FEATURED ARTICLE

The risk of dementia after coronary artery bypass grafting in relation to age and sex

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Abstract

Introduction: We examined the long-term risk of dementia after coronary artery bypass grafting (CABG) in relation to age and sex.

Methods: All CABG patients in Sweden 1992–2015 (n = 111,335), and matched controls (n = 222,396) were included in a population-based study. Adjusted hazard ratios (aHR) for all-cause dementia, vascular dementia, and Alzheimer's disease were calculated.

Results: There was no difference in the risk for all-cause dementia between CABG patients and control subjects (aHR 0.98 [95% confidence interval 0.95 to 1.02]). CABG patients <65 years and 65 to 74 years had higher risk (aHR 1.29 [1.17–1.42] and 1.08 [1.02–1.13], respectively), and patients ≥75 years had lower risk (aHR 0.76 [0.71–0.81]). The highest risk was observed in women <65 years (aHR 1.64 [1.31–2.05]).

Discussion: Overall, the long-term risk for all-cause dementia does not differ between CABG patients and the general population. Younger patients have a higher risk, while older patients have a lower risk, compared to controls.

KEYWORDS
Alzheimer's disease, coronary artery bypass grafting, dementia, vascular dementia

1 | BACKGROUND

Coronary artery bypass grafting (CABG) is the preferred method for myocardial revascularization in patients with complex multi-vessel or left main coronary artery disease.[1] CABG is still the most commonly performed cardiac surgical procedure, with ≈400,000 procedures performed in the United States annually.[1]

1. Systematic review: Previous studies investigating the association between coronary artery bypass grafting (CABG) and dementia have shown conflicting results and are limited by restricted study populations and follow-up times. In addition, no study has been large enough to investigate if potential associations diverge between subgroups of CABG patients. We examined the long-term risk of dementia after CABG in relation to age and sex in a large population-based cohort.

2. Interpretation: We found that CABG patients <75 years have a higher long-term risk of dementia compared to an age- and sex-matched control population, while older patients have a lower risk. The increased risk becomes significant 10 years after CABG. The highest risk was observed in younger women. Cardiovascular risk factors, history of depression, and low socioeconomic status were independent predictors for developing dementia after CABG.

3. Future directions: Increased awareness of the higher risk for dementia in younger CABG patients and in CABG patients with a history of depression, and low socioeconomic status, is required.

Postoperative cognitive dysfunction has been a serious concern since the advent of open cardiac surgery, especially in elderly patients. A high incidence of delirium and cognitive dysfunction during the first weeks after CABG has consistently been reported.[2-4] The early postoperative decline in cognitive function is usually transient, but can sometimes persist for months.[2] The exact mechanism of the early cognitive impairment has not been settled, but cerebral hypoperfusion during cardiopulmonary bypass and microembolization have been suggested to contribute.[5]

While the early cognitive dysfunction after CABG and other cardiac surgery procedures is well recognized and described in the literature, the long-term association between cardiac surgery and chronic cognitive dysfunction (ie, dementia) is less apparent. Previous studies have shown conflicting results, and are often limited by restricted study populations and follow-up times.[2-4,6-10] No previous study has investigated if there are subgroups of CABG patients with an increased risk for incident dementia. One group of special interest is elderly patients, who have an increased risk for early cognitive decline and delirium.[2-4] If this early dysfunction in elderly CABG patients also translates into a high long-term risk of developing dementia, there are direct implications for the choice of treatment. The primary aim of this large population-based cohort study was therefore to assess the long-term risk of developing dementia, in relation to age and sex, in CABG patients and matched control subjects from the general population. We also sought to identify independent predictors for developing dementia among CABG patients.

2 | METHODS

This article was composed according to recommendations in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[11] The study was performed in accordance with the Declaration of Helsinki, and was approved by the Regional Research Ethics Committee in Gothenburg (registration number: 139-16). The ethical committee waived the need for individual informed consent because all cardiac surgery patients in Sweden receive information that patient data are registered in official quality registries and databases and can be used for research after approval from the research ethics committee.

2.1 | Study population

The CABG population was identified in the Swedish Cardiac Surgery Registry,[12] which forms part of the SWEDEHEART registry.[13] Inclusion criteria were having undergone a first isolated CABG procedure, being >18 years old, having no previous diagnosis of dementia, and having ≥1 day of follow-up. For each CABG patient, two controls were

assigned from the Swedish Total Population Register held by Statistics Sweden. Controls were matched by the day of CABG surgery (index date), sex, age, and home county, and did not have a diagnosis of dementia or had undergone a cardiac surgery procedure.

All CABG patients who had surgery between January 1, 1992 and December 31, 2015 were included, and the follow-up ended on December 31, 2015. The follow-up was complete except for patients who emigrated during the follow-up period (n = 5899, 1.8%). These patients were censored at the time of emigration. A flowchart showing included and excluded patients is given in Figure 1.

