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# Higher Risk of Vascular Dementia in Myocardial Infarction Survivors

**Running Title:** *Sundbøll et al. Myocardial Infarction and Dementia*

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## Abstract

***Background*—**Increased risk of dementia after myocardial infarction (MI) may be mediated by shared risk factors (*e.g.*, atherosclerosis) and post-MI stroke. We examined risk of dementia in 1-year survivors of MI.

***Methods*—**Using Danish medical registries, we conducted a nationwide population-based cohort study of all patients with first-time MI and a sex-, birth year-, and calendar year-matched general population comparison cohort without MI (1980–2012). Cox regression analysis was used to compute 1–35 year adjusted hazard ratios (aHRs) for dementia, controlled for matching factors and adjusted for comorbidities and socioeconomic status.

***Results*—**We identified 314,911 patients with MI and 1,573,193 matched comparison cohort members randomly sampled from the general population (median age 70 years, 63% male). After 35 years of follow-up, the cumulative incidence of all-cause dementia in the MI cohort was 9% (2.8% for Alzheimer's disease, 1.6% for vascular dementia, and 4.5% for other dementias). Compared with the general population cohort, MI was not associated with all-cause dementia (aHR = 1.01, 95% confidence interval (CI): 0.98–1.03). Risk of Alzheimer's disease (aHR = 0.92, 95% CI: 0.88–0.95) and other dementias (aHR = 0.98, 95% CI: 0.95–1.01) also approximated unity. However, MI was associated with higher risk of vascular dementia (aHR = 1.35, 95% CI: 1.28–1.43), which was substantially strengthened for patients experiencing stroke after MI (aHR = 4.48, 95% CI: 3.29–6.12).

***Conclusions***—MI was associated with higher risk of vascular dementia throughout follow-up and this asssociation was stronger in patients suffering stroke. The risk of Alzheimer's disease and other dementias was not higher in MI patients.


**Key Words:** epidemiology; myocardial infarction; risk factor; dementia; epidemiology, myocardial infarction, risk factor, dementia

## Clinical Perspective

### What is new?

- Previous studies on the association between myocardial infarction and dementia are scarce and limited by size, equivocal findings, and a sole focus on all-cause dementia.
- In a nationwide population-based cohort including 314,911 patients with myocardial infarction the risk of vascular dementia was higher compared with a matched general population comparison cohort.
- The risk of vascular dementia was incrementally higher in patients who suffered stroke or developed severe heart failure during the first year after myocardial infarction, and in patients who underwent coronary artery bypass grafting.
- There was no association with all-cause dementia, Alzheimer's disease, or other dementia subtypes.

### What are the clinical implications?

- Among one-year survivors of myocardial infarction, attention to the persistently higher risk of vascular dementia is prudent.
- The effect of any formal screening for cognitive decline is unclear.

During recent decades, Western populations have experienced a demographic shift towards an elderly population with increased prevalence of age-related diseases such as myocardial infarction (MI) and dementia.[1,2] This trend is predicted to intensify, creating economic and public health challenges.[2]

Recent advances in managing MI have improved survival rates,[1] further increasing the number of MI survivors.[3] Any associated rise in the incidence of dementia among MI survivors is therefore important to track, with the goal of secondary prevention of dementia after MI.

Putative mechanisms linking MI to increased risk of dementia include chronic hypoperfusion of the brain following MI due to impaired left ventricular ejection fraction and low blood pressure.[4] Common complications after MI, such as atrial fibrillation and hypokinesia of the left ventricle, facilitate formation of intra-cardiac thrombi. The subsequent release of emboli to the brain also could mediate an association with dementia. Consistent with this hypothesis, MI recently was found to be associated with ischemic as well as hemorrhagic stroke,[5] both of which in turn increase the risk of dementia.[6] Also, coronary artery bypass grafting (CABG) performed during an MI admission can induce cerebral hypoperfusion during cardioplegia as well as cerebral embolization following clamping or cannulation of the aorta.[7] Finally, MI and dementia may be independent, but convergent diseases caused by common underlying risk factors (*e.g.*, diabetes mellitus, hypercholesterolemia, hypertension, and atherosclerosis), but with a longer latency period for dementia.

Only two studies have evaluated the risk of all-cause dementia in MI patients and their findings have been equivocal.[8,9] A small cohort study reported a 2-fold higher risk of dementia, but only in men with unrecognized MI (n=159), compared with participants without evidence of

previous MI.[8] A small case-control study, including 916 cases of dementia and 916 age- and sex matched controls, found no association with preceding MI.[9]

In the absence of disease-modifying treatment for most forms of dementia, it is important to identify risk factors with the potential to prevent or delay its onset. We examined the long-term risk of dementia following first-time MI and the impact of common MI treatments and complications.

## Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.



### Setting and design

We conducted this nationwide population-based cohort study in Denmark, which had a cumulative population of 8,262,736 inhabitants during the study period (1 January 1980 to 1 September 2012). The Danish National Health Service provides tax-supported health care, ensuring unfettered access to general practitioners and hospitals for all Danish inhabitants. Accurate linkage of all registries at the individual level is possible in Denmark owing to the unique central personal registry number assigned to each Danish citizen at birth and to residents upon immigration.[10]

### Patients with myocardial infarction

We used the Danish National Patient Registry[11] (DNPR) to identify all patients with a first-time inpatient diagnosis of MI during the study period. The DNPR has recorded information on all admissions to Danish non-psychiatric hospitals since 1977 and on emergency room and outpatient clinic visits since 1995.[11] Each hospital discharge or outpatient visit is recorded in the

DNPR with one primary diagnosis and one or more secondary diagnoses classified according to the *International Classification of Diseases, Eighth Revision* (ICD-8) through 1993 and *Tenth Revision* (ICD-10) thereafter.[11] We identified MI patients using both primary and secondary diagnoses.

**General population comparison cohort**

We created a general population comparison cohort using the Danish Civil Registration System, which has provided daily updates on vital statistics, including dates of birth, emigration, and death, since 1968.[10] For each patient in the MI cohort, 5 individuals from the general population without an MI diagnosis were randomly selected and matched on sex, birth year, and calendar year of MI diagnosis. We used matching with replacement (*i.e.,* individuals from the general population comparison cohort could be matched with more than one MI patient).[12]

The MI admission date was defined as the index date for MI patients and their matched counterparts in the general population cohort. To ensure capture of only incident cases of dementia, we excluded MI patients and persons in the matched comparison cohort who had received a previous diagnosis of dementia, mild cognitive impairment, or an amnestic syndrome, which may represent prodromal dementia. If members of the general population cohort were diagnosed with MI after the index date, follow-up in the comparison cohort was discontinued. They then were transferred to the MI cohort and matched with new members of the general population.

**Dementia**

Data on inpatient and outpatient dementia diagnoses were retrieved from the DNPR[11] and the Danish Psychiatric Central Research Register.[13] Specifically, we identified Alzheimer's disease, vascular dementia, and other dementias (*i.e.*, any specified or unspecified dementia other than

Alzheimer's disease and vascular dementia). In the DNPR, dementia diagnoses are available for hospital admissions since 1977 and for outpatient clinic visits since 1995.[11] The Danish Psychiatric Central Research Register has recorded hospitalizations for dementia since 1969 and outpatient treatment at hospital psychiatric clinics since 1995.[13]

**Covariables**

Using patients' medical histories, available in the DNPR since 1977, we obtained information on comorbidities that may represent shared risk factors for MI and dementia. These consisted of all hospital inpatient and outpatient diagnoses of heart failure, angina pectoris, atrial fibrillation/atrial flutter, heart valve disease, hypercholesterolemia, hypertension, stroke, intermittent claudication, obesity, diabetes mellitus, chronic pulmonary disease (as an indicator of chronic smoking), myxedema, alcoholism-related diseases, head trauma, osteoarthritis (as an indicator for use of nonsteroidal anti-inflammatory drugs), anemia, chronic kidney disease, depression, and a modified Charlson Comorbidity Index (CCI) score (excluding congestive heart failure, MI, cerebrovascular disease, dementia, chronic pulmonary disease, diabetes mellitus, and chronic kidney disease from the index). We also obtained information on personal gross income, employment status during the year preceding the index date, and highest education achieved from the Integrated Database for Labour Market Research.[14]

**Surgical procedures**

We obtained information on CABG, percutaneous coronary intervention, and pacemaker implantation from the DNPR, which has coded surgery according to the Danish Classification of Surgical Procedures and Therapies until 1 January 1996 and according to the NOMESCO Classification of Surgical Procedures thereafter.[11]

**Statistical analyses**

We characterized the MI and general population comparison cohorts according to 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), comorbidities, and socioeconomic status at baseline and at 1 year after MI. We followed all MI patients and members of the general population comparison cohort until the occurrence of any dementia diagnosis, emigration, death, or 31 December 2014, whichever came first. *A priori*, we disregarded the first year after MI and initiated follow-up thereafter, since dementia diagnosed shortly after admission for MI is unlikely to be a consequence of MI. Figure 1 provides a flowchart of exclusions within the first year of MI and the resulting final study population.

