# Depression, stroke, and dementia in patients with myocardial infarction

— Studies of risk and prognosis —

PhD dissertation

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## Thesis papers

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II. Sundbøll J, Schmidt M, Adelborg K, Pedersen L, Bøtker HE, Videbech P, Sørensen HT. Impact of pre-admission depression on mortality following myocardial infarction. *Br J Psychiatry* 2017;210:356–361.

III. Sundbøll J, Horváth-Puhó E, Schmidt M, Pedersen L, Henderson VW, Bøtker HE, Sørensen HT. Long-term Risk of Stroke in Myocardial Infarction Survivors: Thirty-Year Population-Based Cohort Study. *Stroke* 2016;47:1727-1733.

IV. Sundbøll J, Horváth-Puhó E, Adelborg K, Schmidt M, Pedersen L, Bøtker HE, Henderson VW, Sørensen HT. Long-term Risk of Dementia in Myocardial Infarction Survivors. Submitted.

## Abbreviations

| | |
|---|---|
| CABG | Coronary artery bypass grafting |
| CI | Confidence interval |
| DAPT | Dual antiplatelet therapy |
| DNPR | Danish National Patient Registry |
| DPCR | Danish Psychiatric Central Research Register |
| ECG | Electrocardiogram |
| HR | Hazard ratio |
| ICH | Intracerebral hemorrhage |
| MI | Myocardial infarction |
| MRR | Mortality rate ratio |
| NSTEMI | Non-ST-segment elevation myocardial infarction |
| PCI | Percutaneous coronary intervention |
| PPV | Positive predictive value |
| SAH | Subarachnoid hemorrhage |
| SRR | Stroke rate ratio |
| STEMI | ST-segment elevation myocardial infarction |
| WHO | World Health Organization |

# Contents

# 1. Thesis structure

This dissertation examines outcomes after myocardial infarction (MI), focusing on the relation with cerebral diseases including depression, stroke, and dementia.

Four studies form the basis of the dissertation and are referred to throughout the text by Roman numerals (I–IV). Studies II–IV are registry-based and, as such, dependent on adequate data quality in the registries used, primarily the Danish National Patient Registry (DNPR). Therefore, study I focused on examining the validity of all major cardiovascular diagnoses in the DNPR, as these codes are used extensively in the subsequent studies II–IV. Throughout the dissertation, study I is described separately, whereas studies II–IV are described together where appropriate.

The dissertation comprises nine chapters. The introduction describes the epidemiology, definition, and pathophysiology of MI and, in light of a review of existing literature, the relation with exposures and outcomes of studies II–IV. The next three chapters describe the methods and results of the studies, followed by a discussion of our findings in relation to the existing literature, methodological considerations, and perspectives. The final chapters include summaries in English and Danish, references, and appendices, including full versions of the thesis papers.

# 2. Introduction

## 2.1 The heart-brain relation

The heart and brain are vital organs connected physically by the vagus nerve and through the bloodstream, where emboli and chemical substances can travel. Sir William Harvey observed more than 350 years ago that negative emotions adversely affect the heart.[1] Scientific literature supporting this notion was sparse until the 1930s, when two longitudinal studies of psychiatric patients demonstrated that depression may correlate with early death, particularly from cardiovascular disease.[2,3] Today, we know that mental diseases and emotions have the potential to adversely affect the heart, as exemplified by broken heart syndrome, which mimics MI and is associated with emotional stress.[4] Conversely, heart diseases, such as atrial fibrillation, can affect the brain through embolization of intracardiac thrombi, causing ischemic stroke.[5-8] This dissertation examines how a disease of the brain, depression, can affect the prognosis of a heart disease, MI, and, conversely, how MI is associated with subsequent risk of stroke and dementia.

## 2.2 Epidemiology of myocardial infarction

The epidemiology of MI during the second half of the twentieth century exhibits a bimodal pattern, with a rise in incidence up to 1977,[9] followed by a continuous decline until today.[10] However, the burden of coronary artery disease continues to constitute a major global health problem. Coronary artery disease, which precedes MI, is the single most frequent cause of death globally with seven million deaths each year (13% of all deaths) according to the World Health Organization (WHO).[11] In Denmark, approximately 8,000 patients are admitted annually with MI.[10] The incidence has declined by 50% in Denmark during the past few decades,[10] primarily owing to a general improvement in primary prevention.[12] Reduction in the rate of smoking is presumably the single most important contributor to the declining incidence[13] because the prevalence of obesity and diabetes has increased concomitantly.[12,14] The decreasing incidence of MI has been consistent since the early 1980s, apart from a transient increase between 2000 and 2004.[10] The peak around 2002 was presumably attributable to a redefinition of MI in 2000 including sensitive biochemical markers of myocardial injury, such as troponins, which are now a

cornerstone of the diagnostic criteria.[15] Not only the incidence, but also the 30-day and 1-year mortality following MI, decreased by approximately 50% during the same period,[10] leading to an overall increase in the prevalence of MI survivors.[9] The decline in MI mortality is estimated to be equally attributed to primary prevention and improved management of MI.[14,16]

The improved survival after MI implies an increased likelihood of developing chronic medical conditions. The proportion of adults with at least one chronic disease is roughly 90% in individuals older than 65 years of age,[17] who comprise more than half of patients with MI.[18] Therefore, it is increasingly pertinent to identify the risk of age-related diseases (*e.g.*, stroke and dementia) and determinants of increased mortality (*e.g.*, depression) to enable directed tertiary prevention in the ageing population of MI survivors.

### 2.3 Definition of myocardial infarction

In contrast to the previous WHO definition of MI from 1971,[19] the revised definition in 2000 (updated in 2007[20] and 2012[21]) includes myocardial injury as an absolute criterion.[15]
The term 'acute MI' is now used only when there is evidence of myocardial necrosis and the clinical setting suggests acute myocardial ischemia. Under these conditions, the following definition of MI is now universally applicable[21]:

- Detection of an increase and/or decrease in a cardiac biomarker (preferably troponins) with at least one value above the 99th percentile upper reference limit and with ≥1 of the following:
    - Symptoms of ischemia (*e.g.*, chest pain, dyspnea, anxiety, nausea)
    - Electrocardiographic changes indicating new ischemia (new ST-T changes or new left bundle branch block)
    - Development of pathological Q waves on the electrocardiogram (ECG)
    - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
    - Identification of an intracoronary thrombus by angiography or autopsy

Based on electrocardiographic features, MI is divided into ST-segment elevation MI (STEMI) and non-STEMI (NSTEMI).[21] During the past two decades, the proportion of patients with STEMI has steadily declined, and the number with NSTEMI has slightly increased[22] to currently comprise 60–75% of all MIs.[22] This development was presumably prompted by the new, more sensitive definition of MI in 2000.[15] MI is also classified based on the pathophysiology leading to the MI. Type 1 is caused by plaque rupture with thrombus formation, whereas Type 2 is caused by an imbalance between the myocardial oxygen supply and demand.[21] Type 3 is death presumably caused by MI, but without an available cardiac biomarker. Types 4–5 are MIs related to cardiac procedures (percutaneous coronary intervention [PCI], stent thrombosis, or coronary artery bypass grafting [CABG]).[21]

### 2.4 Pathophysiology of myocardial infarction

The pathophysiology underlying the clinical syndrome of MI was first described in Denmark in 1930 by Warburg.[23] The pathophysiology leading to MI typically starts with the formation of an atherosclerotic plaque, which may become vulnerable over the course of several years. A vulnerable plaque is characterized by a thin fibrotic cap covering lipid-laden foam cells. Most MIs result from a rupture of the vulnerable plaque followed by thrombus formation (type I MI).[21,24] Upon rupture, the thrombogenic content of the plaque is exposed, causing platelet activation, initiation of the coagulation cascade, thrombus formation, and eventually occlusion of the coronary artery. Downstream embolization of atherosclerotic debris may contribute to the rupture of additional vulnerable plaques, causing the formation of several culprit lesions.[25] When the resulting myocardial ischemia is prolonged, the myocytes ultimately necrotize and release troponin into the bloodstream. Thus, the infarcted myocardium is unveiled by elevated troponin levels in the peripheral blood, a mainstay in the diagnosis of MI.[21] The factors influencing final infarct size include degree of coronary artery occlusion (total *vs*. subtotal), duration of occlusion, and volume of myocardium supplied.[21] The presence of collateral circulation between coronary arteries has also been associated with improved survival after an MI.[26] Collaterals develop and expand proportionally with the level of coronary artery stenosis. The established collateral

circulation connects epicardial coronary arteries, providing an alternative route for the blood supply to the myocardium at risk.[26]

### 2.5 Risk factors and prognostic factors for myocardial infarction

The rise in incidence of MI after World War II reached epidemic proportions in the US, prompting the initiation of the Framingham Heart Study in 1948.[27] Studies from this initiative identified important modifiable risk factors for MI, including a family history of MI, hypercholesterolemia, hypertension, diabetes, smoking, abdominal obesity, and physical inactivity.[27,28]

According to the Global Registry of Acute Coronary Events (GRACE) hospital discharge prediction model, important prognostic factors for 6-month mortality after MI include older age, history of congestive heart failure or MI, elevated resting heart rate at presentation, lower systolic blood pressure at presentation, ST-segment depression on presenting ECG, elevated initial serum creatinine levels, elevated initial cardiac biomarker levels, and not having PCI.[29] These prognostic factors have been demonstrated to also accurately predict mortality beyond 6 months after MI.[30]

### 2.6 Literature review

To review the existing literature on research topics contained in this dissertation, we searched Medline using Medical Subject Headings (MeSH), creating the search builder from "AND/OR" combinations of Major or non-Major MeSH terms. All searches were restricted to papers in English, apart from the search for study I, which also included papers in Danish. Titles and abstracts were reviewed and relevant papers selected according to the PICO criteria (population, intervention/exposure, comparison, and outcome).[31] Furthermore, for each selected paper, we reviewed the reference lists and related papers highlighted by Medline to screen for further relevant publications. The search for study I (validation study) did not identify all relevant papers because validation is often included as a part of studies with another primary aim. Therefore, for study I, we included the majority of papers from the reference lists of papers identified in the search and included additional studies known to us beforehand. An overview of the literature is provided in Tables 1–4, and search terms are provided after Table 4.

## Table 1. Summary of literature review (study I).

| Study I: Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry | | | |
|---|---|---|---|
| **Author, journal, year** | **ICD codes/algorithm, contact type, diagnosis type** | **Study period, reference standard, sample size, outcome** | **Results*, limitations** |
| ***Diagnosis: Myocardial infarction*** | | | |
| **- Coloma *et al.*[32]**<br>- *BMJ Open*<br>- 2013 | - ICD-10: I21<br>- IN<br>- Primary diagnoses | - 2000–2009<br>- Medical record review<br>- N=148<br>- PPV | - PPV = 100 (97.5–100)<br>- NPV, sensitivity, and specificity not included |
| **- Thygesen *et al.*[33]**<br>- *BMC Med Res Methodol*<br>- 2011 | - ICD-10: I21, I22, I23<br>- IN/OUT<br>- Primary diagnoses | - 1998–2007<br>- Discharge summaries<br>- N=50<br>- PPV | - PPV = 98.0 (89.5–99.7)<br>- NPV, sensitivity, and specificity not included; review restricted to discharge summaries |
| **- Joensen *et al.*[34]**<br>- *J Clin Epidemiol*<br>- 2009 | - ICD-8: 410; ICD-10: I21<br>- IN/OUT/ED<br>- Primary and secondary diagnoses | - 1993–2003<br>- Medical record review, discharge summary, blood tests, ECG<br>- N=1072<br>- PPV | - PPV(IN/OUT/ED) = 81.9 (79.5–84.1)<br>- PPV(IN; primary and secondary diagnoses) = 92.4 (90.4–93.9)<br>- PPV(IN; primary diagnoses) = 94.4 (92.6–95.7)<br>- Only one reviewer; NPV, sensitivity, and specificity not included |
| **- Madsen *et al.*[35]**<br>- *J Clin Epidemiol*<br>- 2003 | - ICD-8: 410, 427.24, 427.27, 427.91, 427.97<br>- IN/OUT<br>- Primary and secondary diagnoses | - 1982–1991<br>- DANMONICA (definite or possible cases including cardiac arrest)<br>- N= 5022<br>- PPV and sensitivity | - PPV(primary diagnoses) = 94.3 (93.6–94.9)<br>- PPV(primary and secondary diagnoses) = 93.4 (92.6–94.0)<br>- Sensitivity(primary diagnoses) = 62.8 (61.7–64.0)<br>- Sensitivity(primary and secondary diagnoses) = 69.5 (68.4–70.6)<br>- NPV and specificity not included |
| ***Diagnosis: Unstable angina pectoris*** | | | |
| **- Joensen *et al.*[34]**<br>- *J Clin Epidemiol*<br>- 2009 | - ICD-10: I20.0<br>- IN/OUT/ED<br>- Primary and secondary diagnoses | - 1993–2003<br>- Medical record review, discharge summary, blood tests, ECG<br>- N=444<br>- PPV | - PPV(IN/OUT/ED) = 27.5 (23.5–31.8)<br>- PPV(IN) = 42.0 (36.0–48.0)<br>- Only one reviewer; NPV, sensitivity, and specificity not included |
| ***Diagnosis: Heart failure*** | | | |
| **- Thygesen *et al.*[33]**<br>- *BMC Med Res Methodol*<br>- 2011 | - ICD-10: I50, I11.0, I13.0, I13.2<br>- IN/OUT<br>- Primary diagnoses | - 1998–2007<br>- Discharge summaries<br>- N=50<br>- PPV | - PPV = 100 (92.9–100)<br>- NPV, sensitivity, and specificity not included; review restricted to discharge summaries |
| **- Mard *et al.*[36]**<br>- *Clin Epidemiol*<br>- 2010 | - ICD-10: I11.0, I13.0, I13.2, I42.0, I42.6–9, I50.0–I50.1, I50.9<br>- IN/OUT<br>- Primary and secondary diagnoses | - 2005–2007<br>- Medical record review<br>- N=758<br>- PPV | - PPV(overall) = 84.0 (81.3–86.5)<br>- PPV(first-time events) = 77.9 (74.1–81.6)<br>- NPV, sensitivity, and specificity not included<br>- Only patients at university hospital cardiac care unit |
| ***Diagnosis: Arterial hypertension*** | | | |
| **- Schmidt *et al.*[37]**<br>- *BMJ Open*<br>- 2013 | - ICD-8: 400–404; ICD-10: I10–I15 (essential hypertension in males)<br>- IN/OUT<br>- Primary and secondary diagnoses | - 1977–2010<br>- Prescription registry<br>- N=524<br>- PPV | - PPV = 88.2 (85.4–90.9)<br>- NPV, sensitivity, and specificity not included; reference based on redeemed prescriptions for antihypertensive medications; only males included. |
| **- Nielsen *et al.*[38]**<br>- *Ugeskr Laeg*<br>- 1996 | - ICD-8: 401.99<br>- IN<br>- Primary diagnoses | - 1983–1990<br>- Medical record review<br>- N=310<br>- PPV | - PPV = 40 (26–55) to 60 (49–70)<br>- Restricted to inpatients and primary diagnoses; NPV, sensitivity, and specificity not included |

