using an intention-to-treatment analysis to evaluate the association of risk factors with dementia incidence, adjusted for all baseline characteristics listed in **Table 1**. To address biases in the allocation of treatment due to lack of randomization, a 1:1

TABLE 1 Baseline Characteristics of All Patients and by Dementia Classifications

	Overall (N = 202,121)	No Dementia (n = 179,976)	Dementia (n = 22,145)	*P* Value[a]	Alzheimer's Disease (n = 5,936)	Vascular Dementia (n = 4,008)	Unspecified Dementia (n = 12,201)	*P* Value[b]
Age, y	75.3 ± 13.0	74.7 ± 13.3	80.7 ± 8.6	<0.001	81.2 ± 8.3	78.5 ± 0.0	81.1 ± 8.5	<0.001
Male	98,361 (48.7)	90,378 (50.2)	7,983 (36.0)	<0.001	1,855 (31.2)	1,640 (40.9)	4,488 (36.8)	<0.001
Smoking	44,928 (22.2)	40,361 (22.4)	4,567 (20.6)	<0.001	1,192 (20.1)	794 (19.8)	2,581 (21.2)	<0.001
Alcohol	5,083 (2.5)	4,561 (2.5)	522 (2.4)	0.118	147 (2.5)	105 (2.6)	270 (2.2)	0.170
Comorbidities								
Hypertension	90,932 (45.0)	79,490 (44.2)	11,442 (51.7)	<0.001	2,877 (48.5)	2,300 (57.4)	6,265 (51.3)	<0.001
Diabetes	55,696 (27.6)	49,675 (27.6)	6,021 (27.2)	0.198	1,461 (24.6)	1,249 (31.2)	3,311 (27.1)	<0.001
Obesity	1,937 (1.0)	1,787 (1.0)	150 (0.7)	<0.001	27 (0.5)	35 (0.9)	88 (0.7)	<0.001
Stroke	24,247 (12.0)	20,629 (11.5)	3,618 (16.3)	<0.001	664 (11.2)	1,149 (28.7)	1,805 (14.8)	<0.001
Anemia	28,314 (14.0)	24,794 (13.8)	3,520 (15.9)	<0.001	1,038 (17.5)	643 (16.0)	1,839 (15.1)	<0.001
Coronary artery disease	68,984 (34.1)	61,350 (34.1)	7,634 (34.5)	0.257	1,929 (32.5)	1,457 (36.4)	4,248 (34.8)	<0.001
Peripheral vascular disease	26,694 (13.2)	22,469 (12.5)	4,225 (19.1)	<0.001	743 (12.5)	1,253 (31.3)	2,229 (18.3)	<0.001
Dyslipidemia	22,266 (11.0)	19,939 (11.1)	2,327 (10.5)	0.011	515 (8.7)	534 (13.3)	1,278 (10.5)	<0.001
Atrial fibrillation	50,007 (24.7)	43,817 (24.3)	6,190 (28.0)	<0.001	1,484 (25.0)	1,269 (31.7)	3,437 (28.2)	<0.001
Other arrhythmia	12,578 (6.2)	11,093 (6.2)	1,485 (6.7)	0.002	411 (6.9)	270 (6.7)	804 (6.6)	0.013
Cirrhosis	2,104 (1.0)	1,947 (1.1)	157 (0.7)	<0.001	39 (0.7)	35 (0.9)	83 (0.7)	<0.001
Chronic renal failure	21,983 (10.9)	20,037 (11.1)	1,946 (8.8)	<0.001	447 (7.5)	378 (9.4)	1,121 (9.2)	<0.001
Other chronic kidney diseases	34,837 (17.2)	31,936 (17.7)	2,901 (13.1)	<0.001	686 (11.6)	593 (14.8)	1,622 (13.3)	<0.001
Hearing loss	1,942 (1.0)	1,686 (0.9)	256 (1.2)	0.002	69 (1.2)	34 (0.8)	153 (1.3)	0.002
Head injury	13,507 (6.7)	11,519 (6.4)	1,988 (9.0)	<0.001	509 (8.6)	350 (8.7)	1,129 (9.3)	<0.001
Cancer	19,110 (9.5)	17,511 (9.7)	1,599 (7.2)	<0.001	401 (6.8)	289 (7.2)	909 (7.5)	<0.001
Parkinson's disease	2,344 (1.2)	1,869 (1.0)	475 (2.1)	<0.001	173 (2.9)	78 (1.9)	224 (1.8)	<0.001
Rheumatism	13,133 (6.5)	11,132 (6.2)	2,001 (9.0)	<0.001	527 (8.9)	355 (8.9)	1,119 (9.2)	<0.001
Depression	4,099 (2.0)	3,489 (1.9)	610 (2.8)	<0.001	184 (3.1)	119 (3.0)	307 (2.5)	<0.001
Sleep apnea	3,289 (1.6)	3,065 (1.7)	224 (1.0)	<0.001	47 (0.8)	51 (1.3)	126 (1.0)	<0.001
Drugs								
Aspirin	92,825 (45.9)	82,628 (45.9)	10,197 (46.0)	0.707	2,688 (45.3)	1,849 (46.1)	5,660 (46.4)	0.546
Angiotensin-converting enzyme inhibitor	44,001 (21.8)	38,910 (21.6)	5,091 (23.0)	<0.001	1,075 (18.1)	978 (24.4)	3,038 (24.9)	<0.001
Angiotensin receptor blocker	11,268 (5.6)	10,287 (5.7)	981 (4.4)	<0.001	222 (3.7)	201 (5.0)	558 (4.6)	<0.001
Beta-blocker	47,979 (23.7)	42,693 (23.7)	5,286 (23.9)	0.63	1,170 (19.7)	1,029 (25.7)	3,087 (25.3)	<0.001
Calcium-channel blocker	57,443 (28.4)	50,645 (28.1)	6,798 (30.7)	<0.001	1,504 (25.3)	1,340 (33.4)	3,954 (32.4)	<0.001
Diuretic agents	59,935 (29.7)	52,487 (29.2)	7,448 (33.6)	<0.001	1,778 (30.0)	1,378 (34.4)	4,292 (35.2)	<0.001
Statins	35,691 (17.7)	32,404 (18.0)	3,287 (14.8)	<0.001	650 (11.0)	687 (17.1)	1,950 (16.0)	<0.001
Other antiplatelet drugs	163 (0.1)	143 (0.1)	20 (0.1)	0.681	4 (0.1)	2 (0.0)	14 (0.1)	0.495
Insulin	1,2247 (6.1)	11,105 (6.2)	1,142 (5.2)	<0.001	224 (3.8)	215 (5.4)	703 (5.8)	<0.001
Other antidiabetes drugs	33,950 (16.8)	30,297 (16.8)	3,653 (16.5)	0.208	773 (13.0)	738 (18.4)	2,142 (17.6)	<0.001