2.2 | Data sources

Perioperative details were collected from the SWEDEHEART registry. Dementia diagnoses during the follow-up period were collected from the Swedish National Patient Registry (NPR), which has complete national coverage since 1987.[14] Registration of diagnoses in NPR is mandatory for all hospital admissions in Sweden, using the International Classification of Diseases (ICD) system; version 9 from 1987 to 1996 and version 10 from 1997 onward. Principal and contributing diagnoses of all-cause dementia, vascular dementia, and Alzheimer's disease (AD) were collected from NPR using ICD-9 code 290 and ICD-10 codes F00, F01, F02, F03, G30, and G31. Analyses including vascular dementia and AD were only performed from 1997 onward, due to more specific diagnosis codes being available in ICD-10. Diagnoses for comorbidities in CABG patients and control subjects were collected in NPR before the date of admission for CABG surgery (Table S1 in supporting information). The Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA) was used to obtain data on socioeconomic factors.[15] Length of education was stratified into <10 years, 10 to 12 years, and >12 years. Annual disposable household income at year of surgery was stratified into quintiles from Q1 (lowest) to Q5 (highest), with the consumer price index used to make adjustments over time. Index marital status was divided into married/cohabitating, unmarried/not cohabitating, divorced, and widowed.

2.3 | Statistical analysis

Due to a high correlation between the incidence of dementia and patients' age, and observed interactions between age categories and CABG regarding incident dementia, the study population was divided into three age groups: <65, 65 to 74, and ≥75 years. Baseline characteristics are presented as number and percentage or mean and standard deviation (SD). Incidence rates for all-cause dementia, vascular dementia, and AD were estimated as the number of individuals diagnosed with the event divided by the total follow-up time in the study, and reported as number of cases per 1000 person-years. Cumulative incidence adjusted for death as competing risk was estimated and compared between treatment groups using Gray's test for each endpoint separately. A P-value of < .05 was considered statistically
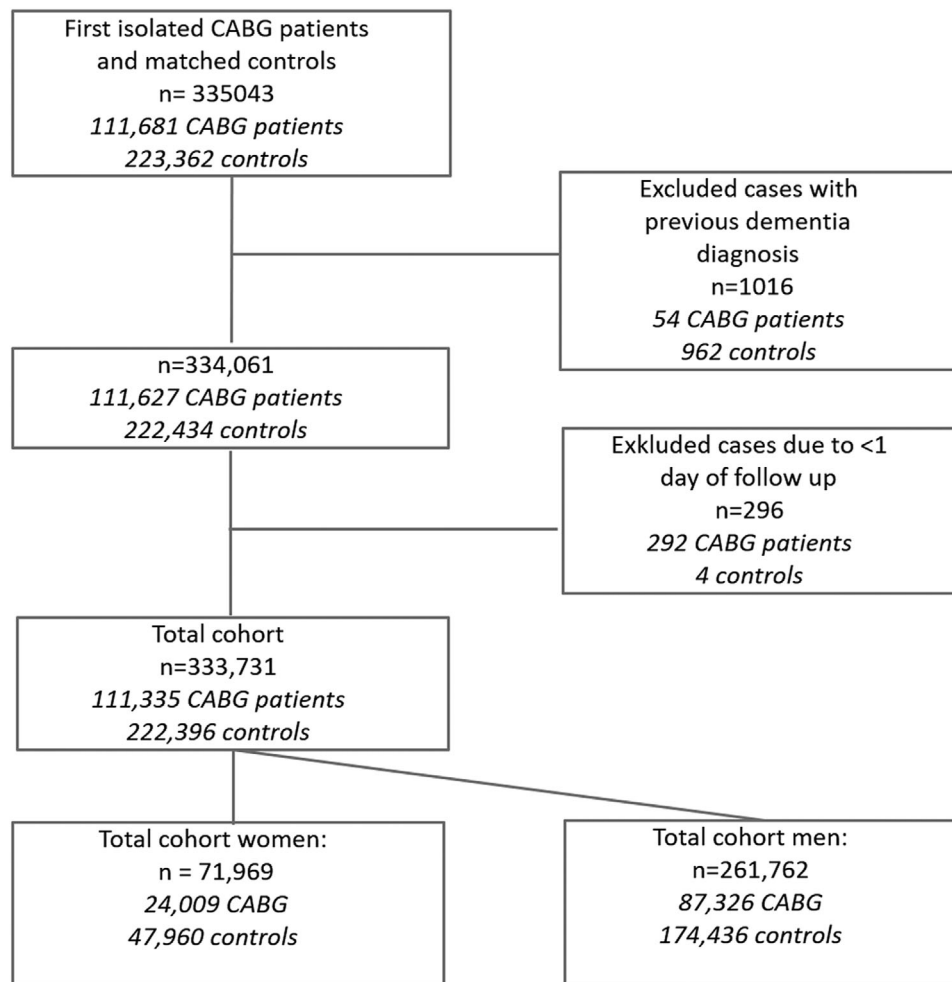
FIGURE 1 Flowchart for coronary artery bypass grafting (CABG) patients and age- and sex-matched control subjects from the general population

significant. Cox proportional hazards regression with 95% confidence intervals (CI) was used to investigate the risk of all-cause dementia, vascular dementia, and AD in CABG patients using matched individuals from the general population as reference group. All final models were adjusted for age, sex, year of surgery, comorbidities at baseline (myocardial infarction, hypertension, diabetes, heart failure, atrial fibrillation, stroke, peripheral vascular disease, renal failure, chronic respiratory disease, malignancy, depression, and hyperlipidaemia), and socioeconomic factors (education, marital status, and income). The selection was based on previously identified predictors in the literature.