We used cumulative incidence functions with death as a competing risk to calculate dementia risks during 1-35 years of follow-up. Using multivariable stratified Cox proportional hazards regression models with cencoring at death, we computed hazard ratios (HRs) with 95% confidence intervals (CIs), comparing MI patients with members of the general population comparison cohort.[15] HRs were controlled for sex, birth year, and calendar year by the matched study design and in multivariable analyses adjusted for preadmission diagnoses of heart failure, stable angina pectoris, atrial fibrillation or atrial flutter, valvular heart disease, hypercholesterolemia, hypertension, stroke, intermittent claudication, obesity, diabetes mellitus, chronic pulmonary disease, myxedema, alcoholism-related disease, head trauma, osteoarthritis, anemia, chronic kidney disease, depression, a modified CCI score, and socioeconomic status (income and employment). The proportional-hazards assumption was assessed graphically using log–log plots and there was no evidence of violation within the follow-up period. The ICD codes used in the study are provided in Supplemental Tables 1 and 2.

**Additional analyses**

To identify clinical pathways with a potential impact on the association between MI and dementia, we stratified by cardiac procedures performed during hospital admissions for MI and by complications occurring between MI and start of follow-up 1 year later. For heart failure, we performed two additional analyses to further examine the impact of increasing severity of post-MI heart failure. First, we examined the impact of increasing daily doses of loop diuretics (furosemide or bumetanide), which previously have been demonstrated to correlate with heart failure mortality.[16] We categorized patients into non-users (no loop diuretics), low-dose users (≤40 mg/day), medium-dose users (41–80 mg/day), and high-dose users (≥81 mg/day). The daily dose was obtained by multiplying the number of pills across all prescriptions redeemed within the first year after MI by the furosemide-equivalent dose per pill (1 mg bumetanide = 80 mg furosemide)[17] and then dividing by 365.25 days. As the nationwide prescription registry was initiated in 1995,[18] this analysis was restricted to the post-1995 part of the study period. Second, we categorized MI patients according to the number of inpatient admissions for heart failure during the first year after MI as a proxy for heart failure severity (1980–2012).

The presence of potential interactions was examined in strata of sex, age groups, underlying preadmission comorbidity, and different levels of comorbidity measured using modified CCI scores. We also investigated temporal differences in risk of dementia following MI by splitting up the index periods (1980−1994 and 1995−2012). In this analysis, we limited follow-up to ten years, to allow sufficient follow-up time for patients in both time periods. We selected these periods because ICD-10 diagnostic codes were introduced in 1994, and outpatient specialist clinic diagnoses became available in 1995. We further stratified the analyses by type of MI diagnosis (primary or secondary), because the positive predictive value is lower (80%) for

secondary diagnoses.[19] As a higher cognitive reserve may modify any association between MI and dementia,[20] we examined the associations by socioeconomic status (income, employment, and education). In the analyses stratified by underlying preadmission comorbidity, modified CCI scores, and socioeconomic status, the matching was dissolved and HRs additionally adjusted for matching variables. Dissolving the matching introduced a lack of independence among members of the comparison cohort because they were matched with replacement.[12] We therefore employed a robust variance estimator in these analyses to account for the lack of independence.

**Sensitivity analyses**

We performed several sensitivity analyses. First, given the assumed latency period for development of clinically overt dementia following MI, we repeated the analyses sequentially excluding the initial two, three, five, and ten years of follow-up. Second, we redefined Alzheimer's disease to also include the ICD code for unspecified dementia. Third, we additionally adjusted for education, which was not included in the main analysis because data were unavailable for 43% of participants and because we assumed a strong collinearity with the other socioeconomic factors (income and employment). Fourth, we divided follow-up time into periods of 1–10 years, 11–20 years, and 21–35 years to examine whether associations weakened over time. Fifth, we repeated the analyses for subgroups of MI [ST-segment elevation MI (STEMI) and non-STEMI]. Sixth, we continued follow-up for members of the comparison cohort who experienced an MI during follow-up.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). The study was approved by the Danish Data Protection Agency (record number: 1-16-02-268-14). According to Danish legislation, no approval from an ethics committee or informed consent from patients are required for registry-based studies in Denmark.

## Results

We identified 314,911 patients with a first-time MI and 1,573,193 matched individuals from the general population [median age 70.3 years, 63% male (Table 1)]. One-year survivors numbered 209,754 patients with MI and 1,003,763 persons from the comparison cohort (Supplemental Figure 1 and Supplemental Table 3). Median follow-up time was 7.7 years (25th–75th percentile: 4.0–13.1 years) for MI patients and 9.8 years (25th–75th percentile: 5.2–16.0 years) for members of the comparison cohort. The difference in follow-up time arose mainly from the competing risk of death after MI. All comorbidities were more common among MI patients than among members of the comparison cohort both at baseline (Table 1) and among one-year survivors (Supplemental Table 3). MI patients also had slightly lower income, educational, and employment levels.

### Risk of dementia

During 1–35 years of follow-up, 11,334 patients in the MI cohort were diagnosed with dementia [3615 (32%) with Alzheimer's disease, 2092 (18%) with vascular dementia, and 5627 (50%) with other dementias (Table 2)]. The cumulative incidence of all-cause dementia in the MI cohort after 35 years of follow-up was 8.7% (2.8% for Alzheimer's disease, 1.6% for vascular dementia, and 4.5% for other dementias). Due to the competing risk of death, the cumulative incidence of dementia was consistently higher in the general population comparison cohort than in the MI cohort (Table 2). We found no association with all-cause dementia (adjusted HR = 1.01, 95% CI: 0.98–1.03) or other dementias (adjusted HR = 0.98, 95% CI: 0.95–1.01) compared with the general population cohort. For Alzheimer's disease, the risk was marginally lower (adjusted HR = 0.92, 95% CI: 0.88–0.95), whereas risk of vascular dementia was significantly higher (adjusted HR = 1.35, 95% CI: 1.28–1.43).

**Additional analyses**

The incremental risk of vascular dementia was higher in patients who experienced a stroke within one year of MI (adjusted HR = 4.48, 95% CI: 3.29–6.12), whereas atrial fibrillation or flutter were associated with only moderately higher risk (adjusted HR = 1.55, 95% CI: 1.28–1.87). The risk of vascular dementia was also accentuated in patients who underwent pacemaker implantation (adjusted HR = 3.38, 95% CI: 1.42–8.06) or CABG (adjusted HR = 3.99, 95% CI: 1.31–12.18) during their MI admission, although CIs were overlapping with CIs of the main vascular dementia estimate (Table 3). Higher risk of vascular dementia was not present in MI patients undergoing percutaneous coronary intervention during the MI admission, and was not associated with the development of hypertension, cardiogenic shock/pulmonary edema, or unspecified heart failure during the first year after MI. However, the incremental risk of vascular dementia was greater with increasing levels of heart failure severity, as measured by the number of admissions for heart failure during the first year after MI [adjusted HR = 2.24 (95% CI: 1.21–4.14) for ≥3 admissions). This pattern was also present for other subtypes of dementia, although less pronounced (Table 4). Among MI patients who developed symptomatic heart failure, as measured by the need for loop diuretics, the risk of vascular dementia was only slightly higher [adjusted HR = 1.50 (95% CI: 1.11–2.02) for a low daily furosemide-equivalent dose of ≤40 mg and without additional risk for doses above 40 mg].