Values are mean ± SD or (n (%). [a]Comparison for the no dementia and dementia subgroups. [b]Comparison for the 3 dementia types.

propensity score matching was used. Covariates that were considered prognostically significant, including age (age ≥75 years vs age <75 years), sex, education level (nil/less than primary vs primary and higher in the subgroup of patients with education information), as well as those that clinically influenced the incidence of dementia, were logistically regressed to the probability of being assigned.[20] To investigate the interaction of age and sex, age was regarded as a dichotomous variable based on the mean value (75 years old), and the following 4 dummy variables were created: group 1, male patients aged <75 years (reference group); group 2, female patients aged <75 years; group 3, male patients aged 75 or more years; group 4, female patients aged 75 or more years. We then used stratified Cox regression with the Fine-Gray model to investigate the association between sex and dementia incidence within each age stratum (age ≤65, 66-70, 71-75, 76-80, 81-85, >85 years).

The effect of dementia on HF outcomes, including all-cause mortality, CVD, or non-CVD, was modelled using Cox proportional hazards regression analysis, and a Fine-Gray model was used to adjust for competing risks, with the competing events being all-cause mortality, non-CVD, or CVD. Associations were considered significant if the *P* value was below 0.01. Dementia was modelled as a time-varying covariate to reduce immortal time bias.[18] The baseline variables

TABLE 2 PAF for the Risk Factors of Dementia in HF Population (N = 202,121)