| | | | |
|---|---|---|---|
| ***Diagnosis: Atrial fibrillation or flutter*** | | | |
| - **Rix *et al.***[39]<br>- *Scand Cardiovasc J*<br>- 2012 | - ICD-8: 427.93, 427.94; ICD-10: I48<br>- IN/OUT/ED<br>- Primary and secondary diagnoses | - 1993–2009<br>- Medical record and heart rhythm documentation<br>- N=284<br>- PPV | - PPV(All) = 92.3 (88.6–94.8)<br>- PPV(IN/OUT) = 94.0 (90.5–96.3) (independent of diagnosis type and department specialty)<br>- PPV(ED) = 64.7 (41.3–82.7)<br>- Missing heart rhythm documentation in medical records; selected subjects included in cohort study (Diet, Cancer, and Health) → hampered generalizability; age restricted to 50–64 years; only PPV included. |
| - **Frost *et al.***[40]<br>- *Am J Med*<br>- 2007 | - ICD-8: 427.93, 427.94; ICD-10: I48<br>- N/A<br>- N/A | - 1980–2002<br>- Medical record and heart rhythm documentation<br>- N=174<br>- PPV | - PPV = 98.9 (95.9–99.7)<br>- 13% of the sampled medical records could not be retrieved; NPV, sensitivity, and specificity not included |
| - **Frost *et al.***[41]<br>- *Arch Intern Med*<br>- 2004 | - ICD-8: 427.93, 427.94; ICD-10: I48<br>- N/A<br>- N/A | - 1980–2002<br>- Medical record and heart rhythm documentation<br>- N=116<br>- PPV | - PPV = 96.6 (91.5–98.7)<br>- Only one reviewer; NPV, sensitivity, and specificity not included |
| ***Diagnosis: Cardiac arrest*** | | | |
| - **Joensen *et al.***[34]<br>- *J Clin Epidemiol*<br>- 2009 | - ICD-8: 427.27; ICD-10: I46<br>- IN/OUT/ED<br>- Primary and secondary diagnoses | - 1993–2003<br>- Medical record review, discharge summary, blood tests, ECG<br>- N=42<br>- PPV | - PPV(IN/OUT/ED) = 50.0 (35.5–64.5)<br>- PPV(IN) = 53.1 (36.5–69.1)<br>- Only one reviewer; NPV, sensitivity, and specificity not included |
| ***Diagnosis: Venous thromboembolism*** | | | |
| - **Schmidt *et al.***[42]<br>- *J Thromb Haemost*<br>- 2014 | - ICD-10: I80.1–3, I26 + prescriptions for anticoagulants ≤ 30 days after diagnosis<br>- IN/OUT<br>- Primary and secondary diagnoses | - 2004–2012<br>- Medical record review<br>- N=20<br>- PPV | - PPV=90.0 (69.9–97.2)<br>- NPV, sensitivity, and specificity not included |
| - **Severinsen *et al.***[43]<br>- *J Clin Epidemiol*<br>- 2010 | - ICD-8: 450.99, 451.00, 451.08, 451.09, 451.99; ICD-10: I26, I80.1–I80.9<br>- IN/OUT/ED<br>- Primary and secondary diagnoses | - 1994–2006<br>- Medical record review, discharge summary, blood tests, ultrasound, venography, echo, ventilation-perfusion lung scan, CT scan<br>- N=1100<br>- PPV | - PPV(All) = 58.5 (55.5–61.3)<br>- PPV(IN/OUT) = 75.0 (71.9–77.8)<br>- PPV(ED) = 31.3 (27.2–35.7)<br>- PPV(primary diagnosis) = 77.0 (73.7–80.0)<br>- NPV, sensitivity, and specificity not included |
| ***Diagnosis: Recurrent venous thromboembolism*** | | | |
| - **Schmidt *et al.***[42]<br>- *J Thromb Haemost*<br>- 2014 | - ICD-10: I80.1–3, I26 (>3 months after first–time diagnosis) + ultrasound/CT scan during admission or prescriptions for anticoagulants ≤ 30 days after diagnosis<br>- IN/OUT<br>- Primary and secondary diagnoses | - 2004–2012<br>- Medical record review<br>- N=90<br>- PPV | - PPV(IN/OUT, primary/secondary diagnosis, scan) = 27.5 (16.1–42.8). PPV(IN/OUT, primary/secondary diagnosis, anticoagulant use) = 30.2 (18.6–45.1). PPV(IN, primary/secondary diagnosis, scan) = 79.0 (56.7–91.5), PPV(IN, primary/secondary diagnosis, anticoagulant use) = 56.5 (36.8–74.4)<br>- NPV, sensitivity, and specificity not included |

*Positive predictive values (PPVs) are % (95% confidence interval).
All studies examined the validity of codes in the Danish National Patient registry.
Abbreviations: DANMONICA, Danish Monitoring Trends and Determinants in Cardiovascular Disease project; ED, emergency department; ICD, International Classification of Diseases; IN, inpatients; OUT, outpatients; NPV, negative predictive value

## Table 2. Summary of literature review (study II).

| Study II: Impact of Pre-admission Depression on Mortality following Myocardial Infarction | | | |
|---|---|---|---|
| **Author, journal, year** | **Design, data sources, setting (study period)** | **Population, exposure, outcome** | **Results, limitations** |
| ***Exposure: Depression before myocardial infarction*** | | | |
| **Abrams *et al.***[44]<br>- *Circ Cardiovasc Qual Outcomes*<br>- 2009 | - Cohort study<br>- Registry-based<br>- Veterans Health Administration hospitals across the US (2004–2006) | - MI patients (n=21,745)<br>- Psychiatric comorbidity (1) secondary inpatient diagnosis during MI admission, 2) diagnoses from prior outpatient visits<br>- Reference: no psychiatric comorbidity using both methods<br>- 30- and 365-day all-cause mortality | - Using inpatient secondary diagnosis codes, 2285 (10%) had psychiatric disorders *vs.* 5225 (24%) when using prior outpatient codes<br>- Patients with psychiatric comorbidity had higher adjusted 30- and 365-day mortality based on outpatient codes (aOR 1.19, 95% CI 1.09–1.30 and 1.12, 95% CI 1.03–1.22, respectively), but similar mortality when using inpatient codes (aOR 0.89, 95% CI 0.69–1.01 and 0.93 95% CI 0.82–1.06, respectively)<br>- Older male (98%) population with unique benefits → selection bias and hampered generalizability; broad exposure definition; unknown data quality |
| **Dickens *et al.***[45]<br>- *J Am Coll Cardiol*<br>- 2007 | - Cohort study<br>- Questionnaire, interview, population records<br>- Manchester, UK (1997–1999) | - MI patients (n=588)<br>- Depression immediately preceding MI and 12 months after MI<br>- 8-year all-cause mortality | - No significant difference in survival between those with depression in the week preceding MI (mean survival 89.2 months, 95% CI 84.7–93.8) and those without (mean survival 89.9 months, 95% CI 87.4–92.4, p = 0.75)<br>- Small sample size, questionnaire for depression assessment |
| **Bush *et al.***[46]<br>- *Am J Cardiol*<br>- 2001 | - Cohort study<br>- Clinical interview<br>- US, Single-center study (Jul 1995 – Dec 1996) | - MI patients (n=266)<br>- History of depression<br>- 4-month all-cause mortality | - RR = 1.0 (p=1.0)<br>- Small sample size; unadjusted estimates; all-cause mortality was determined by phone call to surviving contact; history of depression determined by medical record review |
| ***Exposure: Depression after myocardial infarction*** | | | |
| **- Smolderen *et al.***[47]<br>- *Circulation*<br>- 2017 | - Cohort study<br>- SRQ<br>- US, 24 hospitals (data from the TRIUMPH study) (2005–2008) | - MI patients ≥18 years (n=4,062)<br>- Depression during admission ('treated' [discharge diagnosis / medication / referral for counseling], or 'untreated' if none of these)<br>- 1 year all-cause mortality | - 759 (18.7%) patients with depression; 231 (30.4%) were treated<br>- Patients with treated depression had 1-year mortality risks similar to patients without depression (6.7% *vs.* 6.1%, aHR=1.12, 95% CI 0.63–1.99)<br>- Patients with untreated depression had higher 1-year mortality than patients without depression (10.8% *vs.* 6.1%, aHR = 1.91, 95% CI 1.39-2.62) |
| **de Miranda *et al.***[48]<br>- *Health Psychol*<br>- 2015 | - Meta-analysis<br>- BDI<br>- 1975–2011 | - MI patients (n=6,775 in 9 studies)<br>- Depression during admission<br>- All-cause mortality | - aHR = 1.14 (95% CI 1.04–1.25)<br>- Left ventricular ejection fraction available only for 4,744 patients; missing depression data (imputated); study heterogeneity, publication bias |
| **Meijer *et al***.[49]<br>- *Br J Psychiatry*<br>- 2013 | - Meta-analysis<br>- SRQ or standardized structured diagnostic interviews | - MI patients (n=2225 in 3 studies)<br>- Depression within 3 months after MI<br>- All-cause mortality | - Pooled aHR = 1.23 (95% CI 1.15–1.31)<br>- Study heterogeneity; publication bias |
| **Smolderen *et al.***[50]<br>- *Circ Cardiovasc Qual Outcomes*<br>- 2009 | - Cohort study<br>- MR; MI databases; SRQ<br>- US, 19 hospitals (2003–2004) | - MI patients (n=2347)<br>- Depression, depressive symptoms (somatic/cognitive) during admission<br>- 4-year all-cause mortality | - aHR (depression) = 1.41 (95% CI 1.12–1.76); aHR (cognitive symptoms) = 1.10 (95% CI 0.97–1.25); aHR (somatic symptoms) = 1.07 (95% CI 0.94–1.21)<br>- Medical record review and questionnaire as data sources |
| **Carney *et al.***[51]<br>- *Psychosom Med*<br>- 2009 | - Post-hoc analyses of RCT<br>- ENRICHD trial data, diagnostic interview, SRQ<br>- US, 8 hospitals (1996–1999) | - MI patients and depression (n=920)<br>- Patients with MI but no depression<br>- All-cause mortality | - aHR (first depression) = 3.1 (95% CI 1.6–6.1); aHR (recurrent major depression) = 2.2 (95% CI 1.1–4.4)<br>- Study population composed of participants enrolled in a clinical trial; no information on duration of depression |
| **Parakh *et al.***[52]<br>- *Am J Cardiol*<br>- 2008 | - Cohort study<br>- SRQ (incl. BDI)<br>- US (Jul 1995 – Dec 1996) | - MI patients (n=284)<br>- Depression evaluated within 5 days of MI admission<br>- 8-year all-cause mortality | - aHR (any depression) = 0.76 (95% CI 0.47–1.24); aHR (BDI score ≥10) = 0.79 (95% CI 0.48–1.30)<br>- Single-center study; small sample size |
| **Drago *et al.***[53]<br>- *Int J Cardiol*<br>- 2006 | - Cohort study<br>- Diagnostic interview; SRQ (BDI)<br>- Italy (Jan 1999 – Dec 1999) | - MI patients (n=100)<br>- Major Depressive Disorder between the 7th and 14th day from admission<br>- 5-year all-cause mortality | - OR 12 (95% CI 2.6–56)<br>- Single-center study; small sample size with following imprecise estimates |