In age-stratified analyses, the association was attenuated with increasing age for all dementia subtypes. The risk of vascular dementia remained higher in older age groups, while the risks of all-cause dementia [adjusted HR = 0.88 (95% CI: 0.84–0.92)], other dementias [adjusted HR = 0.87 (95% CI: 0.81–0.93)], and particularly Alzheimer's disease [adjusted HR = 0.80 (95% CI: 0.74–0.87)] were moderately lower in MI patients ≥80 years. The slightly lower risk of

Alzheimer's disease observed in the overall results and in older age groups was not present in younger age groups [adjusted HR = 1.02 (95% CI: 0.89–1.15) for <60 years and 0.96 (95% CI: 0.89–1.04) for 60–69 years]. For all-cause dementia and other dementias, a positive association was observed for MI patients aged <60 years [adjusted HR = 1.19 (95% CI: 1.11–1.27) for all-cause dementia and 1.17 (95% CI: 1.07–1.28) for other dementias]. No difference was observed between men and women (Supplemental Table 4). Results remained robust in subgroup analyses of cardiac and non-cardiac comorbidity and CCI levels (Supplemental Table 5). We observed no temporal difference in the association observed during early (1980–1994) *vs*. late (1995–2012) time periods (Supplemental Table 6). In analyses stratified by primary *vs*. secondary diagnoses of MI, the risks of all-cause and vascular dementia were slightly higher for secondary diagnoses (Supplemental Table 6). Across levels of income, employment status, and education, results agreed with those of the main analysis (Supplemental Table 7).

**Sensitivity analyses**

Results of the sensitivity analyses are presented in Supplemental Table 8. The results changed insignificantly when we sequentially excluded the initial 1-10 years of follow-up. The results also remained robust when ICD codes for unspecified dementia were included in the definition of Alzheimer's disease, when the model was extended to adjust for education, and when the three follow-up periods were considered separately (1–10 years, 11–20 years, and 21–35 years). As well, type of MI (STEMI/non-STEMI) did not substantially impact the results. Finally, results were consistent when we continued follow-up for members of the population comparison cohort who experienced MI during follow-up (data not shown).

## Discussion

In this nationwide matched population-based cohort study with virtually complete follow-up of 209,890 MI survivors for 35 years, we found a higher risk of vascular dementia compared with the general population. The incremental risk was even greater in patients who underwent CABG during their admission for MI or who experienced stroke during the first year following MI. In patients who developed heart failure requiring hospitalization, the association with vascular dementia was moderately strengthened. The risk of Alzheimer's disease was marginally lower, whereas we found no association with all-cause dementia. We observed a progressively smaller increment in risk for all subtypes of dementia with increasing age. This was presumably due to a low absolute risk of dementia in younger age groups where the relative association with an MI is stronger. In particular, the attenuation of the risk of vascular dementia with age may reflect that many individuals with a heavy burden of cardiovascular risk factors do not survive to old age. Accordingly, earlier studies have demonstrated that for men, the incidence of vascular dementia is higher in younger age groups,[21] while mixed underlying pathologies are more common in older individuals with dementia.[22] Our results did not differ substantially between 1980–1994 and 1995–2012 despite considerable improvement during the whole study period in primary and secondary prevention of MI[23] and in diagnostic modalities for Alzheimer's disease, such as structural magnetic resonance imaging, biomarkers in cerebrospinal fluid, fluorodeoxyglucose-positron emission tomography, and amyloid positron emission tomography.[24]

Available studies on the association between MI and dementia are few and results have been equivocal with either no association or a slightly increased risk.[8,9] In a small cohort study conducted in Rotterdam,[8] participants were classified into groups of recognized MI (n=424), unrecognized MI (n=345), and no MI (n=5578, reference group) based on electrocardiograms at

baseline combined with self-reported history of MI. In men, unrecognized MI (n=159) was associated with higher risk of all-cause dementia (adjusted HR = 2.14, 95% CI 1.37–3.35). Unrecognized MI also was associated with more cerebral white matter lesions and more frequent brain infarction on magnetic resonance imaging. In women, there was no association between unrecognized MI and risk of all-cause dementia. Recognized MI was not associated with risk of dementia in either sex. Our study did not include unrecognized MI. However, the null result in the Rotterdam study for all-cause dementia in patients with recognized MI is in line with our findings. In a case-control study of 916 patients with dementia in Rochester, Minnesota, no association was found between MI and all-cause dementia (odds ratio 1.00, 95% CI, 0.62–1.62).[9] In Western societies, Alzheimer's disease accounts for approximately half of all dementia cases and vascular dementia accounts for 20%,[25,26] a distribution also reflected in our findings (Table 2). Previous studies have focused solely on all-cause dementia,[8,9] disregarding these dominant subtypes despite different underlying pathophysiologies. Thus, Alzheimer's disease is characterized by the accumulation of β-amyloid and tau in plaques and tangles,[27] while vascular dementia has a cerebrovascular pathology, characterized by strategically located infarctions and hemorrhages.[28]

Our finding of higher risk of vascular dementia may point to several mechanisms. Atherosclerosis may be the underlying factor driving the development of MI, ischemic stroke, and, ultimately, vascular dementia, but with a longer latency period for vascular dementia. In support of this assumption, only risk of vascular dementia was higher in our study. MI has been associated with higher risk of both ischemic stroke and hemorrhagic stroke,[5] which in turn have been associated with higher risk of all-cause dementia.[6] In our study, we identified stroke as a strong modifier of the association with vascular dementia, but without any substantial impact on

the association with other dementia subtypes. Ischemic stroke is plausible as a modifier, due to emboli following MI. Such emboli may occur when MI is complicated by atrial fibrillation or regional wall motion abnormalities, both increasing the risk of thrombus formation within the left atium and ventricle with the possibility of cerebral embolization. Like ischemic stroke, hemorrhagic stroke may lie on the causal pathway to dementia, prompted by the standard regimen of dual antiplatelet therapy [*i.e.*, aspirin plus an adenosine diphosphate (ADP) receptor inhibitor] during the first year after MI, followed by lifelong aspirin treatment.[29]

Other potential factors influencing the risk of vascular dementia after MI may include a history of hypertension, especially when complicated by episodes of hypotension.[30] Acute and chronic hypotension after MI may be caused by cardiogenic shock, heart failure, and atrial fibrillation with low or high ventricular rate response.[31] Hypotension can lead to watershed infarctions in the vulnerable border-zone regions of the brain supplied by the major cerebral arteries.[32] The blood supply to these areas is precarious and may become compromised if cerebral perfusion drops, especially if the supplying arteries are stenosed[33] or the aortic root is stiffened.[34] In line with these premises, we found an incrementally higher risk of vascular dementia in patients with symptomatic heart failure or atrial fibrillation or flutter during their first year following MI. However, the risk of vascular dementia remained largely unchanged when we restricted the analysis to MI patients with complications of cardiogenic shock or pulmonary edema.

In addition to stroke, we identified CABG performed during admission for MI as a factor strengthening the association with vascular dementia. This may relate to the specific subset of MI patients for whom CABG is indicated, *e.g.*, patients with triple-vessel disease or stenosis involving the left main stem, which indicate more widespread atherosclerotic disease,

including cerebral atherosclerosis. It is also well established that CABG is associated with serious, yet common, post-operative neurological deficits and stroke[35] plausibly increasing risk of dementia. However, it remains controversial whether CABG itself increases the risk of long-term dementia.[36] In contrast, patients undergoing percutaneous coronary intervention during their hospitalization for MI were not at higher risk of vascular dementia compared with the general population. Patients selected for percutaneous coronary intervention are likely characterized by less generalized atherosclerosis[37,38] and less risk of procedure-related cerebral embolization compared with patients undergoing CABG.[35] Furthermore, our study period covers the transition during the 1990s from thrombolytic therapy to percutaneous coronary intervention as standard therapy for MI. Compared with percutaneous coronary intervention, thrombolytic therapy increases risk of hemorrhagic stroke,[39] which in turn is associated with all-cause dementia.[6] This may also underlie the lack of association with vascular dementia observed in MI patients selected for percutaneous coronary intervention.