	Relative Risks for Dementia (95% CI)	Prevalence, %	Communality, %	PAF, %	Weighted PAF, %
Demographic variables or nonmodifiable factors					
Elder age, ≥75 y	2.3 (2.3 to 2.4)	59.1	56	44.2 (42.9 to 45.6)	17.4 (16.6 to 17.7)
Female, %	1.7 (1.6 to 1.7)	51.3	51	25.9 (24.7 to 27.2)	10.2 (9.6 to 10.6)
Clinical variables					
Hypertension	1.3 (1.3 to 1.3)	45.0	38	12.2 (11.2 to 13.3)	4.8 (4.3 to 5.1)
Stroke	1.4 (1.4 to 1.5)	12.0	67	4.9 (4.5 to 5.4)	1.9 (1.7 to 2.1)
Anemia	1.2 (1.1 to 1.2)	14.0	43	2.2 (1.7 to 2.7)	0.9 (0.6 to 1.1)
Coronary artery disease	1.0 (1.0 to 1.0)	34.1	40	0.7 (−0.3 to 1.3)	0.3 (−0.1 to 0.5)
Peripheral vascular disease	1.6 (1.5 to 1.6)	13.2	68	6.8 (6.2 to 7.3)	2.7 (2.4 to 2.9)
Atrial fibrillation	1.2 (1.2 to 1.2)	24.7	51	4.3 (3.6 to 4.9)	1.7 (1.4 to 1.9)
Other arrhythmia	1.1 (1.0 to 1.1)	6.2	44	0.5 (0.2 to 0.9)	0.2 (0.1 to 0.3)
Hearing loss	1.2 (1.1 to 1.4)	1.0	35	0.2 (0.1 to 0.3)	0.1 (0.0 to 0.1)
Head injury	1.4 (1.3 to 1.4)	6.7	42	2.5 (2.1 to 2.9)	1.0 (0.8 to 1.1)
Parkinson	1.9 (1.7 to 2.0)	1.2	18	1.0 (0.9 to 1.2)	0.4 (0.3 to 0.4)
Depression	1.43 (1.3 to 1.6)	2.0	45	0.74 (0.5 to 1.0)	0.3 (0.2 to 0.3)
Rheumatism	1.51 (1.4 to 1.6)	6.5	21	2.71 (2.3 to 3.1)	1.0 (0.9 to 1.1)
Overall weighted PAF					42.8 (38.9 to 45.4)

HF = heart failure; PAF = population attributable fraction.

were classified into demographic variables, clinical variables, and medications to analyze the relative contribution of each factor to the risk of incident dementia using the explained risk statistic in Cox proportional hazards model. In model 2, we used the same variables as in model 1, but included data of socioeconomic status (education level) in patients with education information (n = 90,030).[21]

SUBGROUP ANALYSIS. To determine the association of education level on incidence of dementia among the cohort, a subgroup of 90,030 patients with education information on CDARS were derived and categorized into 4 groups: nil/less than primary education, primary education, secondary education, tertiary and higher education (Supplemental Table 2). Modeling methods described in the preceding text were repeated to estimate the association of risk factors, including education levels, with the incidence of dementia in this subgroup. Cox regression was used to analyze the interactions among education, age, and sex. All statistical analyses were performed using R v4.0.3 (R Foundation for Statistical Computing). Cox proportional hazards assumptions were confirmed using log-log plots and the Schoenfeld residuals test. A value of $P < 0.05$ was considered to be significant for all analyses.