| | | | |
|---|---|---|---|
| **Nicholson *et al.*** [54]<br>- *Eur Heart J*<br>- 2006 | - Meta-analysis<br>- SRQ, diagnostic interview, physician diagnosis, antidepressants | - MI patients (n= 17,842 in 34 studies)<br>- Depression at baseline<br>- All-cause mortality | - Pooled RR 1.80 (95% CI 1.50–2.15)<br>- Study heterogeneity |
| **Parashar *et al.*** [55]<br>- *Arch Intern Med*<br>- 2006 | - Cohort study<br>- SRQ<br>- US, 19 medical centers (Jan 2003 – Jun 2004) | - MI patients (n=1873)<br>- Depressive symptoms (transient [only during hospitalization], new [only at 1 month after discharge], or persistent [at both times])<br>- 6-months all-cause rehospitalization or mortality | - The aHRs = 1.34, 1.71, and 1.42 (all p<0.05, CIs only available as whiskers) for transient, new, and persistent depression, respectively<br>- Only 63% of approached patients gave consent → selection bias of the exposure; depressive symptoms, not definite diagnosis; moderate sample size; composite endpoint |
| **Sørensen *et al.*** [56]<br>- *Acta Psychiatr Scand*<br>- 2006 | - Cohort study<br>- SRQ (MDI)<br>- Denmark (17 hospitals) (Mar 1999 – Dec 2000) | - MI patients (n=763)<br>- Depression at discharge<br>- 1-year all-cause mortality | - aHR = 1.1 (95% CI 0.1–9.0)<br>- Sample size and mortality rate low → imprecise estimates; only 41% consented → selection bias of the exposure; only 17 of 44 invited hospitals participated |
| **Carney *et al.*** [57]<br>- *Arch Intern Med*<br>- 2005 | - Cohort study (patients from the ENRICHED trial)<br>- BDI and DSM-IV<br>- USA (4 hospitals) (1997–2000) | - MI patients (n=678)<br>- Depression at discharge<br>- 30-month all-cause mortality | - aHR = 2.8 (95% CI 1.4–5.4)<br>- Small sample size; excluded patients who did not meet the inclusion criteria for the ENRICHED trial |
| **Rumsfeld *et al.*** [58]<br>- *Am Heart J*<br>- 2005 | - Post hoc analysis of RCT<br>- SRQ (MOS-D)<br>- Multicenter international setting (Dec 1999 – Dec 2001) | - MI patients with heart failure (n=634) from the EPHESUS trial<br>- Depression at baseline<br>- 2-year all-cause mortality | - aHR = 1.75 (95% CI 1.15–2.68)<br>- Depressive symptoms, not depression diagnosis; more severely depressed patients may have been excluded; selection bias due to eligible patients not completing the MOS-D |
| **Van Melle *et al.*** [59]<br>- *Psychosom Med*<br>- 2004 | - Meta-analysis<br>- SRQ and clinical interviews | - MI patients (n= 3082 in 9 studies)<br>- Depressive symptoms at baseline<br>- All-cause mortality | - OR = 2.38 (95% CI 1.76–3.22)<br>- Study heterogeneity; publication bias; modest sample size |
| **Carney *et al.*** [60]<br>- *Am J Cardiol*<br>- 2003 | - Post-hoc analysis of RCT<br>- Data from the ENRICHD trial, diagnostic interview for depression, SRQ<br>- US (Oct 1997– Jan 2000) | - MI patients (n=766)<br>- Depression at baseline<br>- 30-month all-cause mortality | - aHR = 2.4 (95% CI 1.2–4.7)<br>- Depressed sample consisted of only a subsample of participants in the ENRICHD clinical trial; more severely depressed or ill patients were not enrolled in the trial; small sample size |
| **Lauzon *et al.*** [61]<br>- *CMAJ*<br>- 2003 | - Cohort study<br>- SRQ (BDI)<br>- Canada (10 hospitals in Quebec) (1996–1998) | - MI patients (n=587)<br>- Depression at baseline<br>- 1-year all-cause mortality | - aHR 1.3 (95% CI 0.59–3.05)<br>- Patients who died shortly after admission were not enrolled; exclusion of the sickest patients with MI (likely most depressed and highest death rates) → selection bias |
| **Lane *et al.*** [62]<br>- *Int J Epidemiol*<br>- 2002 | - Cohort study<br>- SRQ (BDI)<br>- UK (1997 – 1998) | - MI patients (n=288)<br>- Depression at baseline<br>- 3-year all-cause mortality | - OR = 1.04 (95% CI 0.50–2.16)<br>- Small sample size, unadjusted estimates |
| **Bush *et al.*** [46]<br>- *Am J Cardiol*<br>- 2001 | - Cohort study<br>- Clinical interview; SRQ (BDI)<br>- US, Single-center study (1995–1996) | - MI patients (n=285)<br>- Depression at baseline<br>- 4-month all-cause mortality | - Depressive symptoms: RR = 2.6 (p=0.06); depression disorder: RR = 2.0 (p=0.18)<br>- Small sample size; only unadjusted estimates; all-cause mortality based on phone call to a surviving contact |
| **Lane *et al.*** [63]<br>- *Psychosom Med*<br>- 2001 | - Cohort study<br>- SRQ (BDI)<br>- UK (1997–1998) | - MI patients (n=288)<br>- Depression at baseline<br>- 1-year all-cause mortality | - OR = 1.15 (95% CI 0.49–2.67)<br>- Small sample size; unadjusted estimates |

Abbreviations: ACS, acute coronary syndrome; aHR, adjusted hazard ratio; aOR, adjusted odds ratio; BDI, Beck's Depression Inventory; CABG, coronary artery bypass grafting; CES-D, Center for Epidemiologic-Depression Scale; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; DIS, the National Institute of Mental Health Diagnostic Interview Schedule; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; HADS-D, Hospital Anxiety and Depression Scale depression subscale; MDI, Major Depression Inventory; MI, myocardial infarction; MOS-D, Medical Outcomes Study–Depression questionnaire; PTCA, percutaneous transluminal angiography; SRQ, self-report questionnaire; RCT, randomized controlled trial; RR, relative risk; US, United States

## Table 3. Summary of literature review (study III).

| Study III: Long-Term Risk of Stroke in Myocardial Infarction Survivors | | | |
|---|---|---|---|
| **Author, journal, year** | **Design, setting, data sources, study period** | **Population, controls (if applicable), outcome, exposure (if applicable)** | **Results, limitations** |
| ***Outcome: Ischemic stroke*** | | | |
| **- Ulvenstam *et al.*[64]**<br>**-** *Stroke*<br>- 2014 | - Population-based cohort study<br>- Sweden<br>- Nationwide registries<br>- 1998–2008 | - MI patients (n=173,233)<br>- 1-year ischemic stroke | - 7185 of 173,233 patients with acute MI had an ischemic stroke within 1 year (4.1%)<br>- 20% relative risk reduction during the study period (1998–2000 *vs*. 2007–2008); relative risk = 0.80 (0.75–0.86)<br>- Short-term (1 year) follow-up; no comparison cohort |
| **- Kajermo *et al.*[65]**<br>- *Stroke*<br>- 2014 | - Population-based cohort study<br>- Sweden<br>- Nationwide registries<br>- 1998–2008 | - MI patients (n=173,233)<br>- 30-day ischemic stroke | - 3571 of 173,233 patients with acute MI had an ischemic stroke within 30 days (2.1%)<br>- Incidence of ischemic stroke was lower during 2007 to 2008 compared to 1998 to 2000 (2.0% *vs*. 2.2%, p=0.02)<br>- Short-term (30 days) follow-up; no comparison cohort |
| **- Koton *et al.*[66]**<br>- *Int J Cardiol*<br>- 2012 | - Community-based cohort study<br>- Israel<br>- 8 hospitals in central Israel<br>- 1992–1993 | - MI patients aged ≤ 65 years (n=1261)<br>- 11-year ischemic stroke<br>- Exposure: Unfavorable socioeconomic status | - aHRs = 1.5 (95% CI 0.9–2.4), 2.0 (95% CI 1.2–3.2), and 2.1 (95% CI 1.2–3.6) for 1, 2, and ≥3 unfavorable socioeconomic factors compared with none<br>- Patients > 65 years old were not included; unfavorable socioeconomic factors were self-reported; findings may not be generalizable |
| **- Ikram *et al.*[67]**<br>- *Neurology*<br>- 2006 | - Community-based cohort study<br>- Rotterdam, the Netherlands<br>- MI: ECG/interview<br>- 1990–1993 | - Recognized MI (n=442), unrecognized MI (n=361), and no MI (reference, n=5636)<br>- Incident ischemic strokes | - Men (but not women) with unrecognized (aHR=3.22, 95% CI 1.96–5.28) and recognized (aHR=1.84, 95% CI 1.16–2.91) MI had increased risk of stroke<br>- MI was ascertained by interview and computer interpretation of ECG; findings may not be generalizable |
| **- Witt *et al.*[68]**<br>- *Am J Med*<br>- 2005 | - Meta-analysis<br>- Population-based studies (restricted to 1978-2004, >100 subjects), reporting the number or percent of ischemic strokes in MI survivors | - MI patients<br>- Ischemic stroke during first year after MI | - 22 articles included<br>- During hospitalization for the index MI, 11.1 ischemic strokes occurred per 1000 MIs compared to 12.2 at 30 days and 21.4 at 1 year<br>- <1 year follow-up; no comparators to MI patients |
| **- Mooe *et al.*[69]**<br>- *Stroke*<br>- 1999 | - Population-based case-control study<br>- The two northernmost counties in Sweden<br>- 1985–1994 | - Cases with ischemic stroke and MI within 28 days (n=103) and controls with ischemic stroke but without a preceding MI within 28 days (n=206) | - The sudden onset of neurological symptoms (76.7% *vs*. 54.9%), impaired consciousness (35.0% *vs*. 18.4%), and a progression of neurological deficits (19.4% *vs*. 8.7%) were more common in cases, whereas the onset of stroke during sleep was rarer in cases (6.8% *vs*. 21.4%)<br>- <1 year follow-up |
| ***Outcome: Hemorrhagic stroke*** | | | |
| **- Binsell-Gerdin *et al.*[70]**<br>- *Int J Cardiol*<br>- 2014 | - Population-based cohort study<br>- Sweden<br>- Nationwide registries<br>- 1998–2008 | - MI patients (n=173,233)<br>- 30-day hemorrhagic stroke | - 375 patients (0.22%) had hemorrhagic stroke within 30 days of MI<br>- Incidence decreased from 0.2% (n = 94) in 1998–2000 to 0.1% (n = 41) in 2007–2008<br>- No differentiation between intracerebral hemorrhage and subarachnoid hemorrhage; no comparison cohort |
| ***Outcome: Both ischemic and hemorrhagic stroke*** | | | |
| **- Hachet *et al.*[71]**<br>- *Stroke*<br>- 2014 | - Community-based cohort study<br>- French region: data from the RICO survey<br>- 2001–2010 | - MI patients (n=8485)<br>- 1-year stroke or transient ischemic attack (n=168, 1.98%) | - 123 MI patients (1.4%) had an in-hospital stroke (86% ischemic, 11% hemorrhagic, 3% undetermined)<br>- During 1-year follow-up, only 45 (0.6% of survivors) had a post-discharge stroke (96% ischemic, 4% hemorrhagic)<br>- Short-term (1 year) follow-up; no comparison cohort; follow-up phone call, letters, or review of medical records (~10% loss to follow-up) |

| | | | |
|---|---|---|---|
| **- Budaj *et al.*[72]**<br>- *Circulation*<br>- 2005 | - Multinational cohort study<br>- 94 hospitals in 14 countries<br>- 1999–2003 | - Patients admitted with ACS (n=35,233, 37% with STEMI, 30% with NSTEMI, and 33% with unstable angina)<br>- In-hospital stroke | - All-cause stroke incidence higher in patients with STEMI than non–STEMI or unstable angina (1.3%, 0.9%, 0.5%, respectively); same pattern for non-hemorrhagic and hemorrhagic stroke<br>- <1 year follow-up; no comparators to MI patients |
| ***Outcome: Unspecified stroke*** | | | |
| **- Saczynski *et al.*[73]**<br>- *Arch Intern Med*<br>- 2008 | - Community-based cohort study<br>- US<br>- 16 Worcester medical centers<br>- 1986–2005 | - MI patients (n=9220)<br>- In-hospital ischemic and hemorrhagic stroke and following mortality rates compared to patients who did not experience a stroke | - 132 (1.4%) experienced an acute stroke during hospitalization; mortality after stroke 3-fold increased in the 1990s (OR=2.91, 95% CI 1.72–5.19) and 5-fold in the 2000s (OR=5.36, 95% CI 2.71–10.64)<br>- <1 year follow-up; no comparators to MI patients; findings may not be generalizable |
| **- Witt *et al.*[74]**<br>- *Ann Intern Med*<br>- 2005 | - Community-based cohort study<br>- Olmsted County, Minnesota, US<br>- 1979–1998 | - MI patients (n=2160)<br>- Comparison: General population<br>- Ischemic/hemorrhagic stroke and mortality after stroke | - 0–30 day SMR = 44 (95% CI 32–59); SMRs between 30 days and 3 years remained 2-3 fold increased, decreasing to 1.6 during 3–5 years.<br>- HR (post-MI stroke mortality) = 2.89 (95% CI, 2.44–3.43)<br>- Unadjusted SMRs; outcomes from medical records |
| **- Tanne *et al.*[75]**<br>- *J Am Coll Cardiol*<br>- 1997 | - Nationwide cohort study<br>- Israel<br>- 1981–1983 and 1992–1994 | - MI admissions (n=5839 in 1981–1983 and n=2012 in 1992–1994)<br>- Cerebrovascular events | - Incidence = 0.74% (43 of 5839) in 1981–1983 (prethrombolysis era) *vs*. 0.75% (15 of 2012) in 1992–1994 (thrombolysis era)<br>- No comparators to MI patients; coronary care units only |

Abbreviations: ACS, acute coronary syndrome; aHR, adjusted hazard ratio; CI, confidence interval; CKD, chronic kidney disease; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; aOR, adjusted odds ratio; STEMI, ST-segment elevation myocardial infarction; RICO, obseRvatoire des Infarctus de Côte-d'Or; SMR, standardized morbidity ratio; US, United States.