Several study strengths and limitations should be considered when interpreting our results. An important strength is the size of the study, allowing precise estimates and the ability to examine several possible interactions and mediators of the association between MI and dementia. The population-based design, within the setting of a tax-supported universal healthcare system with complete follow-up of all patients, largely eliminated selection biases.[10] Registration of the MI diagnosis in the DNPR is accurate, with validation studies consistently reporting positive predictive values above 90% throughout the study period.[11,19,40,41] The accuracy of the major dementia diagnoses in the DNPR and the Danish Psychiatric Central Research Register is also high (positive predictive value = 86% for all-cause dementia), although lower for dementia subtypes.[42]

A concern is the unknown sensitivity of the dementia diagnosis. The sensitivity may be higher in the MI cohort due to surveillance bias, which would lead to overestimation of the risk of dementia compared with the general population. Specifically, attention to vascular dementia may be increased in patients with a history of MI and lead to a channeling effect, *i.e.*, the possibility that demented patients with cardiovascular diseases may be more likely to receive a diagnosis of vascular dementia than other types of dementia. This may explain the marginally decreased risk of Alzheimer's disease, and may indicate an overestimation of the risk of vascular dementia. However, such channeling effect was likely small because the slightly decreased risk of Alzheimer's disease was present only in older age groups, where the risk of vascular dementia concomitantly decreased.

Despite extensive confounder adjustment for sex, age, comorbidity and socioeconomic status, our study is limited by its observational design. Thus, residual and unmeasured confounding cannot be ruled out. Importantly, we lacked information on smoking, which is associated with both MI[43] and dementia.[44] However, we adjusted for hospital diagnoses of chronic obstructive pulmonary disease as a proxy measure for chronic smoking exposure. We also lacked information on physical activity and the apolipoprotein E genotype, which are associated with both MI and dementia[45,46] and hence may contribute in part to the increased risk of vascular dementia observed in our study. Life style in general, however, was indirectly adjusted for by socioeconomic status and life style diseases.

In conclusion, MI was associated with higher risk of vascular dementia. The lack of an association with Alzheimer's disease and other dementias indicates that shared risk factors (*e.g.*, atherosclerosis) combined with post-MI procedures and complications leading to stroke may be the driving mechanisms behind the association with vascular dementia.

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Dr. Sørensen is the guarantor of this work and had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.

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## Disclosures

None

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**Table 1.** Characteristics of patients at hospital admission for first-time myocardial infarction and members of the general population comparison cohort, Denmark, 1980-2012.

| | Myocardial infarction cohort (n=314,911) | Comparison cohort (n=1,573,193) |
|---|---|---|
| **Male** | 198,289 (63.0) | 990,495 (63.0) |
| **Age, years** | | |
| <60 | 71,423 (22.7) | 356,877 (22.7) |
| 60–69 | 78,613 (25.0) | 392,709 (25.0) |
| 70–79 | 94,418 (30.0) | 471,750 (30.0) |
| ≥80 | 70,457 (22.4) | 351,857 (22.4) |
| Median (25th–75th percentile) | 70.3 (60.6–78.6) | 70.3 (60.6–78.6) |
| **Decade of diagnosis / index date** | | |
| 1980−1989 | 116,055 (36.9) | 579,960 (36.9) |
| 1990−1999 | 91,109 (28.9) | 455,294 (28.9) |
| 2000−2012 | 107,747 (34.2) | 537,939 (34.2) |
| **Comorbidity** | | |
| Heart failure | 19,899 (6.3) | 39,373 (2.5) |
| Angina pectoris | 33,745 (10.7) | 59,103 (3.8) |
| Atrial fibrillation or flutter | 15,642 (5.0) | 51,624 (3.3) |
| Valvular heart disease | 6320 (2.0) | 13,755 (0.9) |
| Hypercholesterolemia | 5799 (1.8) | 13,531 (0.9) |
| Hypertension | 36,589 (11.6) | 93,358 (5.9) |
| Stroke | 13,756 (4.4) | 41,936 (2.7) |
| Intermittent claudication | 4758 (1.5) | 7676 (0.5) |
| Obesity | 8459 (2.7) | 19,825 (1.3) |
| Diabetes mellitus | 25,903 (8.2) | 52,554 (3.3) |
| Chronic pulmonary disease | 22,435 (7.1) | 69,764 (4.4) |
| Myxedema | 2747 (0.9) | 8149 (0.5) |
| Alcoholism-related diseases | 5790 (1.8) | 21,871 (1.4) |
| Head trauma | 32,765 (10.4) | 155,899 (9.9) |
| Osteoarthritis | 26,195 (8.3) | 110,197 (7.0) |
| Anemia | 9669 (3.1) | 29,824 (1.9) |
| Chronic kidney disease | 7012 (2.2) | 11,549 (0.7) |
| Depression | 8965 (2.8) | 35,432 (2.3) |
| **Modified CCI score*** | | |
| Normal | 253,307 (80.4) | 1,360,186 (86.5) |
| Moderate | 33,840 (10.7) | 95,715 (6.1) |
| Severe | 20,582 (6.5) | 93,589 (5.9) |
| Very severe | 7182 (2.3) | 23,703 (1.5) |
| **Income** | | |
| Low | 84,772 (26.9) | 378,514 (24.1) |
| Intermediate | 86,182 (27.4) | 403,227 (25.6) |
| High | 75,824 (24.1) | 381,022 (24.2) |
| Very high | 67,867 (21.6) | 403,392 (25.6) |

| | | |
|---|---|---|
| Missing | 266 (0.1) | 7038 (0.4) |
| **Employment** | | |
| Employed | 86,940 (27.6) | 494,231 (31.4) |
| Early retirement | 33,926 (10.8) | 155,267 (9.9) |
| Unemployed | 7253 (2.3) | 31,736 (2.0) |
| State pensioner | 181,516 (57.6) | 874,971 (55.6) |
| Missing | 5276 (1.7) | 16988 (1.1) |
| **Education** | | |
| Basic education or primary school | 96,207 (30.6) | 424,016 (27.0) |
| Youth education, high school, or similar education | 63,784 (20.3) | 323,910 (20.6) |
| Higher education | 21,138 (6.7) | 154,881 (9.8) |
| Unknown | 133,782 (42.5) | 670,386 (42.6) |

Table values are given as n (%). CCI indicates Charlson Comorbidity Index.
*Categories of comorbidity were based on modified Charlson Comorbidity Index scores: 0 (normal), 1 (moderate), 2 (severe), and ≥3 (very severe).

**Table 2.** Cumulative incidence and hazard ratios of dementia in myocardial infarction patients and members of the general population comparison cohort.

| | Comparison cohort | | Myocardial infarction patients | | | |
|---|---|---|---|---|---|---|
| | **Events/No. at risk** | **Cumulative incidence % (95% CI)** | **Events/No. at risk** | **Cumulative incidence % (95% CI)** | **Hazard ratio controlled for matching factors* (95% CI)** | **Adjusted hazard ratio (95% CI)†** |
| **All-cause dementia** | 74,056/1,003,763 | 13.77 (13.63–13.92) | 11,334/209,754 | 8.68 (8.46–8.91) | 1.04 (1.02–1.07) | 1.01 (0.98–1.03) |
| **Alzheimer's disease** | 25,938/1,003,763 | 4.87 (4.77–4.96) | 3615/209,754 | 2.75 (2.63–2.88) | 0.93 (0.89–0.97) | 0.92 (0.88–0.95) |
| **Vascular dementia** | 9902/1,003,763 | 1.87 (1.80–1.93) | 2092/209,754 | 1.57 (1.49–1.66) | 1.43 (1.36–1.51) | 1.35 (1.28–1.43) |
| **Other dementias** | 38,216/1,003,763 | 7.30 (7.18–7.41) | 5627/209,754 | 4.47 (4.28–4.65) | 1.02 (0.99–1.05) | 0.98 (0.95–1.01) |

CI indicates confidence interval.

*Age, sex, and calendar year

†Controlled for matching factors by study design and adjusted for heart failure, stable angina pectoris, atrial fibrillation/atrial flutter, valvular heart disease, hypercholesterolemia, myocarditis, cardiomyopathy, hypertension, stroke, intermittent claudication, obesity, diabetes mellitus, chronic pulmonary disease, myxedema, alcoholism-related disease, head trauma, osteoarthritis, anemia, chronic kidney disease, depression, a modified Charlson Comorbidity Index score, income, and employment.