The Cox models were not adjusted for competing risks.[16] A visual assessment based on Schoenfeld residuals and log(–log[survival]) versus log(time) curves was performed to check for proportionality. Proportionality could not be concluded in all analyses, so in addition to the calculation of overall hazard ratios with 95% CI (interpreted as mean hazard ratio for the study period), time-specific Cox regression was used to investigate the effects for follow-up periods 0 to 5, 5 to 10, 10 to 15, and 15 to 20 years. All calculations were performed using version 9.4 of SAS (SAS Institute Inc., Cary, North Carolina, USA).

3 | RESULTS

3.1 | General

A total of 111,335 CABG patients (87,326 men, 24,009 women) and 222,396 matched control subjects were included in the study (Table 1). Among the CABG patients, 43,750 were <65 years, 44,903 were 65 to 74 years, and 22,682 were ≥75 years. Total median follow-up time was 10.6 years (range: 0–24). Comorbidities were more common in CABG patients than in control individuals, regardless of sex or age (Table 1, Table S2 and S3 in supporting information). In the CABG population, 6733 (6.0%) patients were diagnosed with all-cause dementia, 1172 (1.4%) with vascular dementia, and 1159 (1.4%) with AD during the follow-up period. The corresponding figures for the control population were 12,951 (5.8%), 1768 (1.1%), and 2457 (1.5%), respectively. In total 51,027 (45.8%) CABG patients and 85,155 (38.3%) controls died during follow-up. In patients <65 years the mortality rates per 1000 person-years was 24.0 (95% CI 23.6–24.4) in CABG patients and 13.4 (13.2–13.6) in control subjects. The corresponding figures were 52.4 (51.7–53.1) versus 43.3 (42.9–43.7) for patients aged 65

TABLE 1 Baseline characteristics among coronary artery bypass grafting (CABG) patients and age- and sex-matched controls. Number (percentage) or mean ± standard deviation

	CABG patients	Control subjects
No of patients	111,335	222,396
Age in years	66.3 ± 9.2	66.3 ± 9.2
Men	87,326 (78.4)	174,436 (78.4)
Women	24,009 (21.6)	47,960 (21.6)
Comorbidities		
Myocardial infarction	53,100 (47.7)	9,356 (4.2)
Hypertension	37,992 (34.1)	21,575 (9.7)
Diabetes	22,289 (20.0)	11,245 (5.1)
Heart failure	13,500 (12.1)	6725 (3.0)
Atrial fibrillation	7606 (6.8)	10,335 (4.6)
Previous stroke	5783 (5.2)	9238 (4.2)
Peripheral vascular disease	6842 (6.1)	4553 (2.0)
Renal failure	1918 (1.7)	1640 (0.7)
Chronic respiratory disease	5220 (4.7)	6456 (2.9)
History of malignancy	7642 (6.9)	17,397 (7.8)
Depression	2118 (1.9)	3728 (1.7)
Hyperlipidaemia	21479 (19.3)	5079 (2.3)

to 74 years and 84.7 (83.3–86.1) versus 85.5 (84.5–86.5) for patients aged ≥75 years. Actual mortality in additional subgroups is presented in Table S4 in supporting information.

3.2 | Incidence rates of dementia

The crude cumulative incidence rates of all-cause dementia, vascular dementia, and AD are presented in Table 2. The cumulative incidence of all-cause dementia after adjusting for competing risk of death is given in Figure 2, and the corresponding figures for AD and vascular dementia are given in Figures S1 and S2 in supporting information.

Overall, the incidence rates for all-cause dementia, vascular dementia, and AD increased with age, both in CABG patients and in controls. After adjusting for competing risk of death, the overall cumulative incidence of all-cause dementia at 20 years was 9.6% (95% CI: 9.40%–9.88%) in CABG patients and 9.0% (8.84%–9.17%) in controls (Figure 2A). CABG patients < 65 years and 65 to 74 years showed a higher cumulative incidence of all-cause dementia at 20 years compared to controls, while in the oldest age group (≥75 years), the cumulative incidence for all-cause dementia was lower in CABG patients than in controls (Figure 2B-C). For vascular dementia, the overall cumulative incidence at 15 years was significantly higher among CABG patients compared to controls (2.1% [95% CI: 1.96%–2.22%] vs 1.5% [1.46%–1.62%]) after adjusting for competing risk of death (Figure S1). For AD, there were no overall significant differences in incidence between

CABG patients and controls after 15 years (2.1% [95% CI: 1.98%–2.24%] vs 2.2% [2.05%–2.24%]) after adjusting for competing risk of death (Figure S2).