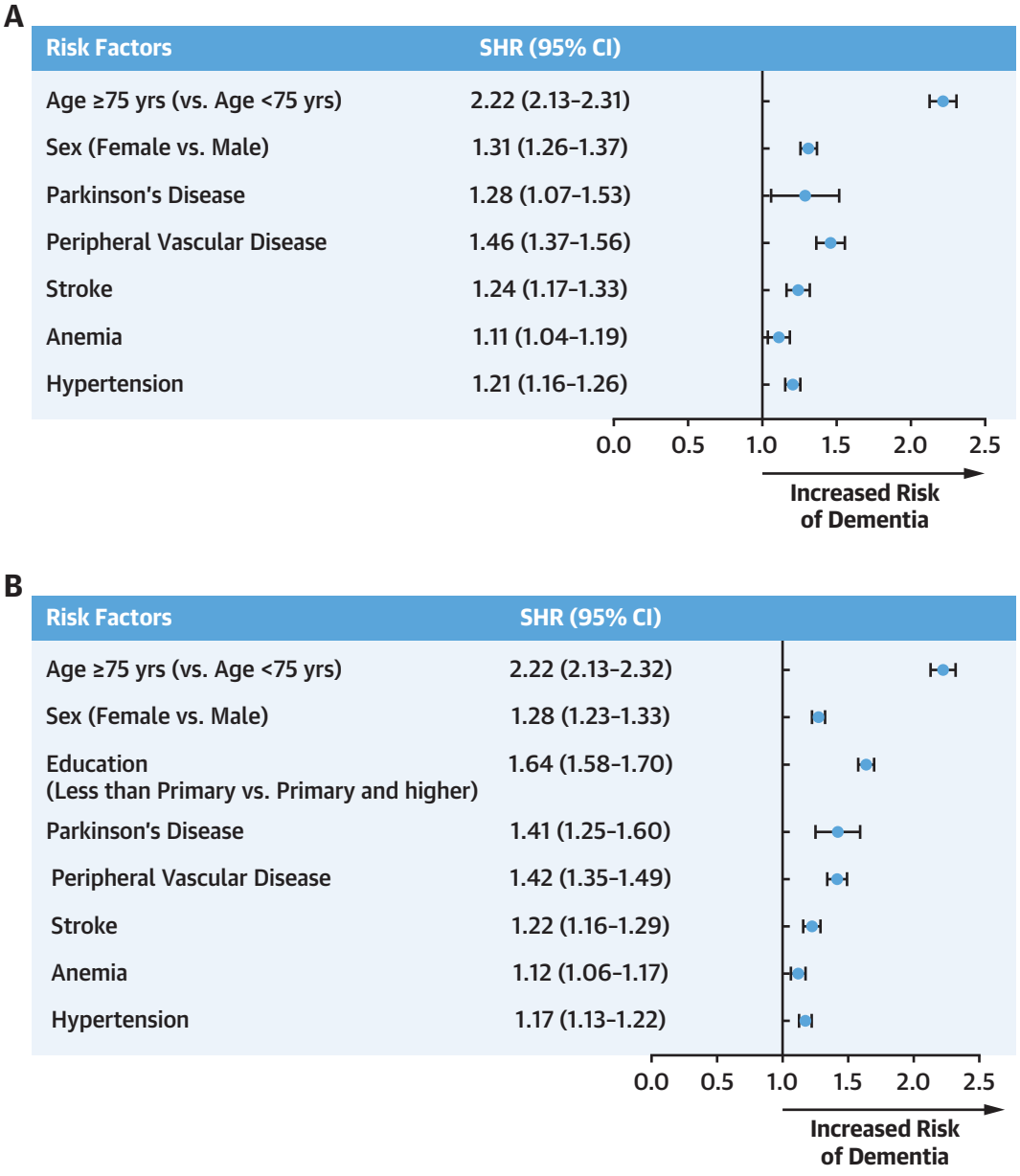
RESULTS

CHARACTERISTICS OF PATIENTS. Between 1995 and 2018, 202,121 patients (aged ≥18 years) diagnosed with HF (mean age 75.3 ± 13.0 years; 51.3% women) were identified. At baseline, about one-half of the patients had comorbid hypertension and cardiovascular diseases, and about one-quarter had atrial fibrillation, diabetes, and chronic kidney disease. The prevalence of other comorbidities and medical therapy are shown in Table 1. Over the study period (median follow-up 4.1 [IQR: 1.2-10.2] years), 22,145 (11.0%) of the cohort developed new-onset dementia, with about two-thirds (64%) in women (Table 1). Of the subtypes, AD occurred in 26.8%, VD in 18.1% and unspecified dementia in 55.1% (Table 1). Patients who developed new-onset dementia (vs no dementia) were older, more likely women, with comorbid hypertension, anemia, stroke, peripheral vascular disease, atrial fibrillation, rheumatism, depression, and Parkinson's disease, and had sustained prior head injury, but were less likely to be on statins (all $P < 0.001$) (Table 1).

Characteristics of the dementia subgroups (AD, VD, unspecified dementia) are also shown in Table 1. Compared with other dementia subgroups, patients with VD were younger, but had higher prevalence of hypertension, diabetes, stroke, coronary artery disease, peripheral vascular disease, atrial fibrillation, and chronic kidney disease (all $P < 0.001$) (Table 1). By contrast, patients with AD were elderly and predominantly women.

INDEPENDENT PREDICTORS OF DEMENTIA AND THEIR ASSOCIATED PAFs. Accounting for the competing risk of all-cause mortality and with propensity score matching, Parkinson's disease, head

CENTRAL ILLUSTRATION **Risk Factors for Dementia Incidence**



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Risk factors for dementia incidence **(A)** in the entire cohort and **(B)** subgroup with education status. In these multivariable models, candidate variables included demographics, history of diseases, and medical history listed in Table 1. We calculated the subdistribution hazard ratio (SHR) and 95% CI using the Fine-Gray test for equality of the cumulative functions between each group after 1:1 propensity score matching and accounting for all-cause mortality as a competing risk.

injury, depression, peripheral vascular disease, stroke, anemia, hypertension, alcohol intake, hearing loss, advancing age, female sex, diabetes, and atrial fibrillation were independently associated with increased hazards of developing dementia (Table 2, Central Illustration).