**Table 4. Summary of literature review (study IV).**

| Study IV: Long-term Risk of Dementia in Myocardial Infarction Survivors | | | |
|---|---|---|---|
| **Author, journal, year** | **Design, setting, data sources, study period** | **Population, controls (if applicable), outcome** | **Results, limitations** |
| ***Outcome: All-cause dementia*** | | | |
| **- Ikram et *al.*[76]**<br>- *Stroke*<br>- 2008 | - Cohort study and cross-sectional study<br>- Rotterdam, the Netherlands<br>- MI based on ECG/interview<br>- Dementia based on MMSE, Cambridge examination, and neuropsychological testing<br>- 1990–1993 | - Recognized MI (n=424), unrecognized MI (n=345), and no MI (reference, n=5578)<br>- Incident, all-cause dementia (cohort study), white matter lesions, and brain infarctions (cross-sectional study) | - In men (but not women), unrecognized MI was associated with an increased risk of dementia (aHR = 2.14; 95% CI 1.37–3.35) and with more white matter lesions and brain infarction on MRI<br>- Recognized MI was not associated with dementia in either sex<br>- Men (but not women), with recognized MI more often had brain infarction, but not white matter lesions<br>- Small sample size |
| **- Bursi *et al.*[77]**<br>- *Am J Epidemiol*<br>- 2006 | - Case-control study<br>- Minnesota, United States<br>- Registry-based diagnoses<br>- 1985–1994 (dementia patients) | - 916 cases of all-cause dementia and 916 age- and sex-matched controls<br>- Preceding MI (n=36 in both cases and controls) were identified | - Odds ratio for MI among cases with dementia compared to controls = 1.00 (95% CI 0.62–1.62)<br>- Small sample size, case-control design |
| ***Outcome: Cognitive impairment*** | | | |
| **Haring *et al.*[78]**<br>- *J Am Heart Assoc*<br>- 2013 | - Cohort study<br>- United States (Women's Health Initiative Memory Study (WHIMS))<br>- Questionnaire for CVD, MMSE for dementia<br>- 1996–1999 | - Cognitively intact, postmenopausal women (65–79 years, n=6455)<br>- CVD, including MI<br>- Mild cognitive impairment or probable dementia (median follow-up 8.4 years) | - Women with CVD tended to be at increased risk for cognitive decline compared to those free of CVD (aHR = 1.29; 95% CI 1.00–1.67); women with MI were at highest risk (aHR = 2.10; 95% CI 1.40–3.15)<br>- Small sample size, questionnaire for CVD assessment; generalizability hampered by the specific study population |

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; CVD, cardiovascular disease; ECG, electrocardiogram; MI, myocardial infarction; MMSE, Mini-mental State Examination; MRI, magnetic resonance imaging

**Medline search algorithms for the four studies** (relevant papers/total hits + other relevant = total number of relevant papers):
**Study I:** ("positive predictive value"[All Fields] AND "Cardiovascular Diseases"[Majr]) AND ("Danish National Patient Registry"[All Fields] OR "Danish National Registry of Patients"[All Fields] OR "Danish National Hospital Register"[All Fields] OR "Danish National Health Registry"[All Fields] OR "Danish National Patient Register"[All Fields] OR "Danish Hospital Discharge Registry"[All Fields] OR "Danish National Hospital Registry"[All Fields] OR "Danish Hospital Registers"[All Fields]): 3/4 + 13 = 16.
**Study II:** ("myocardial infarction"[MeSH Terms] AND ("depressive disorder"[MeSH Terms] OR "depression"[MeSH Terms])) AND "mortality"[MeSH Terms]. Search was restricted to papers with study periods overlapping with or contained in the study period of study II (1995–2014): 18/67 + 3 = 21.
**Study III:** ("Myocardial Infarction"[Majr]) AND "Stroke"[Majr]:10/1875 + 2 = 12.
**Study IV:** ("Myocardial Infarction"[Mesh]) AND "Dementia"[Mesh]: 2/141 + 1 = 3.

## 2.7 The demographic shift of age

Most Western societies experience a demographic shift towards an elderly population. The fraction of individuals older than 60 years of age worldwide is predicted to increase from 12% in 2013 to 21% by 2050.[79] The prevalence of age-related diseases, such as MI, stroke, and dementia, will subsequently increase and challenge the societal economy and public health.[9,80] In addition, the prevalence of depression is predicted to increase and therefore will become increasingly pertinent to consider as a prognostic factor in MI survivors.[9,80] Preventive measures may provide part of the solution to the challenges ahead. However, both risk factors and prognostic factors need to be identified to target such preventive strategies. The subsequent sections provide an introduction to the epidemiology of depression, stroke, and dementia and their relation with MI.

## 2.8 Myocardial infarction and depression

Depression is a very common disease with a lifetime prevalence of approximately 12% in men and 20% in women.[81] Depression produces the greatest decrease in health compared with chronic diseases, such as angina, arthritis, asthma, and diabetes. Furthermore, the deterioration in health becomes substantially more pronounced when depression coexists with these diseases.[82] By 2030, depression and ischemic heart disease are projected to be the two leading causes of disability in high-income countries, and the second and third leading causes of disability globally.[80] Thus, the impact of the two diseases on public health is enormous and growing.

Important risk factors for depression include other psychiatric disorders, serious or chronic illness, psychological stress, low socioeconomic status, female gender, and a family history of depression.[83]

The association between depression and MI has been studied previously. Depression has been established both as a risk factor for MI[84] and a prognostic factor for mortality following MI.[84] However, almost every previous study examining the impact of depression on mortality after MI has focused on depression arising after the occurrence of MI (Table 2). This approach gives rise to concern because an MI may induce depressive symptoms. Essential diagnostic

criteria for depression (fatigue, disturbed sleep, and poor appetite) are common in the course of an MI and plausibly correlate with severity of the MI. Therefore, post-MI depressive symptoms may merely be a marker of MI severity and in turn predict increased mortality. In the few post-MI depression studies that adjusted for MI severity (Killip class or left ventricular ejection fraction), the association with mortality was attenuated by 25% after adjustment,[49] further emphasizing the influence of MI severity in such studies.

Despite the difficulty of studying the association between depression and MI mortality, it seems plausible that depression can affect the outcome of MI. Numerous potential mechanisms have been suggested to link depression and MI prognosis. A biological pathway suggests that altered autonomic nervous system activity in depressed patients may worsen the prognosis through an elevated heart rate and low heart rate variability[84] – factors that have been associated with increased post-MI mortality.[85] Other potential biological mechanisms include increased cortisol levels in depressed patients,[86] which may lead to increased plasma volume and hypertension, hyperglycemia, insulin resistance, and dyslipidemia.[87] A behavioral pathway includes a sedentary life style and poor adherence to recommended medication and life style changes (*e.g.*, diet, exercise, and smoking cessation).[88] Finally, exogenous factors, such as treatment with antidepressants, may drive an association with mortality. This is controversial, however, and seems unlikely as treatment with SSRIs has been shown to reduce cortisol and insulin resistance,[89] and randomized clinical trials of SSRIs have shown no[90,91] or even slightly positive[92] effects on MI mortality.

### 2.9 Myocardial infarction and stroke

Stroke is a feared complication after MI that is costly for society and often very disabling for the patient. The cumulative incidence of ischemic stroke after MI ranges from 0.75% to 2% after 30 days[65,72,73,75] and from 2% to 4% after 1 year.[64,68]

MI and stroke share several risk factors. The most important risk factor for stroke is hypertension, which is strongly correlated with both ischemic and hemorrhagic stroke and highly prevalent in the general population.[93] Other shared risk factors include diabetes, arrhythmias

(including atrial fibrillation), high cholesterol levels, smoking, physical inactivity, chronic kidney disease, family history of stroke, and poor diet.[93]

Previous studies of the association between MI and stroke have been limited by a sole focus on ischemic stroke[64-69] or hemorrhagic stroke,[70] small sample sizes (<2500),[66,67,69,74] and lack of a comparison cohort without MI, reporting only the incidence of stroke after MI.[64,65,69-73,75] Only one study compared the risk of stroke with a general population reference.[74] Apart from three studies,[66,67,74] all previous studies followed patients only up to 1 year after MI, and no study has followed patients beyond 12 years after MI.

The risk of stroke seems exceedingly high in the first 30 days after MI, after which the stroke risk is only moderately increased.[74] Mechanisms underlying the association between MI and increased risk of ischemic stroke may be different for early and late stroke after MI. Early ischemic stroke may be attributed largely to cardiac emboli originating from the left atrial appendage after complicating atrial fibrillation or from the left ventricle if a mural thrombus forms in hypokinetic segments. Cardio-embolic stroke accounts for 60% of post-MI ischemic strokes,[71] compared to only about 20% of ischemic strokes in general.[94] Other common complications after MI include congestive heart failure and arrhythmias, which may cause chronic and acute reductions in cardiac output, respectively. This can lead to watershed infarctions in the vulnerable border-zone regions of the brain supplied by the major cerebral arteries.[95] These areas have a precarious blood supply, which may become compromised if cerebral perfusion drops, especially if the supplying arteries are stenosed.[95] Post-MI ischemic stroke during long-term follow-up may be attributed more to mutual underlying risk factors (*e.g.*, diabetes, hypertension, smoking, and atherosclerosis); thus, the two diseases may evolve in parallel, but with a longer latency period for ischemic stroke.

Hemorrhagic stroke may be increased after MI due to antithrombotic medication. Hence, dual antiplatelet therapy (DAPT, *i.e.* aspirin plus an P2Y12-inhibitor) is usually continued for 1 year following MI to prevent recurrent MI and ischemic stroke,[96,97] but it may come at the expense of an increased risk of hemorrhagic stroke. Moreover, MI is often complicated by atrial fibrillation, which often implies “triple therapy“ (DAPT plus anticoagulation). Triple therapy is associated with a 3- to 4-fold increased risk of bleeding after MI compared with aspirin alone.[98]

## 2.10 Myocardial infarction and dementia

Predictions of the future global burden of dementia have raised international concern.[99] However, the prevalence has increased less during the past two decades than population ageing alone would have predicted,[100] which may have been driven by a reduced risk of vascular dementia due to a concomitant reduction in vascular risk factors.[10] The most prevalent subtypes of dementia is Alzheimer's disease (~50%) and vascular dementia (~20%).[101,102] Subgroups of older women tend to have particular high risk of Alzheimer's disease while younger men tend to have a higher risk of vascular dementia.[103] The current prevalence of all-cause dementia is ~2% at 70 years of age for both sexes, increasing to ~15% for men and ~30% for women at 90 years of age.[100] The risk of dementia increases exponentially with age; the risk doubles every 5 years for vascular dementia and every 4.5 years for Alzheimer's disease.[103]

Risk factors for dementia largely overlap with those of MI and include age, low socioeconomic status, smoking, hypertension, high cholesterol levels, diabetes, obesity, excessive alcohol consumption, and elevated homocysteine levels.[104,105] In contrast to MI, female sex is a risk factor for dementia. A history of head trauma and family history of dementia may also increase the risk of dementia.[104] Furthermore, certain genotypes have been associated with an increased risk of Alzheimer's disease, especially the apolipoprotein E (APOE) genotype (>50% risk for APOE4 homozygotes).[106]

The pathophysiology of Alzheimer's disease is characterized by the accumulation of β-amyloid and tau in plaques and tangles.[106] Vascular dementia is very different from Alzheimer's disease in terms of pathophysiology; by definition, vascular dementia is caused by a cerebrovascular pathology, including strategically located infarctions and hemorrhages.[107]

Existing knowledge on the association between MI and dementia is scarce. Only two smaller studies (n<500) have examined the risk of dementia after MI with equivocal findings.[76,77] A case-control study[77] demonstrated no association (odds ratio = 1.00, 95% confidence interval [CI] 0.62–1.62), whereas a cohort study[76] demonstrated an increased risk for patients with unrecognized MI (adjusted hazard ratio (HR) = 2.14, 95% CI 1.37–3.35), but not for patients with recognized MI, compared to patients without MI.

Mechanisms that may associate MI with dementia include clinical pathways involving post-MI stroke. Thus, it is well established that the risk of dementia is increased after stroke.[108] In particular, vascular dementia could result from multi-infarction stroke after MI as a consequence of complications, such as atrial fibrillation and hypokinesia of the left ventricle, which can lead to intracardiac thrombi with a potential for embolization. Severe heart failure after MI may also drive the increased risk of vascular dementia via chronic hypoperfusion of the brain, which can lead to watershed infarctions.[95] Hemorrhagic stroke may be facilitated by potent antithrombotic regimens as part of secondary prophylaxis for MI, prompting the development of vascular dementia. Finally, an association between MI and dementia may exist due to shared risk factors (*e.g.*, atherosclerosis) evolving over decades before presenting as an MI, followed by later onset of dementia.

### 2.11 Aims

The overall aim of this dissertation was to gain insight into the relations between MI and cerebral diseases including depression, stroke, and dementia. In study I we aimed to examine the positive predictive value (PPV) of diagnostic codes for all major cardiovascular diseases in the DNPR, as these were the foundation of the following studies. In study II we examined the impact of a history of depression on mortality following MI. In studies III–IV we examined the long-term risks of stroke and dementia following MI compared with the general population.

# 3. Methods

## 3.1 Setting

All studies were conducted in Denmark using Danish medical registries. Study I was performed in the Central Denmark Region, whereas studies II–IV were nationwide. The Danish health care system provides free and unfettered access to general practitioners and hospitals, ensuring a high level of equality in health care regardless of income, education, and geographic region or residence.[109] Each of the Danish registries has the possibility of unambiguous, individual-level data linkage with other registries owing to the unique 10-digit Danish Civil Personal Register number assigned to each Danish citizen at birth and to residents upon immigration.[110]

## 3.2 Data sources

*Medical records (study I)*

Study I used data from the medical records of sampled patients with cardiovascular diagnoses treated at Aarhus University Hospital, Herning Regional Hospital, or Randers Regional Hospital between 1 January 2010 and 31 December 2012.

*The Civil Registration System (studies I–IV)*

The Danish Civil Registration System has kept records of sex, date of birth, change of address, date of emigration, and change in vital statistics, including exact date of death, since 1968.[110]

*The Danish National Patient Registry (studies I–IV)*

The DNPR collects data on diagnoses and procedures for patients discharged from all Danish non-psychiatric hospitals since 1977. Each hospital discharge is assigned one primary diagnosis and up to 19 secondary diagnoses classified according to the *International Classification of Diseases* (Eighth Revision [ICD-8] until the end of 1993 and Tenth Revision [ICD-10] thereafter).[111]

*The National Registry of Causes of Death (study II)*

The National Registry of Causes of Death was established in 1943 and contains data on causes of death in Denmark.[112]

*The Danish Integrated Database for Labour Market Research (studies II and IV)*

The Danish Integrated Database for Labour Market Research (IDA) was established in 1990.[113] The registry holds information on socioeconomic data, including data on income, employment status, education level, and marital status, for the entire population since 1980.

*The Danish Psychiatric Central Research Register (studies II and IV)*

The Danish Psychiatric Central Research Register (DPCR) stores information on all psychiatric admissions since 1969 and outpatient treatment at psychiatric departments since 1995.[114] Diagnoses are classified according to ICD-8 until 1993 and ICD-10 thereafter.

*The Danish Registry of Medicinal Product Statistics (study II)*

The Danish Registry of Medicinal Product Statistics contains information on all prescriptions redeemed for drugs dispensed from community pharmacies in Denmark since 1 January 1995.[115] The information includes type of drug according to the Anatomic Therapeutic Chemical (ATC) classification system and date dispensed.