3.3 | Adjusted risk for dementia

3.3.1 | All-cause dementia

There was no overall difference in the risk for all-cause dementia between CABG patients and control subjects (adjusted hazard ratio [aHR] 0.98 [95% CI 0.95–1.02], Table 2. CABG was associated with an increased long-term risk compared to control subjects for all-cause dementia in patients <65 years (aHR: 1.29, 95% CI: 1.17–1.42, P = < .001) and 65 to 74 years (aHR: 1.08, 95% CI: 1.02–1.13, P = .0045), while in the oldest patient group (≥75 years) CABG was associated with a lower risk for all-cause dementia (aHR: 0.76, 95% CI: 0.71–0.81, P < .001). The highest risk was observed in women < 65 years (aHR: 1.64, 95% CI: 1.31–2.05 P = < .001; Figure 3A, Table S5 in supporting information).

Because the association between CABG and incident dementia changed over time, we also analyzed the adjusted risks for all-cause dementia separately over a 5-year periods (Figure 4, Table S7 in supporting information). Patients <65 and 65 to 74 years showed a reduced risk 0 to 5 years after CABG but a significantly increased risk 10 years after surgery. Patients ≥75 years had a reduced risk 0 to 10 years after surgery.

3.3.2 | Vascular dementia

CABG was associated with increased long-term risk for vascular dementia in patients < 65 years (aHR: 1.39, 95% CI: 1.04–1.86, P = .029), but not overall in patients 65 to 74 years (aHR: 1.11, 95% CI: 0.97–1.27, P = .12; Figure 3B, Table S6 in supporting information). Women aged 65 to 74 years showed greater risk for vascular dementia after CABG compared to controls (aHR: 1.45, 95% CI: 1.07–1.95, P = .016). In patients ≥75 years, CABG was associated with reduced risk of vascular dementia (aHR: 0.85, 95% CI: 0.74–0.98, P = .029). The risks divided in 5-year periods are presented in Table S8 in supporting information.

3.3.3 | Alzheimer's disease

There were no overall associations between CABG and AD in patients < 65 years and 65 to 74 years (P = .53 and 0.96, respectively), but in women < 65 years, CABG was associated with an increased risk (aHR: 1.81, 95% CI: 1.05–3.13, P = .033; Figure 3C, Table S6). In patients ≥75 years, CABG was associated with a lower risk for AD (aHR: 0.81, 95% CI: 0.72–0.92, P ≤ 0.001). The risks divided into 5-year periods are presented in Table S9 in supporting information.

TABLE 2 Dementia diagnosis; incidence rates with 95% confidence intervals; and age-, sex-, and multi-adjusted hazard ratios with 95% confidence intervals by age groups for all-cause dementia, vascular dementia, and Alzheimer's disease

	Diagnosis of dementia n (%)		Incidence rate per 1000 patient years		Hazard ratio CABG vs control subjects	
	CABG	Controls	CABG	Controls	Age- and sex-adjusted	Multi-adjusted*
All-cause dementia[†]						
All ages	6733 (6.0)	12951 (5.8)	5.88 (5.74–6.02)	5.37 (5.28–5.46)	1.12 (1.09–1.15)	0.98 (0.95–1.02)
<65 years	1102 (2.5)	1653 (1.9)	2.06 (1.94–2.18)	1.43 (1.36–1.50)	1.60 (1.49–1.73)	1.29 (1.17–1.42)
65–74 years	3565 (7.9)	6632 (7.4)	8.10 (7.84–8.37)	7.14 (6.97–7.31)	1.22 (1.18–1.28)	1.08 (1.02–1.13)
≥75 years	2066 (9.1)	4666 (10.4)	12.2 (11.7–12.7)	14.2 (13.8–14.6)	0.85 (0.80–0.89)	0.76 (0.71–0.81
Vascular dementia[‡]						
All ages	1172 (1.4)	1768 (1.1%)	1.60 (1.51–1.69)	1.18 (1.12–1.23)	1.33 (1.23–1.43)	1.02 (0.93–1.12)
<65 years	148 (0.5)	140 (0.2)	0.46 (0.39–0.55)	0.21 (0.18–0.25)	2.31 (1.83–2.91)	1.39 (1.04–1.86)
65–74 years	581 (1.8)	844 (1.3)	2.09 (1.92–2.26)	1.47 (1.37–1.57)	1.44 (1.30–1.60)	1.11 (0.97–1.27)
≥75 years	443 (2.4)	784 (2.1)	3.28 (2.98–3.60)	3.01 (2.81–3.23)	1.07 (0.95–1.20)	0.85 (0.74–0.98)
Alzheimer's disease[‡]						
All patients	1159 (1.4)	2457 (1.5)	1.58 (1.49–1.68)	1.64 (1.57–1.70)	0.95 (0.89–1.02)	0.89 (0.82–0.97)
<65 years	150 (0.5)	248 (0.4)	0.47 (0.40–0.55)	0.37 (0.33–0.42)	1.33 (1.09–1.63)	1.09 (0.84–1.41)
65–74 years	606 (1.9)	1246 (2.0)	2.18 (2.01–2.36)	2.18 (2.06–2.30)	1.03 (0.93–1.13)	1.00 (0.89–1.13)
≥75 years	403 (2.2)	963 (2.6)	2.98 (2.70–3.29)	3.71 (3.48–3.95)	0.79 (0.70–0.89)	0.72 (0.63–0.83)