Table 2 shows the PAF and weighted PAF (adjusted for communality) of risk factors to dementia incidence. Elderly age (≥75 years) and female sex, which are both nonmodifiable factors, had the highest weighted PAF of 17.4% and 10.2%, respectively. The weighted PAFs of hypertension,

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TABLE 3 Difference in Dementia Incidence Stratified by Age and Sex

	Overall		Women		Men	
Age, y	No. at Risk	Dementia Incidence	No. at Risk	Dementia Incidence	No. at Risk	Dementia Incidence
≤65	37,885	996 (2.6)	12,988	379 (2.9)	24,897	617 (2.5)
66-70	18,261	1,390 (7.6)	7,429	678 (9.1)	10,832	712 (6.6)
71-75	26,444	2,656 (10.0)	12,135	1,448 (11.9)	14,309	1,208 (8.4)
76-80	35,477	4,557 (12.8)	18,405	2,747 (14.9)	17,072	1,810 (10.6)
81-85	37,642	5,451 (14.5)	21,653	3,637 (16.8)	15,989	1,814 (11.3)
>85	46,412	7,095 (15.3)	31,150	5,273 (16.9)	15,262	1,822 (11.9)
Age-standardized incidence rate, %		10.15		12.97		7.44

Values are n or n (%).

peripheral vascular disease, stroke, and atrial fibrillation were also higher relative to other risk factors.

INTERACTION BETWEEN AGE AND SEX ON THE INCIDENCE OF DEMENTIA IN HF. Table 3 shows the crude proportions of dementia across age groups for the whole cohort and by sex. Age-standardized incidence rate of dementia was 1,297 (95% CI: 1,276-1,318) per 10,000 in women and 744 (95% CI: 723-765) per 10,000 in men. Crude rate of dementia was lowest among the youngest age group (≤65 years, 2.6%) but highest among the oldest age group (>85 years, 15.3%). However, greatest increment (of +5% change) was observed among those in the 66-70 years age group, with gradual increment, but declining rate, in older age groups. Age group ≥75 (vs <75) years was associated with a subdistribution hazard ratio (SHR): 2.22 (95% CI: 2.13-2.31) of new-onset dementia; female (vs male) sex had a SHR: 1.31 (95% CI: 1.26-1.37), comparable to other independent predictors of dementia (eg, stroke, peripheral vascular disease, anemia, hypertension) (Central Illustration). Notably, a significant interaction of age and sex on dementia incidence was found ($P_{interaction} < 0.001$) (Table 4), such that risk of new-onset dementia increased more steeply with age in women than men with HF (Table 4, Figures 2 and 3). In the multivariable regression model, adjusting for demographics, history of diseases, and medical history (listed in Table 1), as well as all-cause mortality as a competing risk, women in both age groups (<75 years, ≥75 years) had a 40% to 125% higher risk of incident dementia compared with men ($P < 0.001$) (Table 4).

TABLE 4 Interaction Between Age and Sex on Dementia Incidence

	Multivariable Adjusted SHR (95% CI)[a]	*P* Value	$P_{interaction}$
			<0.001
Men, <75 y	Ref.	Ref.	
Women, <75 y	1.4 (1.3-1.5)	<0.001	
Men, ≥75 y	3.8 (3.7-4.0)	<0.001	
Women, ≥75 y	5.1 (4.9-5.3)	<0.001	

[a]In these multivariable models, candidate variables in the model included demographics, history of diseases, and medical history (Table 1). A Fine-Gray model was used to adjust for all-cause mortality as a competing risk.

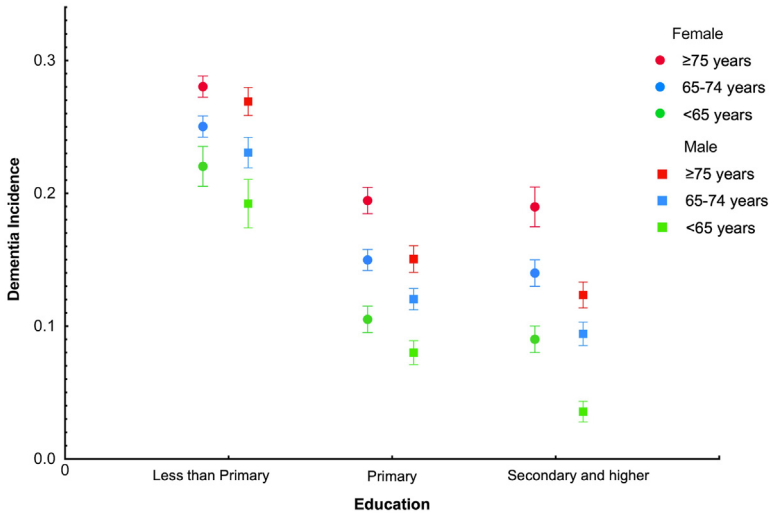
SHR = subdistribution hazard ratio.