**Table 3.** Cumulative incidence and hazard ratios of dementia in myocardial infarction patients and members of the general population cohort, by procedures and complications after myocardial infarction.

| | **Adjusted hazard ratio (95% CI)*** | | | |
|---|---|---|---|---|
| | All-cause dementia | Alzheimer's disease | Vascular dementia | Other dementias |
| **Procedures and complications during admission for myocardial infarction** | | | | |
| **Coronary artery bypass grafting** | | | | |
| Yes | 1.43 (0.99–2.06) | 1.79 (0.97–3.31) | 3.99 (1.31–12.18) | 0.70 (0.36–1.36) |
| No | 1.01 (0.98–1.03) | 0.91 (0.88–0.95) | 1.35 (1.27–1.43) | 0.98 (0.95–1.01) |
| **Percutaneous coronary intervention** | | | | |
| Yes | 0.94 (0.87–1.01) | 0.99 (0.88–1.11) | 1.10 (0.91–1.33) | 0.85 (0.76–0.95) |
| No | 1.01 (0.99–1.04) | 0.91 (0.87–0.95) | 1.38 (1.30–1.46) | 0.99 (0.96–1.03) |
| **Pacemaker** | | | | |
| Yes | 0.99 (0.72–1.34) | 0.65 (0.36–1.16) | 3.38 (1.42–8.06) | 0.78 (0.48–1.25) |
| No | 1.01 (0.98–1.03) | 0.92 (0.88–0.95) | 1.35 (1.27–1.42) | 0.98 (0.95–1.01) |
| **Cardiogenic shock or pulmonary edema** | | | | |
| Yes | 0.88 (0.65–1.19) | 0.70 (0.37–1.29) | 1.20 (0.50–2.91) | 0.81 (0.52–1.25) |
| No | 1.01 (0.98–1.03) | 0.92 (0.88–0.95) | 1.35 (1.28–1.43) | 0.98 (0.95–1.01) |
| **Complications during first year after myocardial infarction** | | | | |
| **Stroke (ischemic or hemorrhagic)** | | | | |
| Yes | 1.39 (1.20–1.62) | 0.76 (0.55–1.04) | 4.48 (3.29–6.12) | 1.13 (0.90–1.41) |
| No | 1.00 (0.98–1.02) | 0.92 (0.88–0.96) | 1.30 (1.23–1.37) | 0.98 (0.94–1.01) |
| **Heart failure** | | | | |
| Yes | 1.06 (0.99–1.12) | 0.94 (0.84–1.05) | 1.39 (1.19–1.63) | 1.06 (0.97–1.16) |
| No | 1.00 (0.98–1.02) | 0.91 (0.88–0.95) | 1.35 (1.27–1.43) | 0.97 (0.93–1.00) |
| **Hypertension** | | | | |
| Yes | 1.00 (0.94–1.06) | 0.88 (0.79–0.98) | 1.36 (1.17–1.57) | 0.99 (0.90–1.08) |
| No | 1.01 (0.99–1.03) | 0.92 (0.88–0.96) | 1.36 (1.28–1.44) | 0.98 (0.94–1.01) |
| **Atrial fibrillation or flutter** | | | | |
| Yes | 1.02 (0.94–1.11) | 0.93 (0.80–1.07) | 1.55 (1.28–1.87) | 0.96 (0.86–1.08) |
| No | 1.01 (0.98–1.03) | 0.92 (0.88–0.95) | 1.35 (1.27–1.43) | 0.98 (0.94–1.01) |

CI indicates confidence interval.

*Controlled for matching factors by study design and adjusted for heart failure, stable angina pectoris, atrial fibrillation/atrial flutter, valvular heart disease, hypercholesterolemia, myocarditis, cardiomyopathy, hypertension, stroke, intermittent claudication, obesity, diabetes mellitus, chronic pulmonary disease, myxedema, alcoholism-related disease, head trauma, osteoarthritis, anemia, chronic kidney disease, depression, a modified Charlson Comorbidity Index score, income, and employment.

**Table 4.** Risk of dementia following myocardial infarction compared with the general population, by daily dose of loop diuretics (1995–2012) and number of heart failure admissions (1980–2012) during the first year after hospitalization for myocardial infarction.

| | **Adjusted hazard ratio (95% CI)*** | | | |
|---|---|---|---|---|
| | All-cause dementia | Alzheimer's disease | Vascular dementia | Other dementias |
| **Furosemide-equivalent dose** | | | | |
| Non-users (no loop diuretics) | 0.91 (0.85–0.98) | 0.93 (0.82–1.04) | 1.20 (1.01–1.43) | 0.81 (0.73–0.90) |
| Low-dose users† (≤40 mg/day) | 0.89 (0.79–1.01) | 0.73 (0.59–0.91) | 1.50 (1.11–2.02) | 0.88 (0.74–1.05) |
| Medium-dose users† (41– 80 mg/day) | 1.02 (0.92–1.13) | 0.95 (0.78–1.16) | 1.48 (1.13–1.95) | 0.96 (0.83–1.12) |
| High-dose users† (≥81 mg/day) | 1.03 (0.92–1.14) | 0.81 (0.65–1.00) | 1.27 (0.96–1.69) | 1.08 (0.94–1.25) |
| **Number of heart failure admissions** | | | | |
| 0 | 1.00 (0.97–1.02) | 0.92 (0.88–0.96) | 1.33 (1.25–1.41) | 0.96 (0.93–1.00) |
| 1 | 1.05 (0.97–1.13) | 0.93 (0.81–1.06) | 1.44 (1.21–1.72) | 1.04 (0.94–1.16) |
| 2 | 1.08 (0.92–1.27) | 0.80 (0.60–1.07) | 1.91 (1.26–2.90) | 1.09 (0.87–1.37) |
| ≥3 | 1.45 (1.18–1.78) | 0.97 (0.65–1.45) | 2.24 (1.21–4.14) | 1.56 (1.19–2.05) |

CI indicates confidence interval.

*Controlled for matching factors by study design and adjusted for heart failure, stable angina pectoris, atrial fibrillation/atrial flutter, valvular heart disease, hypercholesterolemia, myocarditis, cardiomyopathy, hypertension, stroke, intermittent claudication, obesity, diabetes mellitus, chronic pulmonary disease, myxedema, alcoholism-related disease, head trauma, osteoarthritis, anemia, chronic kidney disease, depression, a modified Charlson Comorbidity Index score, income, and employment.

†Restricted to patients with myocardial infarction who received a diagnosis of heart failure during first year after myocardial infarction or redeemed at least one prescription during their first year after myocardial infarction for (1) a beta blocker and (2) an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker.

## Figure Legend

**Figure 1.** Study flowchart. Population of first-time myocardial infarction survivors and members of the matched general population comparison cohort. *6,625 patients out of these 6,648 were censored because they had a myocardial infarction during the first year of follow-up, while the remainder were inactive individuals in the Danish Civil Registration System.

MI indicates myocardial infarction.

Source

All first-time MI patients
in Denmark, 1980–2012
N=321,842

History of dementia or mild cognitive impairment (N=6,931)

Study populaiton

Comparison cohort at index date (N=1,573,193)

MI patients at index date (N=314,911)

**Excluded during first year after MI**

Comparators of excluded MI patients (N=525,397)

Death during first year (N=32,200)

Dementia (N=4,493)

Emigration (N=692)

Incomplete observation (N=6,648)*

**Excluded during first year after MI**

Death during first year N=103,313

Dementia N=1,758

Emigration N=85

Incomplete observation N=1

Comparison cohort at 1 year of follow-up (N=1,003,763)

MI patients at 1 year of follow-up (N=209,754)