## 3.3 Study designs

Within the Danish healthcare system, we conducted one validation study (I) and three population-based cohort studies (II–IV).[116] In studies III-IV we employed a matched cohort design in which individuals from the general population served as comparators for the MI patients (Tables 5 and 6).[116]

**Table 5. Summary of methods.**

| | Study I | Study II | Study III | Study IV |
|---|---|---|---|---|
| Objectives | To examine the PPV of cardiovascular diagnoses in the DNPR | To examine the association between depression and all-cause mortality following first-time MI | To examine the long-term risk of stroke after first-time MI compared to risks in the general population | To examine the long-term risk of dementia after first-time MI compared to risks in the general population |
| Design | Population-based validation study | Population-based cohort study | Matched population-based cohort study | Matched population-based cohort study |
| Data sources | DNPR, CRS, medical records | DNPR, DPCR, CRS, IDA, Danish Registry of Medicinal Product Statistics, Danish Register of Causes of Death | DNPR, CRS | DNPR, DPCR, IDA, CRS |
| Study region and period | Central Denmark Region; 1 January 2010 to 31 December 2012 | Nationwide; 1 July 1995 to 1 February 2014 (end of follow-up: 1 September 2014) | Nationwide; 1 January 1980 to 31 December 2009 (end of follow-up: 31 December 2012) | Nationwide; 1 January 1980 to 1 September 2012 (end of follow-up: 31 December 2014) |
| Exposures | – | Pre-admission depression | MI | MI |
| Outcomes | PPV | All-cause mortality | Ischemic stroke, ICH, SAH | All-cause dementia and dementia subgroups (Alzheimer's disease, vascular dementia, and other dementias) |
| Matching | – | – | Year of birth, sex, calendar year | Year of birth, sex, calendar year |
| Covariables | – | Age groups, sex, hypertension, atrial fibrillation/atrial flutter, stroke, cancer, obesity, diabetes, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking abuse, dementia, income, employment, and calendar year interval | Congestive heart failure, angina pectoris, atrial fibrillation or flutter, heart valve disease, intermittent arterial claudication, venous thromboembolism, hypertension, obesity, diabetes, chronic kidney disease, and chronic pulmonary disease | Heart failure, stable angina pectoris, atrial fibrillation/atrial flutter, valvular heart disease, hypercholesterolemia, hypertension, stroke, intermittent claudication, obesity, diabetes, chronic pulmonary disease, myxedema, alcoholism-related disease, head trauma, osteoarthritis, anemia, chronic kidney disease, depression, a modified CCI score, income, and employment |
| Statistics | Wilson score method | Cox proportional hazards regression | Cox proportional hazards regression | Cox proportional hazards regression |
| Confounder control | – | Restriction, stratification, multivariable adjustment | Matching, stratification, multivariable adjustment | Matching, stratification, multivariable adjustment |
| Stratification | Sex, age group, calendar year (2010, 2011, and 2012), hospital type (regional or university hospital), type of diagnosis (primary or secondary), and type of hospital contact (inpatient or outpatient) | Sex, age groups, MI type (STEMI or NSTEMI), comorbidity, medication use, socioeconomic factors, calendar year intervals | Sex, age groups, comorbidity, calendar year intervals | Sex, age groups, comorbidity, CCI scores, socioeconomic status (income, employment, and education), calendar year intervals, primary or secondary MI diagnosis, complications and procedures during admission, complications during 1st year of follow-up (stroke and heart failure) |
| Sensitivity analyses | For venous thromboembolism, PPVs were recalculated according to ultrasound and/or CT scans during admission | First depression diagnosis (DNPR or DPCR); restriction to depression diagnoses made 90 days and 1, 2, and 3 years before the index date; additional adjustment for education, anxiolytics/hypnotics, antipsychotics, and cardiovascular diseases and drugs; omitting diabetes, stroke, and hypertension from the model | Specified ischemic stroke *vs.* unspecified stroke; redefinition of hypertension and diabetes to also include relevant medication (available 2005–2009) | Exclusion of the initial 2, 3, 5, and 10 years of follow-up; redefinition of Alzheimer's disease to also include the ICD code for unspecified dementia; additional adjustment for education |

Abbreviations: CCI, Charlson Comorbidity Index; CRS, Civil Registration System; DNPR, Danish National Patient Registry; DPCR, Danish Psychiatric Central Research Register; ICH, intracerebral hemorrhage; IDA, Integrated Database for Labour Market Research; MI, myocardial infarction; PPV, positive predictive value; SAH, subarachnoid hemorrhage

**Table 6. Design considerations of matched cohort studies and application in studies III–IV.**

| | Definition | Study III (MI-stroke) | Study IV (MI-dementia) |
|---|---|---|---|
| **Matching criteria** | | Year of birth, sex, calendar year | Year of birth, sex, calendar year |
| **Matching strategy** | *With replacement*: individuals from the general population comparison cohort can be matched with more than one MI patient.<br>*Without replacement*: Comparison cohort members can be matched with only one MI patient. | With replacement | With replacement |
| **Index date** | | Admission date for MI | Admission date for MI |
| **Exclusion criteria for MI/CC** | | Previous stroke or transient ischemic attack | Previous dementia, mild cognitive impairment or amnestic syndromes |
| **Approach when a member of the comparison cohort experiences an MI** | *"As treated"*: Transferred to the MI cohort and matched with new comparison cohort members from the general population, and discontinuation (censoring) of follow-up in the comparison cohort.<br>*"Intention-to-treat"*: Continue follow-up in the comparison cohort. | As treated | As treated |
| **Censoring at first outcome?** | | Censoring at first outcome | Censoring at first outcome |

Abbreviations: CC, comparison cohort; MI, myocardial infarction.

## 3.4 Study populations

The study population in all three cohort studies (studies II–IV) was patients with first-time MI, however, the study periods and follow-up intervals differed. We restricted the studies to first-time MI because patients with recurrent MI may differ substantially from patients with first-time MI. Moreover, recurrent MI is prone to coding errors (false positives, *e.g.*, during a follow-up visit in the outpatient clinic after first-time MI), although the PPV for recurrent MI (88%) is high compared with other recurrent events in the DNPR.[117]

In addition to excluding MI patients with the outcome of interest, in studies III and IV we also excluded MI patients with previous diseases relating to the outcome (*i.e.*, transient ischemic attack for study III, and mild cognitive impairment or amnestic syndromes for study IV). In study

IV, we disregarded *a priori* the first year of follow-up after MI because dementia is unlikely to be an immediate consequence of MI and detection bias shortly after MI was a major concern (*i.e.*, the possibility that demented, but undiagnosed, MI patients would be diagnosed due to surveillance and diagnostic work-up as part of post-MI management). The final study population for study IV is described in Figure 1.

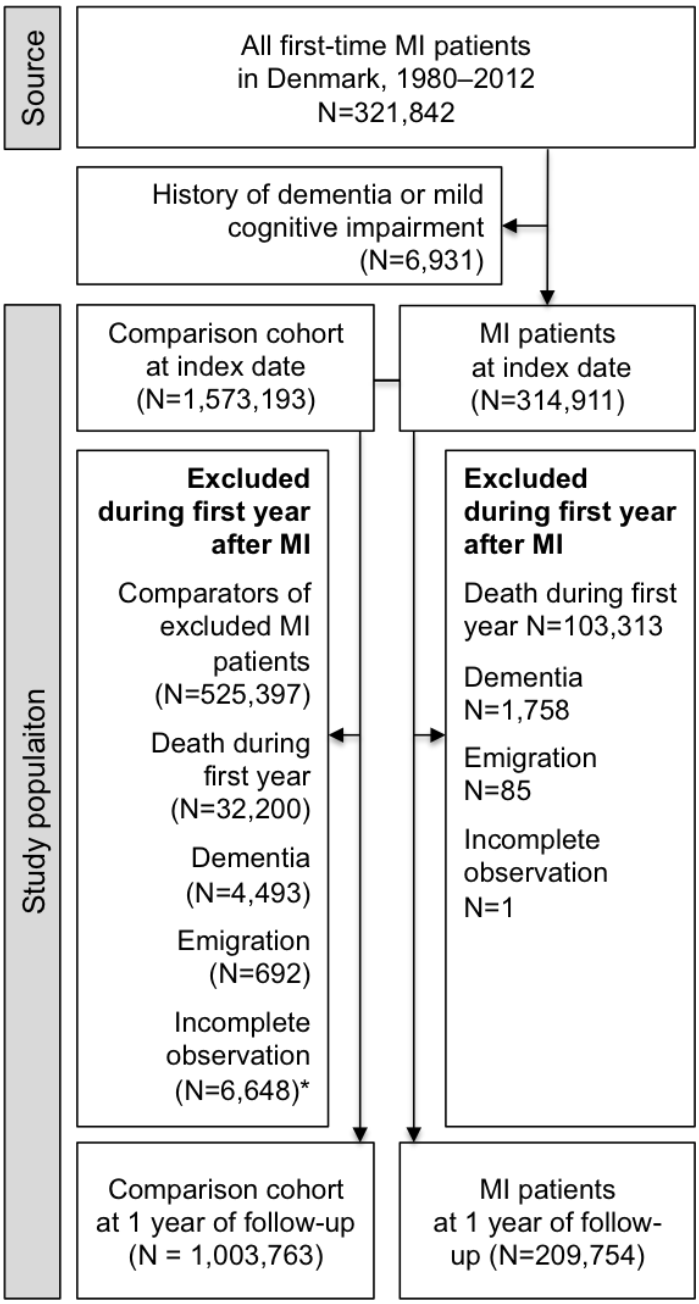


**Figure 1.**[118] Population of first-time myocardial infarction (MI) survivors and the general population comparison cohort for study IV. *6,625 of the 6,648 patients were censored because they had MI during the first year of follow-up, whereas the remainder became inactive in the Civil Registration System.

## 3.5 Exposures

*Depression (study II)*

The primary exposure in study II was defined as a first-time depression *diagnosis* prior to admission for MI. We included depression diagnoses recorded in both the DNPR[111] and DPCR.[114] To examine any trend in the severity of depression, we classified depression as mild, moderate, or severe disease using ICD-10 codes.[119]

As the majority of patients with depression are managed solely by their general practitioner and not included in hospital registries, we sought to increase the sensitivity of the depression exposure by including redeemed prescriptions for antidepressants in the definition. Based on this approach, we grouped patients into six categories by depression diagnoses and current/former antidepressant use (Table 8). We defined 'current users' as patients who redeemed a prescription for antidepressants within 90 days of MI and 'former users' as patients who redeemed their last prescription more than 90 days before the MI.

*Myocardial infarction (studies III–IV)*

In studies III–IV, the exposure and study population were identical and comprised first-time MI, which was compared with a general population cohort matched on age, sex, and calendar year. An external reference from the general population is necessary to provide comparators to the MI patients, who also comprise the study population. A general population comparison cohort enables the examination of MI as risk factor for the outcome, going beyond a mere description of the incidence after MI. Matching with a comparison cohort further provides an index date that can serve as a benchmark for the identification of covariables for multivariable adjustment.

## 3.6 Outcomes

In study II, all-cause mortality was retrieved from the Danish Civil Registration System.[110] As a secondary outcome, we examined immediate causes of deaths using data from the Danish Register of Causes of Death.[112] Specifically, we estimated non-cardiovascular and cardiovascular mortality, defining the latter as deaths caused by arrhythmia, venous thromboembolism, stroke, MI, or heart failure.

In study III, outcomes included first-time ischemic stroke, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH). From the DNPR,[111] we retrieved information on all inpatient hospitalizations for these stroke subtypes after MI admission. We used both primary and secondary stroke diagnoses to identify incident strokes.

In study IV, the primary outcome was dementia from any cause. In addition, we studied diagnoses of Alzheimer's disease, vascular dementia, and other dementias (defined as any specified or unspecified dementia other than Alzheimer's disease and vascular dementia) as secondary outcomes. Data on inpatient or outpatient dementia diagnoses were retrieved from the DNPR[111] and DPCR,[114] and we included both primary and secondary dementia diagnoses.

### 3.7 Covariables

A range of covariables was used in studies III–IV to enable characterization of the study populations, confounder adjustment, and stratification to identify potential effect modification. We obtained data on pre-MI comorbidity and the Charlson Comorbidity Index[33,120] from inpatient and outpatient diagnoses,[111,114] as well as data on age, sex, vital status,[110] procedures,[121] comedication use,[115] and socioeconomic data.[113]

### 3.8 Statistical analysis

The statistical analyses are summarized in Table 5 and will be described below. Statistical analyses were performed using STATA version 13.1 (studies I–III) and SAS version 9.4 (study IV).

For study I, we computed the PPV with 95% CIs according to the Wilson score method[122] for every cardiovascular disease included in the study. The PPV was computed as the proportion of diagnoses from the DNPR sample that could be confirmed as correct using the discharge summary or medical record as reference standard.

For studies II–IV, we tabulated patient characteristics for MI patients with and without depression (study II), and for MI and comparison cohort members (studies III–IV) to create contingency tables.[123] The matched cohort design in studies III–IV is summarized in Table 6.

The absolute risks of the outcomes were evaluated using the Kaplan Meier method (study II) and cumulative incidence functions taking death as a competing risk into account

(studies III-IV). The rationale for accounting for death as a competing risk is that death will prevent the outcome of interest from occurring. If death had not been considered as a competing risk, we would have overestimated the cumulative risk of outcomes in studies III–IV.[124] Death will act as a competing risk in any study in which the outcome is not all-cause mortality and is especially important to account for in studies with long-term follow-up (studies III–IV).[124]

Relative estimates were computed in time-to-event analyses[125] following all patients until the relevant outcome, death, emigration, or end of follow-up, whichever came first. We performed Cox proportional hazards regression modeling with time since MI admission as the underlying time scale to calculate HRs as a measure of the mortality rate ratio (MRR, study II) and incidence rate ratio (IRR, studies III–IV). The HR can be interpreted as a relative risk under the assumption that the HR is constant throughout the follow-up period (*i.e.*, hazards are proportional). We assessed the proportionality of hazards graphically using log minus log plots and found no violation of the assumption within the analyzed follow-up periods. We computed crude and adjusted HRs and 95% CIs for the studied outcomes.

We sought to circumvent possible confounding in studies II-IV by restriction, matching, adjustment, and stratification (Table 5). We based confounder selection on clinical knowledge and the published literature. Covariables were included if they were likely to be associated with both the exposure and outcome. We generally stratified results by age, sex, and clinically relevant diseases or drugs that could potentially modify the studied association (Table 5).[126]

We performed an array of sensitivity analyses to test the robustness of our results by employing different definitions of exposures and outcomes, as well as different statistical approaches (Table 5).