SUBGROUP ANALYSIS WITH EDUCATION STATUS. Among the subcohort with education status data (n = 90,030), about one-quarter had nil/less than primary education, and 38.5% had only primary education. Those with nil/less than primary education were older, more likely women, and more likely to have hypertension, atrial fibrillation, anemia, and peripheral vascular disease, but were less likely to receive HF medications and statins (all $P < 0.001$). Patients with new-onset dementia were predominantly those with primary (or lower) education, constituting 68.6% compared with 25.8% with secondary education and 5.6% with tertiary education (Supplemental Table 3).

Nil/less than primary (vs higher) education was associated with a higher hazard (SHR: 1.64; 95% CI: 1.58-1.70; $P < 0.001$) (Central Illustration) of new-onset dementia. Supplemental Table 4 shows the PAFs of dementia risk factors among HF patients with education recordings. Adding education status into the model increased the total weighted PAF to 53.2% (vs 42.8% for the whole cohort).

Figure 2 shows the dementia incidence by sex and age groups stratified by education status among a subcohort of patients with education status. Interestingly, lowest education status (nil or less than primary education) was associated with the highest incidence of dementia in both men and women, compared with primary and secondary or higher education ($P < 0.001$). Across all education strata,

FIGURE 2 **Interaction of Education, Sex, and Age (Subgroup With Education)**



The **circles** (for women) and **squares** (for men) represent the estimated incidence rate of dementia with the error bars serving as the 95% CIs.

women consistently had a higher incidence of dementia compared with men ($P < 0.001$), with greater difference between sexes among those with secondary or higher education.

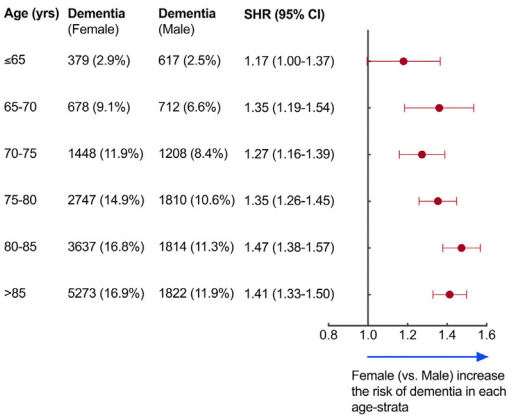
EXPLAINED-RISK STATISTIC: THE RELATIVE CONTRIBUTIONS OF COVARIATES TO THE RISK OF INCIDENT DEMENTIA TO DEMENTIA INCIDENCE. Table 5 shows the explained-risk statistic that determined the relative contributions of demographics, clinical variables, and medications to the risk of incident dementia in the overall cohort. These categories of variables explained 42.3% of the risk of incident dementia, of which demographics contributed to 36.1% and clinical variables 3.1% of the risk. Including education status (in a subcohort) increased the relative contribution of the variables to 48.2% of the risk.

OUTCOMES: ALL-CAUSE MORTALITY, CVD, AND NON-CVD. Over the study period, there were 153,348 (75.8%) crude all-cause deaths, with median follow-up of 4.1 [IQR: 1.2-10.2] years. Proportions of crude deaths was 88.6 % vs 74.3% among patients with dementia compared with the no dementia group ($P < 0.001$). Using 1:1 propensity score matching between groups, dementia (vs no dementia), when modelled as a time-varying covariate, was observed to be associated with a high risk (SHR: 4.5; 95% CI: 4.4-4.6; $P < 0.001$) of all-cause mortality in this cohort of patients with HF. Separately, dementia was also associated with SHR: 5.4 (95% CI: 5.3-5.6) for CVD and SHR: 3.8 (95% CI: 3.7-3.9) for non-CVD, accounting for competing risk (Table 6).

DISCUSSION

Among this large territory-based cohort of patients with index HF followed longitudinally, incident

FIGURE 3 **Sex Differences on Dementia Incidence by Age Stratification**



In these multivariate models, candidate variables for inclusion in the model included demographics, history of diseases, and medical history (Table 1). We calculated the subdistribution hazard ratio (SHR) and 95% CI using the Fine-Gray test for equality of the cumulative functions between each group after 1:1 propensity score matching and accounting for all-cause mortality as a competing risk. Within each age stratum, male was the reference group.