# Higher Risk of Vascular Dementia in Myocardial Infarction Survivors

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# SUPPLEMENTAL MATERIAL

**Supplemental Table 1**. *International Classification of Diseases* codes used in the study.

| | ICD-8 codes | ICD-10 codes | Procedure codes | ATC codes |
|---|---|---|---|---|
| **Cardiovascular diseases** | | | | |
| Myocardial infarction | 410 | I21 | | |
| ST-segment myocardial infarction (STEMI) | N/A | I211B, I210B, I213 | | |
| Non-STEMI | N/A | I211A, I210A, I214 | | |
| Heart failure | 427.09, 427.10, 427.11, 427.19, 428.99,782.49 | I50, I11.0, I13.0, I13.2 | | |
| Angina pectoris | 413 | I20 (except I20.0), I25.1, I25.9 | | |
| Atrial fibrillation or flutter | 427.93, 427.94 | I48 | | |
| Valvular heart disease | 394-398 | I05, I06, I07, I08.0, I09.8, I34-I37, I39.0, I39.3, I51.1A, Q22 | | |
| Hypercholesterolemia | 272.00 | E780 | | |
| Myocarditis | 422 | I40, I41, I090, I514 | | |
| Cardiomyopathy | 425 | I42-I43 (exluding I42.6) | | |
| Hypertension | 400-404 | DI10-DI15, I67.4 | | |
| Stroke (ischemic and intracerebral) | 431, 433-434 | I61, I63-I64 | | |
| Intermittent claudication | 443.89–443.99 | I73.9 | | |
| Cardiogenic shock and pulmonary edema | 427.10, 427.11 | J81, I501B, R570 | | |
| **Non-cardiovascular diseases** | | | | |
| Obesity | 277 | E65-E68 | | |
| Diabetes mellitus | 249, 250 (excluding 249.02, 250.02) | E10 (excluding E10.2), E11 (excluding E11.2), H36.0 | | |
| Chronic pulmonary disease | 490-493; 515-518 | J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3 | | |
| Myxedema | 244 | E00, E03, E890 | | |
| Alcoholism-related diseases | 980, 291.09-291.99, 303.09-303.99, 571.09-571.11, 577.10 | F10 (except F10.0), G31.2, G62.1, G72.1, I 42.6, K29.2, K86.0, Z72.1 | | |
| Head trauma | 800-803, 850-854, 810-874 | S00-S09 | | |
| Osteoarthritis (patients often use NSAIDs which therefore may modify the risk of dementia). Other connective tissue diseases associated with use of NSAIDs are included in the CCI index | 713 | M15-M19 | | |
| Anemia | 280-281, 283-285 | D50-55, D59, D61-D64 | | |
| Chronic kidney disease | 249.02, 250.02, 753.10-753.19, 582-584, 590.09, 593.20, 792 | E102, E112, E142, N03, N05, N110, N14, N16, N18-N19, N269, Q611-Q614 | | |
| Depression | 296.09, 296.29, 298.09, 300.49 | F32-F33 | | |

| | | | | |
|---|---|---|---|---|
| **Outcomes** | | | | |
| Alzheimer's disease | 290.10, 290.09 | F00 series (includes F00.0x, F00.1x, F00.2x, and F00.9x); G30 (includes G30, G30.0, 30.1, 30.8, 30.9) | | |
| Vascular dementia | 293.09, 293.19 | F01 series (includes F01.0x, F01.1x, F01.2x, F01.3x, F01.8x, & F01.9x) | | |
| Other dementias | 094.19 and 292.09, 290.11, 290.18, 290.19, | F02 series; F03 series; F1x.73 series (F10.73 through F19.73); G23.1; G31.0, G31.1, G31.8B, G31.8E, G31.85 | | |
| Diagnoses related to dementia (mild cognitive impairment and amnestic syndromes) | 291.19 | F04, F04.9, F05.1, F06.7 and F06.7x; F1x.6 (F10.6, F18.6, F19.6) | | |
| **Procedures during admission** | | | | |
| CABG | | | Before 1996: 30009, 30019, 30029, 30039, 30049, 30059, 30069, 30079, 30089, 30099, 30109, 30119, 30120, 30129, 30139, 30149, 30159, 30169, 30179, 30189, 30199, 30200<br>After 1996: KFNA-E, KFNH20 | |
| Percutaneous coronary intervention | | | Before 1996: 30350, 30354, 30240<br>After 1996: KFNG, KFNF | |
| Pacemaker | | | Before 1996: 30930, 32140, 32199, 32490<br>After 1996: BFCA | |
| **Heart failure drugs** | | | | |
| Furosemide | | | | C03CA01, C03CB01 |
| Bumetanide | | | | C03CA02, C03CB02 |
| Angiotensin converting enzyme inhibitor | | | | C09A, C09B |
| Angiotensin receptor blocker | | | | C09C, C09D |
| Beta blocker | | | | C07 |

**Supplemental Table 2.** Modified Charlson Comorbidity Index conditions.

| Disease | Weight | |
|---|---|---|
| Peripheral vascular disease | 1 | ICD-8: 440, 441, 442, 443, 444, 445; ICD-10: I70, I71, I72, I73, I74, I77 |
| Connective tissue disease | | ICD-8: 712, 716, 734, 446, 135.99; ICD-10: M05, M06, M08, M09, M30, M31, M32, M33, M34, M35, M36, D86 |
| Ulcer disease | | ICD-8: 530.91, 530.98, 531-534; ICD-10: K22.1, K25-K28 |
| Mild liver disease | | ICD-8: 571, 57301, 57304; ICD-10:B18, K70.0-K70.3, K70.9, K71, K73, K74, K76.0 |
| Hemiplegia | 2 | ICD-8: 344; ICD-10: G81, G82 |
| Non-metastatic solid tumor | | ICD-8: 140-194; ICD-10: C00-C75 |
| Leukemia | | ICD-8: 204-207; ICD-10: C91-C95 |
| Lymphoma | | ICD-8: 200-203, 275.59; ICD-10: C81-C85, C88, C90, C96 |
| Moderate to severe liver disease | 3 | ICD-8: 070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00-456.09; ICD-10: B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85 |
| Metastatic cancer | 6 | ICD-8: 195-198, 199; ICD-10: C76-C80 |
| AIDS | | ICD-8: 079.83; ICD-10: B21-B24 |

**Supplemental Table 3.** Characteristics of myocardial infarction survivors and members of the general population comparison cohort at 1 year after myocardial infarction, Denmark, 1980-2012.

| | Myocardial infarction cohort (n=209,754) | Comparison cohort (n=1,003,763) |
|---|---|---|
| **Male** | 137,967 (65.8) | 661419 (65.9) |
| **Age, years** | | |
| <60 | 62,180 (29.6) | 307491 (30.6) |
| 60–69 | 58,993 (28.1) | 287568 (28.6) |
| 70–79 | 57,068 (27.2) | 270457 (26.9) |
| ≥80 | 31,513 (15.0) | 138247 (13.8) |
| Median (25th–75th percentile) | 66.9 (57.5–75.5) | 66.4 (57.2–74.9) |
| **Decade of diagnosis / index date** | | |
| 1980−1989 | 67,362 (32.1) | 322973 (32.2) |
| 1990−1999 | 60,379 (28.8) | 288802 (28.8) |
| 2000−2012 | 82,013 (39.1) | 391988 (39.1) |
| **Comorbidity** | | |
| Heart failure | 7689 (3.7) | 17528 (1.7) |
| Angina pectoris | 20,984 (10.0) | 34592 (3.4) |
| Atrial fibrillation or flutter | 7919 (3.8) | 27052 (2.7) |
| Valvular heart disease | 2977 (1.4) | 7778 (0.8) |
| Hypercholesterolemia | 4491 (2.1) | 9758 (1.0) |
| Hypertension | 22,821 (10.9) | 57239 (5.7) |
| Stroke | 7276 (3.5) | 23039 (2.3) |
| Intermittent claudication | 2714 (1.3) | 4653 (0.5) |
| Obesity | 5349 (2.6) | 12586 (1.3) |
| Diabetes mellitus | 13,748 (6.6) | 30504 (3.0) |
| Chronic pulmonary disease | 12,191 (5.8) | 39565 (3.9) |
| Myxedema | 1545 (0.7) | 4615 (0.5) |
| Alcoholism-related diseases | 3787 (1.8) | 15669 (1.6) |
| Head trauma | 21,395 (10.2) | 97415 (9.7) |
| Osteoarthritis | 16,910 (8.1) | 65029 (6.5) |
| Anemia | 4336 (2.1) | 14248 (1.4) |
| Chronic kidney disease | 3518 (1.7) | 6291 (0.6) |
| Depression | 5598 (2.7) | 21831 (2.2) |
| **Modified CCI score*** | | |
| Normal | 175,448 (83.6) | 884071 (88.1) |
| Moderate | 19,511 (9.3) | 55963 (5.6) |
| Severe | 11,430 (5.4) | 51629 (5.1) |
| Very severe | 3365 (1.6) | 12100 (1.2) |
| **Income** | | |
| Low | 44,295 (21.1) | 195417 (19.5) |
| Intermediate | 53,391 (25.5) | 231083 (23.0) |
| High | 55,461 (26.4) | 257582 (25.7) |
| Very high | 56,399 (26.9) | 314403 (31.3) |
| Missing | 208 (0.1) | 5278 (0.5) |
| **Employment** | | |
| Employed | 73,345 (35.0) | 391082 (39.0) |
| Early retirement | 26,872 (12.8) | 117882 (11.7) |
| Unemployed | 6277 (3.0) | 26461 (2.6) |
| State pensioner | 102,758 (49.0) | 456962 (45.5) |
| Missing | 502 (0.2) | 11376 (1.1) |
| **Education** | | |
| Basic education or primary school | 73,249 (34.9) | 311478 (31.0) |
| Youth education, high school, or similar education | 52,482 (25.0) | 257187 (25.6) |
| Higher education | 17,709 (8.4) | 124182 (12.4) |
| Unknown | 66,314 (31.6) | 310916 (31.0) |

Table values are given as n (%). CCI indicates Charlson Comorbidity Index.