# 4. Results

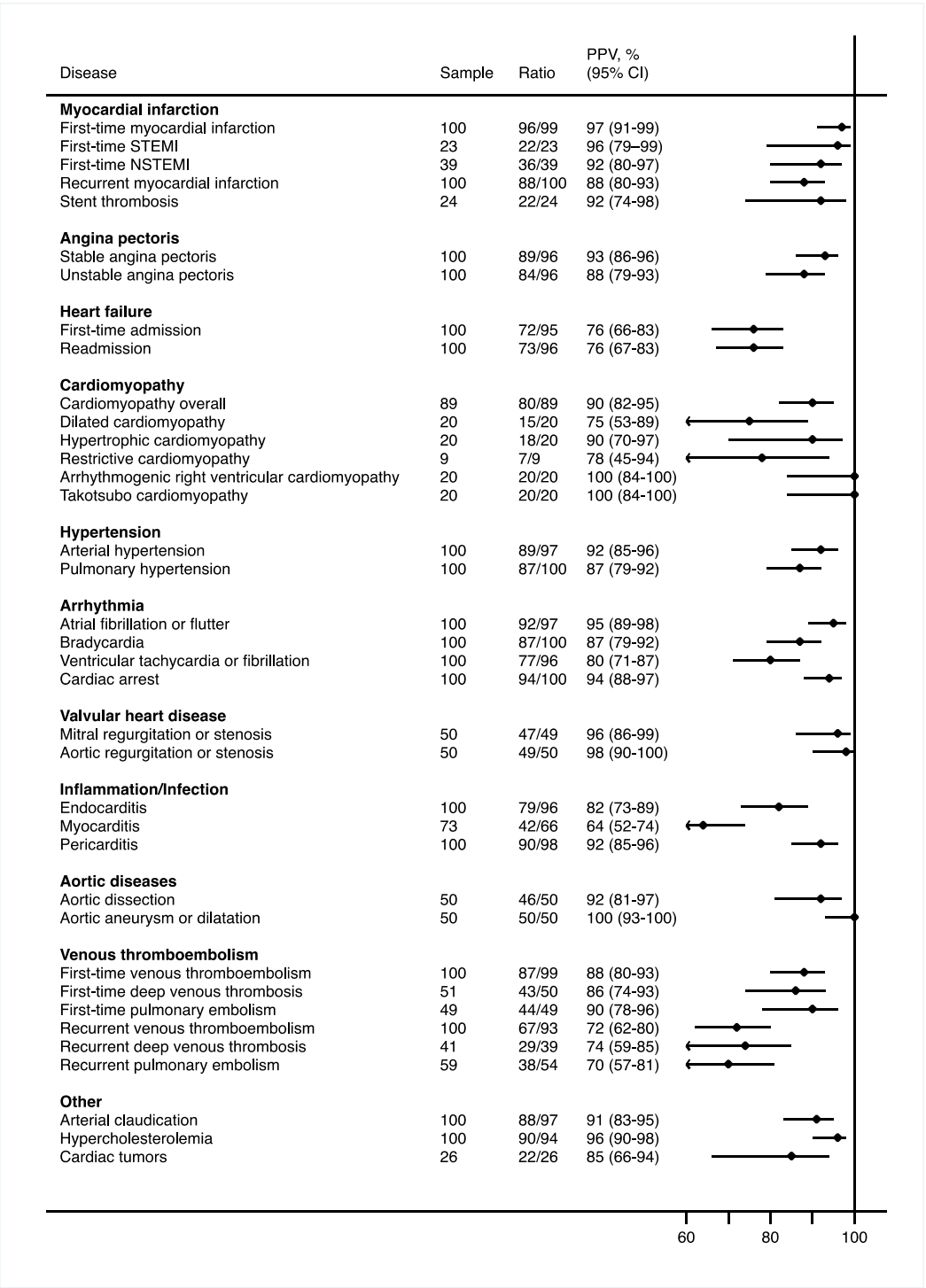


**Figure 2**.[117] Positive predictive values of cardiovascular diagnoses in the Danish National Patient Registry. Abbreviations: Ratio, confirmed diagnoses/available records; PPV, positive predictive value; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-STEMI.

### 4.1 Positive predictive value of cardiovascular diagnoses in the DNPR (study I)

We reviewed a total of 2153 medical records (97% of the entire sample) of patients with a cardiovascular diagnosis in the DNPR during 2010–2012. We reviewed a total of 11 disease entities corresponding to 36 individual diagnoses (Figure 2). For this dissertation, an essential diagnosis is that of first-time MI (study population in studies II–IV), including first-time STEMI and NSTEMI (additional analyses in studies II and IV). These diagnostic codes had very high PPVs (97% for first-time MI, 96% for first-time STEMI, and 92% for first-time NSTEMI). For all cardiovascular diagnostic codes examined, the PPV ranged from 64% to 100%, with a mean PPV of 88% (Figure 2). The PPVs were consistent within age, sex, calendar year, and hospital categories as well as for type of diagnosis (primary or secondary) and type of hospital contact (inpatient or outpatient) (Tables 2–4 in Appendix I).

### 4.2 Impact of depression on mortality following myocardial infarction (study II)

We identified a total of 170,771 patients with first-time MI (1995–2014, 3.5% with a previous depression diagnosis). Throughout the follow-up period, patients with MI and a prior diagnosis of depression had a higher mortality risk than those without a previous depression diagnosis (33% *vs.* 26% at 1 year and 87% *vs.* 78% at 19 years). The overall adjusted MRR was 1.11 (95% CI 1.07–1.15) when depression was based only on diagnoses in the DNPR and DPCR (Table 7), increasing to 1.22 (95% CI 1.17–1.27) when the definition included current use of antidepressants (Table 8). The severity of depression did not impact the results (Table 7). However, restricting to recent depression diagnosis strengthened the association equally for depression within 90 days, 1, 2, and 3 years of the MI (Table DS4 in Appendix II). The results remained largely unchanged when restricting to patients with either STEMI or NSTEMI (Table 4 in Appendix II). Further supporting the robustness of our results, we found similarly increased risks of mortality in strata of age group, gender, comorbidity, medication use, income, employment, and education (Figures DS1–5 in Appendix II).

**Table 7**.[127] Mortality estimates in myocardial infarction patients with and without a prior depression diagnosis, overall and by depression severity.

| | Mortality rate per 1000 PY (95% CI) | Crude mortality rate ratio (95% CI) | Adjusted mortality rate ratio (95% CI)[a] |
|---|---|---|---|
| No depression | 104.2 (103.6–104.9) | 1.0 (reference) | 1.0 (reference) |
| Depression overall (n=6015) | 168.1 (162.9–173.5) | 1.43 (1.38–1.47) | 1.11 (1.07–1.15) |
| Mild depression (n=798) | 209.2 (192.2–227.6) | 1.63 (1.50–1.77) | 1.11 (1.02–1.21) |
| Moderate depression (n=1778) | 170.3 (160.4–180.9) | 1.37 (1.29–1.46) | 1.14 (1.07–1.21) |
| Severe depression (n=768) | 179.2 (163.9–196.0) | 1.45 (1.32–1.58) | 1.15 (1.05–1.26) |

[a]Adjusted for age groups, sex, hypertension, atrial fibrillation/atrial flutter, stroke, cancer, obesity, diabetes, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking abuse, dementia, income, employment, and calendar year interval.
Abbreviations: CI, confidence interval; PY, person-years.

**Table 8**.[127] 19-year mortality rate ratios in myocardial infarction patients with and without previous depression (defined by depression diagnoses and use of antidepressants before the index date).

| | Crude mortality rate ratio (95% CI) | Adjusted mortality rate ratio (95% CI)[a] |
|---|---|---|
| **No prior depression diagnosis** | | |
| No use (n=138,405) | 1.0 (reference) | 1.0 (reference) |
| Former use (n=13,184) | 1.14 (1.11–1.17) | 1.06 (1.04–1.09) |
| Current use (n=13,167) | 1.79 (1.76–1.83) | 1.29 (1.26–1.32) |
| SSRI (n=8782) | 1.91 (1.86–1.96) | 1.30 (1.27–1.33) |
| TCA (n=2348) | 1.59 (1.52–1.67) | 1.27 (1.21–1.33) |
| **Prior depression diagnosis** | | |
| No use (n=1348) | 1.28 (1.19–1.36) | 1.01 (0.95–1.08) |
| Former use (n=1522) | 1.17 (1.10–1.26) | 1.10 (1.02–1.18) |
| Current use (n=3145) | 1.83 (1.76–1.91) | 1.22 (1.17–1.27) |
| SSRI (n=1771) | 1.93 (1.82–2.04) | 1.17 (1.11–1.24) |
| TCA (n=592) | 1.78 (1.62–1.95) | 1.34 (1.22–1.47) |

[a]Adjusted for age groups, sex, hypertension, atrial fibrillation/atrial flutter, stroke, cancer, obesity, diabetes, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking abuse, dementia, income, employment, and calendar year interval.
Abbreviations: CI, confidence interval; SSRI, selective serotonin inhibitors; TCA, tricyclic antidepressants.

## 4.3 Myocardial infarction and risk of stroke (study III)

We identified 258,806 patients with first-time MI and 1,244,773 matched comparators (1980–2009). Cumulative risks for ischemic stroke, ICH, and SAH were higher in the MI cohort throughout the first year of follow-up (Table 9). The cumulative risk during 1–30 years of follow–up was consistently higher in the MI cohort for ischemic stroke; however, for ICH and SAH, the curves crossed during 5–10 years of follow-up (Figure 1 in Appendix III) due to death as a competing risk, which was taken into account in the analyses.

For ischemic stroke, the adjusted stroke rate ratio (SRR) was 31.9 (95% CI 28.4–35.8) during 1–30 days of follow-up when comparing the MI cohort to the matched general population cohort. The adjusted SRR remained elevated during the ensuing 31–365 days (3.1, 95% CI 3.0–3.3) and 1–30 years (1.6, 95% CI 1.6–1.6). For ICH and SAH, the adjusted SRR was increased only during 1–30 days (ICH: 21.8, 95% CI 16.6–28.5; SAH: 16.6, 95% CI 8.7–32.0) and 31–365 days of follow-up (ICH: 2.1, 95% CI 1.9–2.5; SAH: 1.5, 95% CI 1.1–2.1), after which it approximated unity (ICH: 1.1, 95% CI 1.0–1.2; SAH: 1.1, 95% CI 0.94–1.2). Temporal trends revealed a decline in SRR during the first half of the study period, especially for ischemic stroke (Figure 2 in Appendix III).

**Table 9.**[128] Risk of stroke following myocardial infarction

| | **Stroke risk [a] % (95% CI)** | **Stroke rate[b] (95% CI)** | **Stroke rate ratio (95% CI)** Unadjusted | Adjusted[c] |
|---|---|---|---|---|
| **Ischemic stroke** | | | | |
| 1–30 days | | | | |
| Comparison cohort | 0.04 (0.03–0.04) | 4.6 (4.2–5.1) | 1 (reference) | 1 (reference) |
| MI cohort | 1.0 (0.92–1.0) | 146.0 (140.4–151.9) | 32.0 (28.6–35.7) | 31.9 (28.4–35.8) |
| 31–365 days | | | | |
| Comparison cohort | 0.43 (0.41–0.44) | 4.7 (4.6–4.9) | 1 (reference) | 1 (reference) |
| MI cohort | 1.3 (1.2–1.3) | 15.1 (14.5–15.7) | 3.3 (3.1–3.5) | 3.1 (3.0–3.3) |
| 1–30 years | | | | |
| Comparison cohort | 11.9 (11.8–12.0) | 7.9 (7.8–8.0) | 1 (reference) | 1 (reference) |
| MI cohort | 12.6 (12.4–12.8) | 10.8 (10.6–11.0) | 1.7 (1.6–1.7) | 1.6 (1.6–1.6) |
| **ICH** | | | | |
| 1–30 days | | | | |
| Comparison cohort | 0.01 (0.01–0.01) | 0.93 (0.76–1.1) | 1 (reference) | 1 (reference) |
| MI cohort | 0.12 (0.11–0.14) | 18.8 (16.8–21.0) | 21.6 (16.7–28.0) | 21.8 (16.6–28.5) |
| 31–365 days | | | | |
| Comparison cohort | 0.08 (0.08–0.09) | 0.89 (0.84–0.95) | 1 (reference) | 1 (reference) |
| MI cohort | 0.16 (0.13–0.17) | 1.8 (1.6–2.0) | 2.2 (2.0–2.6) | 2.1 (1.9–2.5) |
| 1–30 years | | | | |
| Comparison cohort | 1.6 (1.6–1.7) | 1.1 (1.1–1.1) | 1 (reference) | 1 (reference) |
| MI cohort | 1.2 (1.2–1.3) | 1.1 (1.0–1.1) | 1.1 (1.1–1.2) | 1.1 (1.0–1.2) |
| **SAH** | | | | |
| 1–30 days | | | | |
| Comparison cohort | 0.00 (0.00–0.00) | 0.19 (0.12–0.29) | 1 (reference) | 1 (reference) |
| MI cohort | 0.02 (0.01–0.02) | 2.8 (2.1–3.8) | 14.5 (8.2–25.5) | 16.6 (8.7–32.0) |
| 31–365 days | | | | |
| Comparison cohort | 0.02 (0.01–0.02) | 0.19 (0.17–0.22) | 1 (reference) | 1 (reference) |
| MI cohort | 0.03 (0.02–0.03) | 0.30 (0.23–0.40) | 1.5 (1.1–2.1) | 1.5 (1.1–2.1) |
| 1–30 years | | | | |
| Comparison cohort | 0.29 (0.28–0.30) | 0.20 (0.19–0.21) | 1 (reference) | 1 (reference) |
| MI cohort | 0.24 (0.21–0.27) | 0.22 (0.20–0.25) | 1.1 (0.97–1.3) | 1.1 (0.94–1.2) |

[a]Treating death as a competing risk.
[b]Rates per 1000 person-years.
[c]Adjusted for congestive heart failure, angina pectoris, atrial fibrillation or flutter, heart valve disease, intermittent arterial claudication, venous thromboembolism, hypertension, obesity, diabetes, chronic kidney disease, and chronic pulmonary disease.
Abbreviations: CI, confidence interval; MI, myocardial infarction; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage.