TABLE 5 Explained Risk Statistics for Independent Variables of Dementia Incidence in the Overall Cohort (N = 202,121)

	Explained Risk Statistic, %	SE, %
Demographic variables	39.2	0.4
Demographic + clinical variables	41.8	0.4
Only demographic variables	36.3	0.5
Only clinical variables	3.5	0.2
Demographic + clinical variables+ medications	42.3	0.4
Only demographic variables	36.1	0.5
Only clinical variables	3.1	0.2
Only medications	0.8	0.1

dementia occurred in >22,000 (11.0%) over the study period. Apart from nonmodifiable factors such as advancing age and female sex, nil or primary education status in early life, hypertension, stroke, peripheral vascular disease, and atrial fibrillation were associated with high PAFs, which are targets for surveillance of incident dementia. The findings also highlighted the vulnerability of women across all age groups and both sexes with low educational attainment (as proxy for socioeconomic status) for the development of all-cause dementia. Contrary to selected reports,[22] dementia portends poorer outcomes (with a 4.5-fold increase in all-cause mortality compared with the no dementia group), particularly CVD among patients with HF compared with those without dementia. Furthermore, we observed the rate of increment for incidence of dementia by age group seemed to peak in the age group of 65 to <70 years, before increasing at a declining rate across age strata. This lends insight into modifiable strategies and awareness programs for dementia to be targeted at patients younger than 65 years, and not limited to the elderly. Timely recognition of dementia or even mild cognitive impairment can enhance optimal patient care[23] and could attenuate the natural progression of dementia in HF, which is associated with high mortality rates.

Detailed mechanisms of the heart-brain connection are beyond the purview of this study. However, earlier studies suggest that reduced cardiac output and poor cerebral blood flow had been linked to cognitive impairment in HF.[5] Consequent inflammation, brain microvascular dysfunction, and brain tissue injury caused by neurohormonal activation common in HF might have contributed to cerebral hypoxia and pathogenesis of dementia.[24] Additionally, the Framingham Heart Study reported the association of reduced cardiac indices and left ventricular ejection fraction with cognitive impairment.[25] This study was undertaken to better understand the heart-brain connection in an Asian population because HF afflicts Asian patients at least a decade earlier than their Western counterparts.[13] HF and dementia commonly share several pathological processes and risk factors. Prevalence of both increase with advancing age. Independent predictors of dementia identified were consistent with those reported by the 2020 Lancet Commission.[26] Of the risk factors in our study cohort, hypertension was prevalent in one-half of the patients with all-cause dementia, but higher (57%) among patients with VD. Notably, hypertension accounted for a larger PAF compared with other comorbidities (listed in Table 1) for incident dementia. Regardless, multimorbidity is common among patients with HF, which contribute to the development of dementia. Apart from advancing age and sex, all other clinical correlates and socioeconomic status are modifiable factors, thus serving as targets for risk factor elimination. Nevertheless, all known variables (including education status) only explained about one-half of the explained-risk of new-onset dementia and the weighted PAF of known risk factors, consistent with another study,[17] which suggests that

TABLE 6 The Impact of Dementia on All-Cause Mortality, Cardiovascular Death, and Noncardiovascular Death

Endpoint	No. of Total Cases	Patients Without Dementia (n = 179,976)	Patients With Dementia (n = 22,145)	SHR (95% CI)	*P* Value
All-cause mortality	153,348	133,736 (74.3)	19,612 (88.6)	4.5 (4.4-4.6)[a]	<0.001
Cardiovascular death	86,197	73,900 (41.1)	12,297 (55.5)	5.4 (5.3-5.6)b	<0.001
Noncardiovascular death	67,151	59,836 (33.3)	7,315 (33.0)	3.8 (3.7-3.9)[b]	<0.001

Values are n or n (%) unless otherwise indicated. [a]We calculated the *P* value of the cumulative functions between each group after 1:1 propensity score matching. Dementia was modelled as a time-varying covariate. [b]We calculated the *P* value using the Fine-Gray test for equality of the cumulative functions between each group after 1:1 propensity score matching and accounted for noncardiovascular mortality or cardiovascular mortality as competing risks for cardiovascular and noncardiovascular deaths, respectively. Dementia was modelled as a time-varying covariate to avoid immortal time bias.