*Multivariable model adjusted for age, sex, year of surgery, marital status, education, income, and comorbidities at baseline (previous myocardial infarction, hypertension, diabetes, heart failure, atrial fibrillation, stroke, peripheral vascular disease, renal failure, chronic respiratory disease, malignancy, depression, hyperlipidemia). [†] Maximum 24 years follow-up. [‡] Maximum 18 years follow-up.
Abbreviation: CABG, coronary artery bypass grafting.
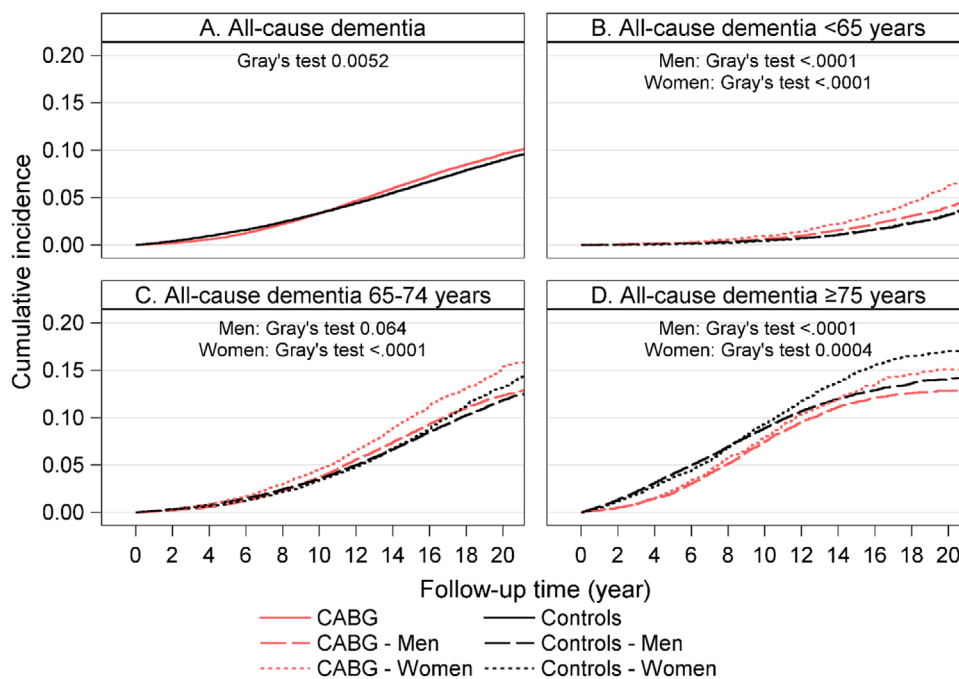
FIGURE 2 Cumulative incidence, adjusted for competing risk of death, of all-cause dementia among coronary artery bypass grafting (CABG) patients and age- and sex-matched control subjects. A. All-cause dementia; B. All-cause dementia <65 years; C. All-cause dementia 65-75 years; D. All-cause dementia ≤75years. Number of patients at risk are reported in Table S8.
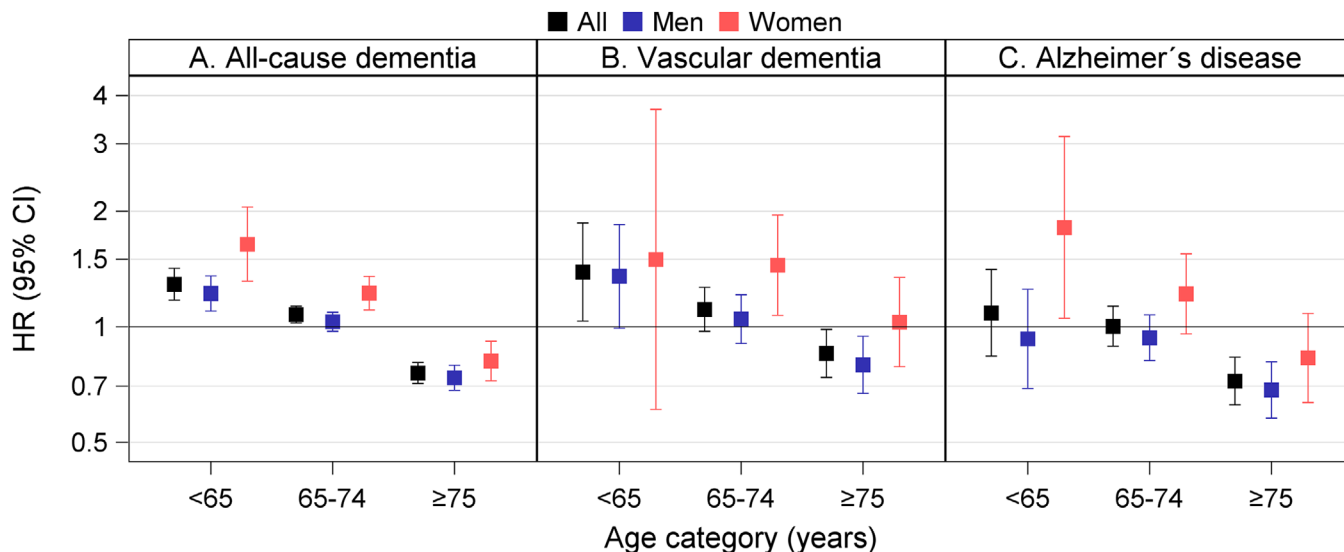
FIGURE 3 Multi-adjusted hazard ratios with 95% confidence intervals for all-cause dementia (A), vascular dementia (B), and Alzheimer's disease (C) among CABG patients compared to age- and sex-matched control subjects
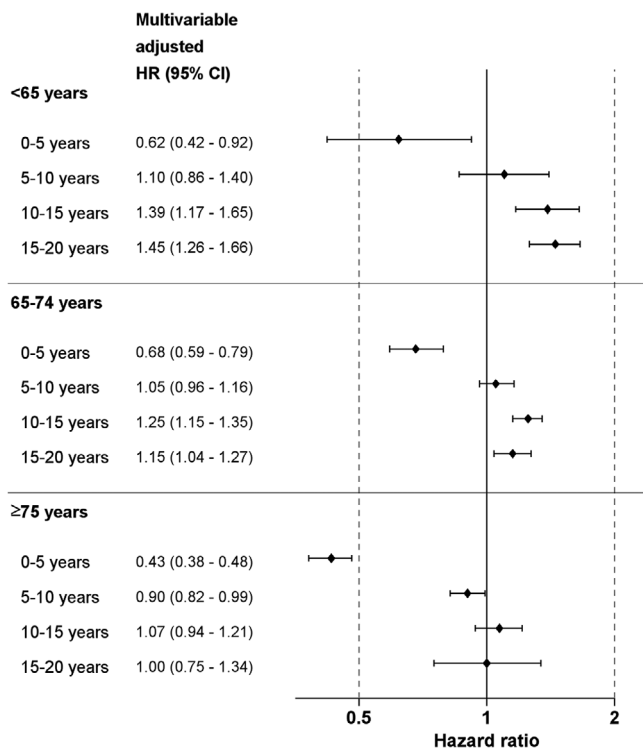