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

**Supplemental Table 4.** Risk of dementia following myocardial infarction compared with the general population cohort, by sex and age.

| | Adjusted hazard ratio (95% CI)* | | | |
|---|---|---|---|---|
| | All-cause dementia | Alzheimer's disease | Vascular dementia | Other dementias |
| Male | 1.00 (0.97–1.04) | 0.93 (0.88–0.98) | 1.32 (1.23–1.42) | 0.96 (0.92–1.00) |
| Female | 1.01 (0.98–1.05) | 0.91 (0.86–0.96) | 1.41 (1.29–1.55) | 1.01 (0.96–1.06) |
| <60 years | 1.19 (1.11–1.27) | 1.02 (0.89–1.15) | 1.61 (1.38–1.88) | 1.17 (1.07–1.28) |
| 60-69 years | 1.07 (1.02–1.12) | 0.96 (0.89–1.04) | 1.39 (1.25–1.54) | 1.05 (0.99–1.12) |
| 70-79 years | 0.98 (0.94–1.02) | 0.92 (0.87–0.98) | 1.32 (1.20–1.44) | 0.93 (0.88–0.99) |
| 80+ years | 0.88 (0.84–0.92) | 0.80 (0.74–0.87) | 1.18 (1.04–1.35) | 0.87 (0.81–0.93) |

CI indicates confidence interval.

*Controlled for matching factors by study design and adjusted for heart failure, stable angina pectoris, atrial fibrillation/atrial flutter, valvular heart disease, hypercholesterolemia, myocarditis, cardiomyopathy, hypertension, stroke, intermittent claudication, obesity, diabetes mellitus, chronic pulmonary disease, myxedema, alcoholism-related disease, head trauma, osteoarthritis, anemia, chronic kidney disease, depression, a modified Charlson Comorbidity Index score, income, and employment.

**Supplemental Table 5**. Risk of dementia following myocardial infarction compared with the general population cohort, by history of comorbidity.

| | Adjusted hazard ratio (95% CI)* | | | |
|---|---|---|---|---|
| | All-cause dementia | Alzheimer's disease | Vascular dementia | Other dementias |
| **Angina pectoris** | | | | |
| Yes | 0.90 (0.84–0.97) | 0.83 (0.73–0.95) | 1.09 (0.92–1.32) | 0.89 (0.81–0.99) |
| No | 1.01 (0.99–1.03) | 0.93 (0.89–0.96) | 1.31 (1.23–1.39) | 0.98 (0.95–1.01) |
| **Atrial fibrillation or flutter** | | | | |
| Yes | 0.96 (0.87–1.06) | 0.80 (0.65–0.96) | 1.07 (0.85–1.35) | 1.01 (0.89–1.17) |
| No | 1.00 (0.98–1.03) | 0.93 (0.89–0.96) | 1.30 (1.24–1.38) | 0.97 (0.94–1.00) |
| **Valvular heart disease** | | | | |
| Yes | 1.05 (0.87–1.25) | 0.96 (0.69–1.30) | 1.22 (0.80–1.89) | 1.05 (0.79–1.36) |
| No | 1.00 (0.98–1.02) | 0.92 (0.89–0.96) | 1.29 (1.23–1.37) | 0.97 (0.94–1.01) |
| **Hypertension** | | | | |
| Yes | 0.94 (0.88–1.01) | 0.79 (0.69–0.90) | 1.10 (0.95–1.30) | 0.96 (0.86–1.07) |
| No | 1.01 (0.99–1.03) | 0.94 (0.90–0.97) | 1.31 (1.25–1.38) | 0.97 (0.94–1.01) |
| **Hypercholesterolemia** | | | | |
| Yes | 0.92 (0.76–1.12) | 0.93 (0.65–1.27) | 0.77 (0.49–1.25) | 0.97 (0.73–1.29) |
| No | 1.00 (0.98–1.03) | 0.92 (0.89–0.96) | 1.30 (1.23–1.38) | 0.97 (0.95–1.01) |
| **Obesity** | | | | |
| Yes | 0.90 (0.77–1.07) | 0.75 (0.55–1.03) | 0.99 (0.69–1.40) | 0.97 (0.77–1.24) |
| No | 1.00 (0.98–1.03) | 0.93 (0.89–0.96) | 1.30 (1.24–1.37) | 0.97 (0.95–1.01) |
| **Diabetes mellitus** | | | | |
| Yes | 1.08 (0.98–1.18) | 0.89 (0.73–1.07) | 1.34 (1.11–1.63) | 1.08 (0.96–1.24) |
| No | 1.00 (0.98–1.02) | 0.93 (0.89–0.96) | 1.29 (1.22–1.36) | 0.97 (0.94–1.00) |
| **Chronic pulmonary disease** | | | | |
| Yes | 1.01 (0.91–1.11) | 0.93 (0.79–1.12) | 1.46 (1.13–1.85) | 0.95 (0.82–1.08) |
| No | 1.00 (0.98–1.03) | 0.92 (0.89–0.95) | 1.29 (1.22–1.36) | 0.98 (0.95–1.01) |
| **Myxedema** | | | | |
| Yes | 0.90 (0.71–1.16) | 0.87 (0.54–1.36) | 0.99 (0.50–1.81) | 0.90 (0.64–1.28) |
| No | 1.00 (0.98–1.03) | 0.92 (0.89–0.96) | 1.29 (1.23–1.37) | 0.97 (0.95–1.01) |
| **Alcoholism-related disease** | | | | |
| Yes | 0.96 (0.82–1.15) | 0.82 (0.52–1.27) | 1.03 (0.64–1.62) | 0.98 (0.80–1.20) |
| No | 1.00 (0.98–1.03) | 0.93 (0.89–0.96) | 1.30 (1.24–1.37) | 0.97 (0.95–1.01) |
| **Head trauma** | | | | |
| Yes | 0.97 (0.90–1.03) | 0.94 (0.83–1.06) | 1.25 (1.07–1.46) | 0.91 (0.83–0.99) |
| No | 1.01 (0.99–1.03) | 0.92 (0.88–0.95) | 1.30 (1.23–1.37) | 0.98 (0.95–1.02) |
| **Osteoarthritis** | | | | |
| Yes | 0.93 (0.87–1.00) | 0.85 (0.75–0.96) | 1.10 (0.92–1.33) | 0.93 (0.84–1.02) |
| No | 1.01 (0.99–1.03) | 0.93 (0.89–0.96) | 1.31 (1.25–1.39) | 0.98 (0.95–1.01) |
| **Anemia** | | | | |
| Yes | 1.09 (0.95–1.26) | 0.94 (0.70–1.27) | 1.44 (1.04–2.01) | 1.06 (0.88–1.28) |
| No | 1.00 (0.98–1.02) | 0.92 (0.89–0.95) | 1.29 (1.23–1.36) | 0.97 (0.94–1.00) |
| **Chronic kidney disease** | | | | |
| Yes | 0.93 (0.74–1.17) | 1.23 (0.75–1.88) | 0.95 (0.55–1.64) | 0.81 (0.58–1.12) |
| No | 1.00 (0.98–1.03) | 0.92 (0.88–0.95) | 1.30 (1.24–1.37) | 0.98 (0.95–1.01) |
| **Modified CCI score** | | | | |
| Normal | 1.01 (0.99–1.03) | 0.94 (0.90–0.97) | 1.28 (1.21–1.36) | 0.98 (0.95–1.02) |
| Moderate | 0.98 (0.91–1.05) | 0.87 (0.75–0.99) | 1.39 (1.19–1.66) | 0.92 (0.83–1.02) |
| Severe | 0.94 (0.86–1.03) | 0.82 (0.70–0.96) | 1.22 (0.98–1.54) | 0.94 (0.84–1.07) |
| Very severe | 0.98 (0.81–1.17) | 0.82 (0.56–1.16) | 1.57 (0.99–2.35) | 0.92 (0.72–1.19) |

CCI indicates Charlson Comorbidity Index and CI indicates confidence interval.