SHR = subdistribution hazard ratio.

several unknown factors, such as genetic, cultural, nutritional, and environmental factors likely come into play. In particular, there is broad recognition that a life-course approach is needed to fully understand the role of socioeconomic status and risk factors, because many diseases in later life have social and physiological antecedents much earlier in life.[27,28]

Of the limited studies that examined HF and dementia, a Swedish study[22] that used 2 datasets (Swedish Heart Failure Registry, N = 55,313, but only 775 identified in the dementia registry had HF and dementia) found no association of dementia with mortality. Mean follow-up was only 1.5 years, much shorter than our study. Several studies had reported 5-fold mortality risk among patients with HF when cognitive impairment is present.[29] Separately, a Danish population-wide cohort study[6] of patients with first HF hospitalization matched by age, sex, and calendar year to a comparison group from the general population, followed for dementia, found that HF was associated with increased risk of dementia compared with the general population. Interestingly, the associations were stronger in men and in patients with HF younger than 70 years. In our study, we did not examine the comparison group (without HF) because our study aims were different. However, we found across all age strata, women were at greater risk than men for incident dementia among a HF cohort. Our study extends previous findings, in addressing the paucity of heart-brain data in Asia, with the use of a large population cohort of patients with HF for incident dementia. As a relatively novel dimension, the weighted PAFs of risk factors contributing to new-onset dementia can inform specific targets for surveillance. Furthermore, this unique study highlights the great disparities of dementia between sexes, across educational categories, and the "intertwining" of these variables.

The pathophysiological rationale behind a higher incidence of dementia among women may be related to genetic and neurologic differences between the sexes. Prior studies have reported that women have higher spinal fluid tau levels[30] with sex-dependent autosomal effects for AD.[31] Women also experienced a faster decline in the progression of hippocampal atrophy despite a later onset of verbal memory deficits compared with men.[32] Beyond these sex-specific biological factors, however, sex-specific roles, and socioeconomic, and cultural factors might increase women's vulnerability compared with men.[33,34] Specifically, in the context of Asia, gender disparity in education and nutrition was particularly widespread in the earlier lives of the elderly populations in the region. In general, lower education levels, lower employment status, financial stress, greater burden associated with caregiving, and poorer physical health and nutrition could render women more susceptible than men to dementia or cognitive decline.[33] Combinations and patterns of risk factors over the life course could explain the sex differences in risk of dementia.[34]

More recently, evolving literature suggested a potential beneficial effect of sodium-glucose-cotransporter 2 inhibitors (SGLT2i) on cognitive impairment, especially in the context of diabetes[2,35] (with cognitive decline being a well-recognized complication of diabetes). Apart from its hypoglycemic effects, SGLT2i has been reported to manifest multiple pleiotropic and antiatherosclerotic effects, leading to attenuation of oxidative stress and inflammatory reaction, which may potentially preserve cognitive function.[36,37]

The strengths of our study lie in the use of a well-validated, electronic, population-based health care database with records of all diagnoses, hospitalizations, and medication dispenses linked to biochemical/laboratory findings, enabling longitudinal trajectories to be examined. Robust methodology was undertaken in general, with critical variables modelled as time-varying covariates for its association with all-cause mortality.

STUDY LIMITATIONS. We lacked diagnostic brain imaging data, hence the diagnosis of dementia was not adjudicated, and accuracy of dementia diagnoses cannot be confirmed. Although the analyses in this study were multivariable adjustments, some confounders might be unaddressed, such as nutritional status and body mass index due to missing recordings in CDARS. Possibility of underdiagnosis of dementia is another limitation. More than one-half of the dementia patients identified had unspecified dementia, suggesting potential misclassification of specific dementia subtypes into this less specific category. Additionally, we lack echocardiographic data to differentiate between HF phenotypes, and we could not adjust for severity of HF in absence of the New York Heart Association class. Cognitive impairment was not examined as an outcome, hence, the burden and impact of HF on the brain may be underestimated.

CONCLUSIONS

New-onset dementia affected more than 1 in 10 patients with index HF, and portended a worse prognosis in these patients. Older women were at highest risk and should be targeted for screening and preventive strategies. Further, nil/low education status as proxy for lower socioeconomic status, increasing age, and common comorbidities were associated with higher hazards of incident dementia. Apart from advancing age and sex (as nonmodifiable factors), a significant proportion of the PAF of dementia is modifiable. The findings can inform preventive measures and target high-risk populations for intensive cognitive surveillance, particularly in the context of Asia where there is a paucity of data.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: New-onset dementia was common in HF patients and portended poorer outcomes. Modifiable risk factors, such as low education status, hypertension, stroke, peripheral vascular disease, and atrial fibrillation, should be targets for surveillance of incident dementia in HF. Women were more likely to experience dementia than men across all age groups. Our findings may assist clinicians in identifying early cognitive impairment in HF patients with associated risk factors.

TRANSLATIONAL OUTLOOK: Further studies focusing on surveillance and risk prevention for dementia incidence in HF patients are warranted.

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APPENDIX For supplemental tables, please see the online version of this paper.