FIGURE 4 Multi-adjusted hazard ratios with 95% confidence intervals for all-cause dementia during 5-year time periods in coronary artery bypass grafting (CABG) patients compared to age- and sex-matched control subjects

3.4 | Risk factors for all-cause dementia in CABG patients

According to the stepwise regression analysis, the strongest predictors at the time of CABG were advanced age (aHR: 1.12 per year, 95% CI:

1.12–1.13, $P \leq$ .001), diabetes (aHR: 1.62, 95% CI: 1.52–1.73, $P \leq$ .001), previous stroke (aHR: 1.47, 95% CI: 1.33–1.62, $P \leq$ .001), history of depression (aHR: 1.58, 95% CI: 1.29–1.93, $P \leq$ .001), heart failure (aHR: 1.20, 95% CI: 1.11–1.29, $P \leq$ .001), and hypertension (aHR 1.15, 95% CI: 1.08–1.21, $P <$ .001). CABG patients with low socioeconomic status had higher risk for all-cause dementia (Table 3). Risk factors for the control population are presented in Table S13 in supporting information. There were no major differences in risk factors between the CABG population and controls.

4 | DISCUSSION

This large nationwide population-based cohort study has three main findings. First, CABG patients < 75 years have a higher long-term risk for incident dementia, compared to a sex- and age-matched control group from the general population. Second, CABG patients ≥75 years have a lower risk for dementia than controls. Third, advanced age, cardiovascular diseases and risk factors, history of depression, and socioeconomic disadvantages are independent predictors for developing dementia after CABG.