## 4.4 Myocardial infarction and risk of dementia (study IV)

We identified 314,911 patients with a first-time MI and 1,573,193 matched comparators (1980–2012). One-year survivors constituted 209,754 MI patients and 1,003,763 comparators (Figure 1). Of 11,334 patients diagnosed with dementia, 32% had Alzheimer's disease, 18% had vascular dementia, and 50% had other dementias. The cumulative incidence of all-cause dementia was 8.7% in the MI cohort at the end of follow-up, which was lower than in the comparison cohort due to competing mortality in the MI cohort (Table 10). No association was found for all-cause dementia or other dementias compared with the general population cohort. For the dominant subtypes, MI was associated with a marginally decreased risk of Alzheimer's disease (adjusted HR = 0.92, 95% CI 0.88–0.95), whereas the risk of vascular dementia was increased (adjusted HR = 1.35, 95% CI 1.28–1.43). We observed an additionally increased risk of vascular dementia in patients experiencing stroke during follow-up (adjusted HR = 4.48, 95% CI 3.29–6.12, Table 3 in Appendix IV). Overall, the results were robust in stratified and sensitivity analyses (Supplementary Tables 3–7 in Appendix IV).

**Table 10**.[118] Cumulative incidence and hazard ratios for dementia.

| | Comparison cohort | | Myocardial infarction patients | | | |
|---|---|---|---|---|---|---|
| **Years since diagnosis** | **Events/No. at risk** | **Cumulative incidence risk, % (95% CI)** | **Events/No. at risk** | **Cumulative incidence risk, % (95% CI)** | **Hazard ratio controlled for matching factors[a] (95% CI)** | **Adjusted hazard ratio (95% CI)[b]** |
| **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) |

[a]Age, sex, and calendar year
[b]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, chronic pulmonary disease, myxedema, alcoholism-related disease, head trauma, osteoarthritis, anemia, chronic kidney disease, depression, modified Charlson Comorbidity Index score, income, and employment.
Abbreviations: CI, confidence interval

# 5. Discussion

## 5.1 Main conclusions

In general, we found high PPVs for cardiovascular diseases in the DNPR, particularly MI diagnoses. Preceding depression was a moderate adverse prognostic factor for all-cause mortality after MI. The association was independent of depression severity but strengthened by recent depression and current use of antidepressants. During the first year after MI, the risk for all stroke subtypes was increased, but only the risk of ischemic stroke was increased thereafter. MI was not associated with all-cause dementia or Alzheimer's disease, but the risk of vascular dementia was continuously increased, especially in patients experiencing stroke during the first year after MI.

## 5.2 Comparison with existing literature

In the following sections, an updated discussion of our findings is provided for each study in light of relevant literature published at the time of writing (Tables 1–4).

### *5.2.1 Positive predictive value of cardiovascular diagnoses in the DNPR*

Only 11 of 36 diagnoses (~30%) included in study I had previously been validated and typically with only one diagnosis examined in each study. For most of these diagnoses, the overall impression was that the PPVs have improved over time. Presumably, this positive development was driven by an increased awareness of the importance of accurate coding, simplified diagnostic criteria for several of the diseases,[15] and improved and readily available diagnostic modalities. The previously studied PPV for the MI diagnosis in the DNPR improved from 93% during 1982–1991[35] and 92% during 1993–2003[34] to 98% during 1998–2007[33] and 100% during 1996–2009.[32] Thus, the PPV for MI has consistently exceeded 90% during the study periods of studies II–IV with a slight tendency to increase over time. For discussion of other validated cardiovascular diagnoses not directly pertinent to studies II–IV, see Table 1 and Appendix I.

Study I was limited by a narrow study period (2010–2012), implying that results cannot necessarily be extrapolated to previous calendar periods. We also acknowledge that we only considered one aspect of data quality, namely the PPV. Other important measures of data quality include sensitivity, specificity, and negative predictive values, which were not included in study I. At the time of writing, no validation studies have been published on cardiovascular diagnoses in the DNPR since the publication of study I.

### *5.2.2 Impact of depression on mortality following myocardial infarction*

Studies of the association between depression and MI mortality are summarized in Table 2. To circumvent the problems related to studies using a post-MI assessment of depression, we considered the impact of preadmission depression on mortality after MI. Employing this approach to the definition of exposure, we found only a moderately increased risk of death in MI patients with prior depression. Supporting only a modest impact of depression on post–MI mortality, the multicenter ENRICHD trial from 2003 (n=2481 MI patients with accompanying depression) demonstrated no effect on the primary outcome (composite of death or recurrent MI) of cognitive behavior therapy or the administration of selective serotonin reuptake inhibitors after MI.[90] However, an observational cohort study published after the acceptance of study II indicated that patients with treated depression did not have different 1-year mortality risks than patients without depression (6.7% *vs*. 6.1%, adjusted HR = 1.12, 95% CI 0.63-1.99), whereas patients with untreated depression had higher 1-year mortality (10.8% *vs*. 6.1%, adjusted HR = 1.91, 95% CI 1.39-2.62).[47]

The majority of post-MI depression studies were included in recent meta-analyses reporting a stronger association with all-cause mortality than our findings (relative risks = 1.23, 95% CI 1.15– 1.31[49] and 1.80, 95% CI 1.50–2.15[54]). Only three studies have examined the impact of preadmission depression on mortality after MI, reporting either no association with mortality[45,46] or a modest increase.[44] However, these studies were limited by a focus on psychiatric comorbidity in general,[44] a lack of power to detect any moderate association with depression,[45,46] short follow-up (<1 year),[44,46] inclusion of selected hospitals,[44-46] and use of self-report questionnaires and medical chart review to detect preadmission depression.[45,46]

In summary, most previous studies examined the effect of post-MI depression and found stronger associations with MI mortality. One study examined preadmission psychiatric comorbidity in general, reporting a moderately increased mortality risk,[44] and only two studies considered pre-admission depression, finding no association with mortality.[45,46] In a large population we were able to detect a moderate impact of preadmission depression. Thus, the timing of exposure assessment seems critical.

### *5.2.3 Myocardial infarction and risk of stroke*

The association between MI and stroke has been examined before, but with the previously described limitations. Importantly, the majority of studies were descriptive or without comparators to the MI patients. Only two studies included comparators without MI.[67,74]

In a community-based cohort study in Rotterdam, Ikram *et al*.[67] examined the association of recognized and unrecognized MI with the risk of ischemic stroke compared with individuals without MI. The discrimination between persons with recognized MI, unrecognized MI, and no MI was based on ECGs at baseline combined with self-reported questions regarding the history of MI. If there were signs of a previous MI in the ECG but no report of a history of MI, the MI was categorized as unrecognized. Patients were followed for a mean of 8 years. Men (but not women) with unrecognized (aHR=3.22, 95% CI 1.96–5.28) and recognized (aHR=1.84, 95% CI 1.16–2.91) MI had increased risk of ischemic stroke. The results support our findings, although we did not capture unrecognized MI.

Witt *et al*.[74] examined the risk of unspecified stroke in MI patients compared with the incident stroke rate in the general population of Rochester, Minnesota, US (1979–1998). They used data from the Rochester Stroke Registry to calculate expected stroke rates based on sex-, age-, and calendar period-specific stroke rates in the general population. The standardized morbidity ratio was computed as the observed number of strokes relative to the expected. Witt *et al*. reported a 44-fold increase in stroke risk during the first 30 days after MI (standardized morbidity ratio = 44, 95% CI 32–59), which is in line with our finding of a 32-fold increased risk of ischemic stroke during 1–30 days of follow-up. During the period from 30 days to 3 years of follow-up, the standardized morbidity ratio decreased from 3 to 2 and remained at 1.6 during 4–

5 years of follow-up. These findings for longer-term risk are likewise very similar to our estimates for ischemic stroke. Although the estimates reported by Witt *et al*. were not adjusted and did not discriminate between ischemic and hemorrhagic stroke, this is the only study with a reference group comparable to ours.

In summary, most previous studies described the incidence of stroke after MI (Table 3), and only two cohort studies made comparisons to individuals without MI.[67,74] Witt *et al*.[74] had comparators similar to ours from the general population, and their results largely agreed with our findings for ischemic stroke, whereas the study by Ikram *et al*.[67] supported our findings overall without being directly comparable.

### *5.2.4 Myocardial infarction and risk of dementia*

The association between MI and dementia has only been examined sparsely in one cohort study[76] and one case control study.[77] Ikram *et al*.[76] used the same approach as described previously[67] to examine the risk of dementia in patients with recognized and unrecognized MI compared with individuals without MI. In men, but not women, unrecognized MI was associated with an increased risk of dementia (adjusted HR = 2.14; 95% CI 1.37–3.35), more white matter lesions, and more frequent brain infarction on MRI. Recognized MI was not associated with dementia in either sex. The study considered only all-cause dementia and had no general population comparison cohort. Despite this, their finding of no association with all-cause dementia after recognized MI is in line with our findings.

Bursi *et al*.[77] conducted a case-control study, identifying 916 cases of all-cause dementia and 916 age- and sex-matched controls. For both cases and controls, preceding MI was present in 36 cases. The corresponding odds ratio for MI was 1.00 (95% CI 0.62–1.62) among cases with dementia compared with controls. Bursi *et al*. also focused only on all-cause dementia and thus agreed with our findings in study IV.

In summary, one cohort study[76] and one case-control study[77] examined the association between MI and dementia (Table 4), both focusing solely on all-cause dementia and reporting no association with MI.

## 5.3 Methodological considerations

Registry-based epidemiological research offers the opportunity to conduct studies of risk, prognosis, and prediction that would be impossible or unethical in a clinical setting. The advantages of registry-based research include the possibility for large, nationwide, population-based research using prospectively collected data. In Denmark, free and equal access to primary and hospital care, together with virtually complete follow-up for every individual, largely eliminate selection bias.[110]

However, the advantages of registry-based research come at the expense of methodological limitations. Between a simple association and causality lie a number of epidemiological phenomena, including random and systematic error that can hinder causal inference. Random error is reflected in the precision of the estimates.[129] Systematic error encompasses selection bias, information bias, and confounding.[130] Selection and information biases are systematic errors inherent to the study design and cannot be corrected in the analysis phase.[130] However, confounding can be controlled for in the design phase by randomization, restriction, and matching, and in the analysis phase by standardization, stratification, and adjustment.[130] Moreover, registry-based studies are dependent on the quality of the registry data, which can be evaluated only through cumbersome validation studies.[131,132]

Below follows a discussion of potential problems and how we sought to limit their impact on our results.

### *5.3.1 Statistical precision*

The width of the CIs reflected the precision in all studies.[129] CIs enable inference based on the strength of an association in combination with the level of precision.[133]

In study I, we reviewed more than 2,000 medical records aiming at a sample of up to 100 cases for each diagnosis in the DNPR to ensure appropriate precision of the estimated PPVs. However, the precision in stratified analyses was lower and could have been avoided with a larger sample, if that had been feasible. The large, population-based cohorts in studies II–IV in combination with a large number of outcomes resulted in high statistical precision in the primary results, which were unlikely to be caused by chance.[129] Furthermore, the large numbers allowed

examination of possible effect modification in subsets of the cohorts while sustaining an appropriate level of precision in most analyses.

### *5.3.2 Selection bias*

Selection bias is systematic error arising when the association between exposure and outcome differs for those included and those excluded from a study.[130] Loss to follow-up may also introduce selection bias when it is related to both the exposure and the outcome. Because the association among non-participants is rarely known, selection bias cannot be fully quantified, only assumed.[130]

For reasons of feasibility, study I was limited to three specific hospitals within the Central Denmark Region, which is one of five regions in Denmark.[109] This restriction was reasonable as the Danish health care system is homogenous across regions in terms of demographic composition, coding practice, socioeconomic characteristics, and healthcare usage.[109] Each region typically has one major university hospital and several smaller regional hospitals.[109] Therefore, we included Aarhus University Hospital and two regional hospitals (Randers and Herning regional hospitals) to reflect the health care structure within a region. In addition, the study period was restricted to 2010–2012; however, the validity of the MI diagnosis during previous calendar periods covered in studies II–IV has been examined in previous studies.[32-35]

In studies II–IV we employed nationwide population-based designs within the setting of a tax-supported universal healthcare system, largely eliminating selection biases stemming from the selective inclusion of specific regions, hospitals, health insurance systems, socioeconomic categories, age groups, or ethnicities. Moreover, studies II–IV were based on nationwide population-based registries (the Danish Civil Registration System[110] and the Danish National Patient Registry[111]) with virtually complete follow-up.

### *5.3.3 Information bias*

Information bias arises when systematic error is present in the measurement of information about study participants, resulting in misclassification of exposure, outcome, or covariables.[130]

Misclassification can be either differential or non-differential. Differential misclassification can bias results in either direction, whereas non-differential misclassification most often biases the estimate of association towards unity, particularly for dichotomous variables, which were predominantly employed in studies II–IV. In studies II–IV, misclassification of exposures would be differential if dependent of the outcomes (and vice versa).[130] All studies in this dissertation were based on prospectively recorded data that eliminate recall bias, reducing the risk of differential misclassification. In the following sections, we discuss misclassification of exposures and outcomes in studies II–IV.

*Misclassification of depression*

For the main analysis in study II, we based the definition of depression only on registry-based diagnoses, yielding a prevalence of only 3.5% rather than the ~20% in previous reports.[134] Depression based only on registry diagnoses misclassifies depression managed solely in primary care. If independent of the outcome, this misclassification would bias the association with MI mortality towards the null, which is reflected by the additionally increased mortality risk in analyses including antidepressants in the definition of depression. In these analyses, we only had 6 months of prescription history for the first patients included in the study, as The Danish Registry of Medicinal Product Statistics was initiated 1 January 1995[115] and our study period started 1 July 1995. This could potentially lead to similar misclassification of depressed patients and bias towards the null. Although depression is the main indication for use of antidepressants, patients with other conditions (*e.g.*, anxiety, stress, pain) are also prescribed these drugs, which likely has caused misclassification of a number of patients with depression. The consequence of this misclassification is less predictable and depends on how the underlying conditions are associated with the outcome. However, in Denmark, as opposed to other European countries, antidepressants are less frequently used for other indications than depression.[135]

The PPV of the depression diagnosis in the DPCR has previously been reported to be high for severe depression (83%) but somewhat lower for moderate (76%) and mild depression (65%).[119] The validity of the depression diagnosis in the DNPR has not been examined; however,

we obtained nearly identical results when separately analyzing individuals with depression registered in the DNPR and the DPCR.