*Adjusted for age, sex, calendar year, heart failure, stable angina pectoris, atrial fibrillation/atrial flutter, valvular heart disease, hypercholesterolemia, myocarditis, cardiomyopathy, hypertension, stroke, intermittent claudication, obesity, diabetes mellitus, chronic pulmonary disease, myxedema, alcoholism-related disease, head trauma, osteoarthritis, anemia, chronic kidney disease, depression, a modified Charlson Comorbidity Index score, income, and employment (except the stratified variable).

**Supplemental Table 6**. Risk of dementia following myocardial infarction compared with the general population cohort, by calendar periods and type of myocardial infarction diagnosis.

| | Adjusted hazard ratio (95% CI)* | | | |
|---|---|---|---|---|
| | All-cause dementia | Alzheimer's disease | Vascular dementia | Other dementias |
| **1980-1994**† | 1.00 (0.95–1.05) | 0.90 (0.83–0.96) | 1.53 (1.36–1.72) | 0.95 (0.88–1.03) |
| **1995-2012**† | 0.97 (0.94–1.00) | 0.89 (0.83–0.95) | 1.29 (1.18–1.41) | 0.93 (0.89–0.98) |
| **Primary diagnosis of myocardial infarction** | 0.99 (0.97–1.02) | 0.91 (0.87–0.95) | 1.32 (1.24–1.40) | 0.97 (0.93–1.00) |
| **Secondary diagnosis of myocardial infarction** | 1.14 (1.05–1.22) | 1.01 (0.89–1.15) | 1.76 (1.46–2.13) | 1.07 (0.96–1.20) |

CI indicates confidence interval.
*Controlled for matching factors by study design and adjusted for heart failure, stable angina pectoris, atrial fibrillation/atrial flutter, valvular heart disease, hypercholesterolemia, myocarditis, cardiomyopathy, hypertension, stroke, intermittent claudication, obesity, diabetes mellitus, chronic pulmonary disease, myxedema, alcoholism-related disease, head trauma, osteoarthritis, anemia, chronic kidney disease, depression, a modified Charlson Comorbidity Index score, income, and employment.
†1–10 year adjusted hazard ratios to allow follow-up during 1995–2012.

**Supplemental Table 7**. Risk of dementia following myocardial infarction compared with the general population cohort, restricted to different socioeconomic status levels in both cohorts.

| | Adjusted hazard ratio (95% CI)* | | | |
|---|---|---|---|---|
| | All-cause dementia | Alzheimer's disease | Vascular dementia | Other dementias |
| **Income** | | | | |
| Low | 0.97 (0.93–1.01) | 0.88 (0.82–0.94) | 1.34 (1.20–1.51) | 0.94 (0.89–1.00) |
| Intermediate | 0.98 (0.94–1.01) | 0.90 (0.85–0.96) | 1.25 (1.15–1.37) | 0.95 (0.90–1.00) |
| High | 1.01 (0.97–1.05) | 0.93 (0.86–1.00) | 1.23 (1.12–1.38) | 0.99 (0.94–1.06) |
| Very high | 1.07 (1.02–1.13) | 1.00 (0.92–1.09) | 1.36 (1.21–1.56) | 1.03 (0.97–1.12) |
| **Employment** | | | | |
| Employed | 1.11 (1.06–1.17) | 1.04 (0.96–1.12) | 1.41 (1.27–1.59) | 1.07 (1.00–1.14) |
| Early retirement | 1.06 (1.00–1.13) | 0.94 (0.83–1.05) | 1.27 (1.09–1.48) | 1.07 (0.98–1.18) |
| Unemployed | 1.02 (0.87–1.21) | 0.96 (0.69–1.30) | 1.52 (1.05–2.32) | 0.92 (0.73–1.15) |
| State pensioner | 0.96 (0.93–0.98) | 0.88 (0.84–0.92) | 1.24 (1.17–1.34) | 0.94 (0.90–0.97) |
| **Education** | | | | |
| Basic education, primary school | 1.00 (0.97–1.04) | 0.91 (0.85–0.97) | 1.24 (1.14–1.38) | 0.99 (0.94–1.04) |
| Youth education, high school or similar education | 1.07 (1.02–1.12) | 0.95 (0.86–1.03) | 1.41 (1.26–1.59) | 1.05 (0.98–1.13) |
| Higher education | 1.02 (0.93–1.11) | 0.85 (0.72–0.98) | 1.42 (1.17–1.73) | 1.04 (0.92–1.17) |
| Unknown | 0.97 (0.94–1.00) | 0.91 (0.86–0.97) | 1.27 (1.17–1.38) | 0.94 (0.90–0.98) |

CI indicates confidence interval.

*Adjusted for age, sex, calendar year, heart failure, stable angina pectoris, atrial fibrillation/atrial flutter, valvular heart disease, hypercholesterolemia, myocarditis, cardiomyopathy, hypertension, stroke, intermittent claudication, obesity, diabetes mellitus, chronic pulmonary disease, myxedema, alcoholism-related disease, head trauma, osteoarthritis, anemia, chronic kidney disease, depression, a modified Charlson Comorbidity Index score, income, and employment (except the stratified variable).

**Supplemental Table 8**. Sensitivity analyses of the association between myocardial infarction and risk of dementia.

| | Adjusted hazard ratio (95% CI)* | | | |
|---|---|---|---|---|
| | All-cause dementia | Alzheimer's disease | Vascular dementia | Other dementias |
| **Excluding initial years of follow-up (years since diagnosis)** | | | | |
| 2-35 years | 1.01 (0.99–1.03) | 0.93 (0.89–0.96) | 1.35 (1.27–1.43) | 0.98 (0.94–1.01) |
| 3-35 years | 1.02 (0.99–1.05) | 0.94 (0.90–0.98) | 1.35 (1.27–1.44) | 0.98 (0.95–1.02) |
| 5-35 years | 1.03 (1.00–1.06) | 0.95 (0.90–1.00) | 1.35 (1.26–1.45) | 1.00 (0.96–1.04) |
| 10-35 years | 1.06 (1.02–1.10) | 0.97 (0.90–1.04) | 1.33 (1.21–1.46) | 1.05 (0.99–1.11) |
| **Including *International Classification of Diseases* code F03 (unspecified dementia) in the definition of Alzheimer's disease** | – | 0.96 (0.93–0.98) | – | – |
| **Additionally adjusting for education** | 1.01 (0.98–1.03) | 0.92 (0.88–0.95) | 1.35 (1.28–1.43) | 0.98 (0.94–1.01) |
| **Disaggregating the follow-up** | | | | |
| 1-10 years | 0.98 (0.95–1.01) | 0.89 (0.85–0.94) | 1.37 (1.28–1.46) | 0.94 (0.90–0.98) |
| 11-20 years | 1.06 (1.02–1.11) | 0.97 (0.89–1.05) | 1.34 (1.21–1.49) | 1.04 (0.98–1.11) |
| 21-35 years | 1.06 (0.97–1.16) | 0.98 (0.84–1.13) | 1.25 (1.00–1.57) | 1.07 (0.95–1.22) |
| **Type of myocardial infarction (from 1995–2012)** | | | | |
| STEMI | 0.91 (0.83–1.01) | 0.88 (0.75–1.04) | 1.46 (1.13–1.88) | 0.82 (0.71–0.96) |
| Non-STEMI | 1.01 (0.95–1.07) | 0.95 (0.86–1.05) | 1.21 (1.05–1.39) | 1.00 (0.92–1.08) |
| Unspecified | 1.01 (0.99–1.04) | 0.91 (0.87–0.95) | 1.38 (1.30–1.47) | 0.99 (0.95–1.02) |

CI indicates confidence interval.

*Controlled for matching factors by study design and adjusted for heart failure, stable angina pectoris, atrial fibrillation/atrial flutter, valvular heart disease, hypercholesterolemia, myocarditis, cardiomyopathy, hypertension, stroke, intermittent claudication, obesity, diabetes mellitus, chronic pulmonary disease, myxedema, alcoholism-related disease, head trauma, osteoarthritis, anemia, chronic kidney disease, depression, a modified Charlson Comorbidity Index score, income, and employment.