Previous studies investigating the association between CABG and dementia have shown diverging results.[2–4,6–10] However, most of these studies are limited by small study populations and short follow-up times. In a longitudinal study using neurocognitive tests in 117 CABG patients, Evered et al. found a high incidence (31%) of dementia 7.5 years after CABG. No specific control group was investigated, but the authors stated that the incidence was higher than had previously been reported from the general population.[4] Lyketsos et al. used neurocognitive tests and questionnaires in 260 CABG patients and found an increased adjusted incidence of dementia starting 5 years after surgery, compared to non-matched controls.[7] Kuźma et al. reported an increased incidence of all-cause dementia in 116 CABG patients

TABLE 3 Associations between potential risk factors at the time of surgery and dementia in CABG patients

	Dementian (%)	No dementian (%)	Age- and sex-adjusted HR(95% CI)	Multi-adjusted HR*(95% CI)
Female sex	1934 (28.7%)	22075 (21.1%)	1.09 (1.03–1.15)	1.04 (0.98–1.10)
Age	70.8 (6.6)	66.0 (9.3)	1.13 (1.12–1.13)	1.12 (1.12–1.13)
Myocardial infarction	3149 (46.8%)	49951 (47.8%)	1.07 (1.02–1.12)	1.00 (0.95–1.05)
Heart failure	798 (11.9%)	12702 (12.1%)	1.33 (1.23–1.43)	1.20 (1.11–1.29)
Hypertension	1981 (29.4%)	36011 (34.4%)	1.34 (1.27–1.41)	1.15 (1.08–1.21)
Diabetes	1311 (19.5%)	20978 (20.1%)	1.79 (1.68–1.90)	1.62 (1.52–1.73)
Renal failure	63 (0.9%)	1855 (1.8%)	1.78 (1.39–2.29)	1.38 (1.08–1.78)
History of stroke	440 (6.5%)	5343 (5.1%)	1.68 (1.52–1.85)	1.47 (1.33–1.62)
Atrial fibrillation	510 (7.6%)	7096 (6.8%)	1.25 (1.14–1.37)	1.14 (1.04–1.25)
Peripheral vascular disease	346 (5.1%)	6496 (6.2%)	1.22 (1.09–1.36)	1.08 (0.97–1.21)
Chronic respiratory disease	249 (3.7%)	4971 (4.8%)	1.23 (1.08–1.40)	1.09 (0.95–1.23)
History of cancer	389 (5.8%)	7253 (6.9%)	1.13 (1.02–1.25)	1.05 (0.95–1.16)
History of depression	100 (1.5%)	2018 (1.9%)	1.86 (1.53–2.27)	1.58 (1.29–1.93)
Hyperlipidaemia	877 (13.0%)	20602 (19.7%)	1.18 (1.10–1.27)	0.97 (0.90–1.05)
Marital status				
Married/cohabiting	4503 (66.9%)	67766 (64.8%)	1.00 (Reference)	1.00 (Reference)
Not married	377 (5.6%)	10588 (10.1%)	1.01 (0.91–1.12)	0.93 (0.83–1.05)
Divorced	838 (12.4%)	15550 (14.9%)	1.28 (1.19–1.38)	1.16 (1.06–1.27)
Widowed	1015 (15.1%)	10698 (10.2%)	0.98 (0.91–1.05)	0.93 (0.85–1.01)
Education				
<10 years	3584 (53.2%)	49301 (47.1%)	1.00 (Reference)	1.00 (Reference)
10–12 years	2232 (33.2%)	38171 (36.5%)	1.04 (0.98–1.09)	1.04 (0.98–1.10)
>12 years	790 (11.7%)	15667 (15.0%)	0.94 (0.87–1.01)	0.96 (0.89–1.05)
Income				
Quintile 1 (lowest)	1557 (23.1%)	19901 (19.0%)	1.00 (Reference)	1.00 (Reference)
Quintile 2	1779 (26.4%)	21704 (20.7%)	0.97 (0.91–1.04)	0.99 (0.91–1.08)
Quintile 3	1613 (24.0%)	22162 (21.2%)	0.92 (0.86–0.99	0.94 (0.86–1.03)
Quintile 4	1157 (17.2%)	21498 (20.6%)	0.91 (0.84–0.99)	0.93 (0.84–1.03)
Quintile 5	627 (9.3%)	19337 (18.5%)	0.82 (0.74–0.90)	0.82 (0.73–0.93)

Abbreviations: CABG, coronary artery bypass grafting; CI, confidence interval; HR, hazard ratio.

*Multivariable adjusted model is adjusted for age, sex, year of surgery, marital status, education, income, and comorbidities at baseline (previous myocardial infarction, hypertension, diabetes, heart failure, atrial fibrillation, stroke, peripheral vascular disease, renal failure, chronic respiratory disease, cancer, depression, hyperlipidemia).

compared to a non-matched control population.[6] A large cohort study by Sundbøll et al. showed that myocardial infarction patients treated with CABG had an increased risk for vascular dementia.[10] In contrast, studies by Knopman et al.[9] and van Dijk et al.[8] and a meta-analysis by Greaves et al.[3] could not demonstrate an increased incidence of dementia in CABG patients.

In the present large population-based study, the overall difference in cumulative incidence of all-cause dementia between CABG patients and matched control subjects was very limited: 0.6% percentage points at 20 years (Figure 2A). It was only after the cohort was divided into different age groups that interesting differences became

evident. We observed an increased risk for all-cause dementia and vascular dementia in CABG patients <65 years, and an increased risk for all-cause dementia in patients 65 to 74 years compared to the general population (Figure 3). This is not surprising given that dementia and coronary artery disease share several risk factors, such as advanced age, diabetes, hypertension, and smoking.[17–19] A large cohort study recently demonstrated that myocardial infarction patients have an increased risk for vascular dementia,[10] further underlining the association between coronary artery disease and dementia. Interestingly, the increased incidence in CABG patients <75 years became statistically significant first after 10 years, indicating that

studies with shorter follow-up times may have missed true group differences.

CABG patients ≥75 years had a lower risk of all-cause dementia, vascular dementia, and AD compared to the age- and sex-matched control population, but a higher risk compared to younger CABG patients. The lower risk compared to the control population may reflect a careful preoperative patient assessment process in which elderly coronary artery disease patients with mild to moderate cognitive dysfunction that had not yet reached dementia diagnosis were directed to treatments other than CABG. Older patients who undergo CABG are presumably a highly selected group, with no or very limited signs of preoperative cognitive dysfunction. Older patients who undergo CABG are presumably a highly selected group, with no or very limited signs of preoperative cognitive dysfunction and low incidences of other diseases associated with increased risk for dementia. Alternatively, CABG patients more likely to develop dementia may die before diagnosis. However, there was no difference in overall mortality rate between CABG patients and control subjects aged >75 years; Table S4, which at least partially, argues against this explanation. The true reasons behind the lower incidence of dementia in CABG patients >75 years, compared to control subjects, cannot be identified by the present study. Regardless, our results indicate that older CABG patients, who may suffer from temporary postoperative cognitive impairment, do not have a higher long-term risk of developing dementia after surgery, compared to age- and sex-matched individuals.

The youngest women (<65 years) had the highest risk for both all-cause dementia and AD. The reasons are not obvious, although it is known that younger women undergoing CABG have a high burden of comorbidities, such as hypertension and diabetes, that influence the risks of both coronary artery disease and dementia.[17–19] Interestingly, high cardiovascular fitness in women <60 years is associated with a markedly decreased risk of dementia.[20]

The present study identified several independent predictors of dementia (Table 3). Besides the cardiovascular diseases and risk factors discussed above, marital status, household income, and a history of depression before CABG were also associated with dementia. These findings confirm previous studies indicating associations between socioeconomic disadvantage and dementia[21] and between depression and dementia.[22]

This study has both strengths and limitations. Strengths include the large study population, the complete follow-up, and the long follow-up time, while limitations include those inherent in observational studies, such as residual confounding and selection bias. We did not have information about lifestyle factors, and hence could not include these in our statistical models. Furthermore, medication could not be adjusted for because our national registry about prescribed drugs started in 2006. The potential link between early cognitive dysfunction after CABG and the long-term risk for dementia could not be assessed, because early transient cognitive dysfunction is not registered in SWEDEHEART or NPR. The diagnoses in NPR are limited to hospitalized patients and to outpatients treated at hospitals, while diagnoses for patients exclusively treated at primary care facilities and general practitioners are not included; this may lead to underestimating the incidence of dementia. It is possible that the underestimation is larger in control subjects, as CABG patients may more often be followed in hospitals. However, because almost all CABG patients in Sweden are followed at primary care facilities after the first six postoperative months and dementia in most cases occurred late after the index date, the risk for bias may be limited. If there were a bias due to underestimation in control subjects, the observed higher risk in the younger group would be diminished and observed lower risk in the older group would be more pronounced. National patient registers covering hospital only have previously been used in epidemiologic studies about dementia.[23]

We adjusted for patient characteristics, comorbidity, operation year, and socioeconomic factors in our statistical models. It would have been interesting also to include genetic factors, such as apolipoprotein E (APOE) ε4, which is a significant risk factor for both dementia and coronary artery disease,[24–25] but genetic information is not included in national registries and databases. Most likely the prevalence of APOE ε4 is higher in CABG patients than in the control population. Finally, there are substantial overlaps in symptomatology, pathophysiology, and risk factors in dementia, which makes it challenging to distinguish between different subtypes,[26] so the validity of our conclusions is higher for all-cause dementia than for vascular dementia and AD.

In conclusion, we have demonstrated that there is an increased risk for all-cause dementia among younger CABG patients compared to an age- and sex-matched general population. The highest risk was observed in younger women. Cardiovascular disease and risk factors, history of depression, and low socioeconomic status are independent risk factors for developing all-cause dementia after CABG.

CONFLICTS OF INTEREST

FUNDING INFORMATION

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.