In summary, misclassification of depression due to underreporting in the registries has presumably biased the association with MI mortality towards the null in the main analysis employing only diagnoses to detect previous depression.

*Misclassification of myocardial infarction*

MI is one of the most validated diagnoses in the DNPR, and the PPV has consistently ranged between 90% and 100% since 1982,[32-35,117] whereas the sensitivity of the MI diagnosis has been found to be somewhat lower (~70% during 1982–1991 when including both primary and secondary inpatient MI diagnoses).[35] A high PPV is important when identifying a study population as in studies II–IV. In studies III–IV, MI also serves as the exposure, where sensitivity and specificity are also important. However, any misclassification of MI due to low sensitivity or specificity would likely be non-differential and bias the association with outcomes in studies III–IV towards the null, provided that the misclassification of MI patients is independent of the outcomes.

*Misclassification of outcomes*

In study II, all-cause mortality was the primary outcome. We based all-cause mortality on vital status in the Danish Civil Registration System, which holds complete and accurate data with daily electronic updates.[110] Therefore, misclassification of all-cause mortality is unlikely.[110]

In study III, we classified unspecified strokes (~40% of all stroke diagnoses) as ischemic strokes because approximately two-thirds of unspecified strokes have been shown to be ischemic strokes.[136] Despite the known misclassification of a few hemorrhagic strokes as ischemic strokes, the results in sensitivity analyses were robust when separately analyzing specified ischemic stroke and unspecified stroke. The PPV of inpatient stroke diagnoses (primary or secondary) in the DNPR has been estimated to be 97% for ischemic stroke, 74% for ICH, and 67% for SAH.[136] The sensitivity of overall stroke in the DNPR (inpatients with a primary diagnosis) has been reported to be roughly 60%.[137] If the sensitivity of the stroke diagnosis was equally low in the MI

and comparison cohorts, this would not have affected our results. However, if the sensitivity of the stroke diagnosis was higher among MI patients due to surveillance bias, this would lead to differential misclassification of stroke and tend to overestimate the association between MI and stroke.

The same concern applies to the dementia outcomes in study IV. However, as we found a null result for all-cause dementia, the greater concern in study IV is channeling bias within subgroups of dementia, *i.e.* that demented patients with a previous MI are more likely diagnosed with vascular dementia than other types of dementia. Such bias would be differential and may have resulted in an overestimation of the risk of vascular dementia. The PPV for all-cause dementia has been reported to be relatively high (86%), but lower for subtypes of dementia.[138] The sensitivity of dementia in the DNPR is unknown.[111]

In summary, differential misclassification of stroke and vascular dementia among MI patients due to surveillance and channeling bias, respectively, would tend to overestimate the association with MI.

### *5.3.4 Confounding*

To act as a confounder, a factor must be associated with both the exposure and the outcome without being an intermediate step on the causal pathway between exposure and outcome.[130] Thus, a confounder must be a cause (or marker) of the outcome and unbalanced between the exposure groups.[130] In studies II–IV, we aimed to limit potential confounding by matching, adjusting, and stratifying by an array of potential confounding factors. Nevertheless, the observational nature of our study renders it vulnerable to residual and unmeasured confounding.

In study II, we lacked data on smoking, which was likely more prevalent among patients with depression.[88] Paradoxically, depression is associated with a decreased risk of death after MI,[139] and therefore would lead to an underestimation of the association. However, we adjusted for illicit drug/alcohol/smoking abuse and for chronic obstructive pulmonary disease as proxy measures for chronic smoking exposure. Furthermore, in a meta-analysis of the association between depression and mortality after MI, additionally adjusting for smoking only attenuated the association by 1%.[49]

In study III, smoking was a potentially unmeasured confounder and was handled as in study II, although we did not have information on illicit drug/alcohol/smoking abuse. Residual confounding by diabetes and hypertension could also affect the estimates. Diabetes and hypertension are key risk factors for MI and especially stroke.[140] In the main analysis, we only based information on diabetes and hypertension on diagnoses in the DNPR. However, when we included medication in the definition of hypertension and diabetes (data available from 2005 to 2009), the main results remained unchanged.

In study IV, smoking was also a potential confounder associated with both MI[141] and dementia[142] and was handled as in study III. Other potential confounders for which we lacked data in study IV included APOE4 genotype, homocysteine levels, and physical activity, which are all associated with cardiovascular disease and dementia.[105,143,144]

In studies II–IV, life style factors in general (*e.g.*, smoking and physical activity) were potential confounders and were indirectly adjusted for by socioeconomic status (only studies II and IV) and life style diseases, such as chronic obstructive pulmonary disease, diabetes, obesity, and cardiovascular disease other than MI.

### 5.4 Perspectives

The essential aim of medical science is to improve prognosis through the optimization of diagnostic tests and treatments. A major knowledge gap exists in terms of clinical pathways determining mortality after diseases such as MI. Identifying these pathways is essential to guide secondary and tertiary prevention after MI and ultimately improve prognosis.

The studies in this dissertation add to the scientific knowledge regarding the prognostic impact of preadmission depression on MI mortality (study II) and the risk of stroke and dementia following MI (studies III–IV).

Study II adds to an increasing body of evidence suggesting that depression may be a prognostic factor for mortality after MI; however, our results suggest only a modest impact of depression on mortality. Still, our findings merit attention to MI patients with previous depression, as this subset of patients may be additionally vulnerable, especially when depression is active as indicated by a recent depression diagnosis or current use of antidepressants.

Studies III and IV provide new evidence of the long-term risk of stroke and dementia after MI compared with a general population cohort. Clinical attention on ischemic and hemorrhagic stroke is important especially in the early phase after MI. Thereafter, risks subside rapidly to towards unity after 1 year for hemorrhagic stroke whereas the risk of ischemic stroke remains moderately increased for decades after MI. Current management of MI does not adequately protect against stroke, especially shortly after MI. Our reports of the temporal development of stroke risk after MI may assist in determining the appropriate timing and duration of preventive strategies after MI.

In 1-year survivors of MI, attention to the continuously increased risk of vascular dementia seems prudent, although our results need confirmation. In the absence of a disease-modifying treatment for most forms of dementia, the identification of MI as a risk factor for vascular dementia holds the possibility of directing tertiary prevention of dementia after MI.

Looking forward, important questions remain to be answered, including the clinical pathways underlying the increased mortality in depressed MI patients. Identifying these pathways may enable a more targeted preventive strategy following MI. Confirmatory studies of pre-MI depression in other cohorts are also important to approximate the true strength of the association with mortality. Studies III–IV are the first to examine the long-term risk of stroke and dementia, and confirmatory studies are needed to verify our findings beyond 1 year of follow-up. Study IV was the first to include subgroups of dementia, and our findings need confirmation in different settings to clarify the risk distribution among dementia subtypes. Finally, studies of other neurological outcomes that may result from emboli and hypoperfusion after MI are needed.

## 6. Summary

The connection between the heart and mind has been studied since Sir William Harvey observed more than 350 years ago that negative emotions adversely affect the heart. Today, we know that diseases of the mind can affect the heart and, conversely, that heart diseases can cause both physical and mental diseases of the brain. To explore this relation further, we examined how previous depression affects survival in patients with myocardial infarction (MI) (study II), and how the occurrence of MI affects the risk of ischemic and hemorrhagic stroke (study III) and dementia (study IV). These studies were preceded by a validation study including all major cardiovascular diagnoses in the Danish National Patient Registry (study I). Studies II–IV are population-based cohort studies, of which studies III–IV are matched cohort studies. We identified antidepressant use from prescription registries and used nationwide databases to identify study populations and retrieve data on outcomes and comorbidity.

In study I (2010–2012), we reviewed a total of 2,153 medical records from one university hospital and two regional hospitals in the Central Denmark Region. We randomly sampled up to 100 cases for each cardiovascular diagnosis. Medical record review served as reference standard to compute the positive predictive value for each diagnosis. For first-time MI, the positive predictive value was 97% (95% CI 91%–99%) and exceeded 90% for the most common cardiovascular disease entities.

In study II (1995–2014), we identified 170,771 patients with first-time MI. Previous depression was identified by either a depression diagnosis or the use of antidepressants. Patients with MI and a previous depression diagnosis had higher 19-year mortality risks (87% *vs*. 78%). The overall adjusted mortality rate ratio was 1.11 (95% CI 1.07–1.15), increasing to 1.22 (95% CI 1.17–1.27) when including the use of antidepressants in the definition of depression. The association was stronger in patients with recent depression but was not influenced by depression severity or type of MI.

In study III (1980–2009), we identified 258,806 patients with a first-time MI and 1,244,773 sex-, age-, and calendar year-matched individuals from the general population, and followed them for development ischemic or hemorrhagic stroke. During the first 30 days after MI, the adjusted stroke rate ratio was 31.9 (95% CI 28.4–35.8) for ischemic stroke, 21.8 (95% CI

16.6–28.5) for intracerebral hemorrhage (ICH), and 16.6 (95% CI 8.7–32.0) for subarachnoid hemorrhage (SAH) compared with the general population. The adjusted stroke rate ratio remained increased during 31 to 365 days (3-fold for ischemic stroke, 2-fold for ICH, and 1.5-fold for SAH). During the following 1 to 30 years, the risk remained 1.6-fold increased for ischemic stroke but decreased to near unity for ICH and SAH.

In study IV (1980–2012), we identified 314,911 patients with first-time MI and 1,573,193 sex-, age-, and calendar year-matched individuals from the general population and followed 1-year survivors for development of dementia. Compared with the general population cohort, MI patients were not at increased risk of all-cause dementia (adjusted hazard ratio = 1.01, 95% CI 0.98–1.03). In subgroups of dementia, we observed no substantial association with Alzheimer's disease (adjusted hazard ratio = 0.92, 95% CI 0.88–0.95) or other dementias (adjusted hazard ratio = 0.98, 95% CI 0.95–1.01). However, patients with MI had an increased risk of vascular dementia (adjusted hazard ratio = 1.35, 95% CI 1.28–1.43).

In conclusion, we found that preceding depression was associated with moderately increased mortality after MI, and that MI was associated with an increased risk of stroke and vascular dementia, but not dementia from other causes.

## 7. Dansk resume

Forbindelsen mellem hjerte og sind er blevet studeret siden Sir William Harvey observerede at negative følelser havde skadelig indvirkning på hjertet. I dag ved vi, at mentale sygdomme kan påvirke hjertet og, omvendt, at hjertesygdomme kan forårsage både fysiske og mentale sygdomme i hjernen. For at undersøge dette samspil yderligere, undersøgte vi hvordan tidligere depression påvirker overlevelsen efter blodprop i hjertet (studie II), og dernæst hvordan blodprop i hjertet påvirker risikoen for udvikling af blodprop og blødning i hjernen (studie III) samt demens (studie IV). Disse studier blev forudgået af et valideringsstudie inkluderende størstedelen af kardiovaskulære diagnoser i Landspatientregistret (studie I). Studie II–IV er populations-baserede kohortestudier, hvoraf studie III-IV er matchede kohortestudier. Vi identificerede brug af antidepressiv medicin fra receptregistre og brugte landsdækkende databaser til at identificere studiepopulationer og udtrække data på endepunkter og komorbiditet.

I studie I (2010–2012) gennemgik vi 2.153 patientjournaler fra et universitetshospital og to regionshospitaler i Region Midtjylland. Vi udtrak tilfældigt op til 100 sygdomstilfælde for hver diagnose. Vi anvendte gennemgang af patientjournaler som referencestandard for beregning af den positive prediktive værdi for hver kardiovaskulære diagnose. For blodprop i hjertet var den positive prædiktive værdi 97% (95% CI 91%–99%) og oversteg 90% for de hyppigste kardiovaskulære sygdomme.

I studie II (1995–2014) identificerede vi 170.771 patienter med førstegangs blodprop i hjertet. Vi identificerede forudgående depression som enten en depressionsdiagnose eller brug af antidepressiv medicin. Patienter med blodprop i hjertet og en tidligere depressionsdiagnose havde højere 19 års mortalitetsrisiko (87% *vs*. 78%). Den overordnede justerede mortalitetsrate ratio var 1.11 (95% CI 1.07–1.15), men steg til 1.22 (95% CI 1.17–1.27) når brug af antidepressiv medicin blev inkluderet i definitionen af depression. Associationen var stærkere hos patienter med nylig depression, men var upåvirket af sværhedsgraden af depression og typen af blodprop i hjertet.

I studie III (1980–2009) identificerede vi 258.806 patienter med førstegangs blodprop i hjertet og 1.244.773 køns- og alders- og kalenderårsmatchede individer fra

baggrundsbefolkningen og fulgte dem for udvikling af slagtilfælde (blodprop eller blødning i hjernen). De første 30 dage efter blodprop i hjertet var den justerede incidens rate ratio 31.9 (95% CI 28.4–35.8) for blodprop i hjernen, 21.8 (95% CI 16.6–28.5) for intracerebral blødning og 16.6 (95% CI 8.7–32.0) for subaraknoidalblødning sammenlignet med baggrundsbefolkningen. Den justerede incidens rate ratio for slagtilfælde forblev øget fra 31 til 365 dage efter blodprop i hjertet (3 gange øget for blodprop i hjernen, 2 gange øget for intracerebral blødning og 1,5 gange øget for subaraknoidalblødning). I de følgende 1–30 år forblev risikoen for blodprop i hjernen 1,6 gange øget mens den ikke var øget for intracerebral blødning og subaraknoidalblødning.

I studie IV (1980–2012) identificerede vi 314.911 patienter med førstegangs blodprop i hjertet og 1.573.193 køns-, alders- og kalenderårsmatchede individer fra baggrundsbefolkningen og fulgte 1-års overlevere for udvikling af demens. Sammenlignet med baggrundsbefolkningen var patienter med blodprop i hjertet ikke i øget risiko for udvikling af demens uanset årsag (justeret hazard ratio = 1.01, 95% CI 0.98–1.03). I subgrupper af demens observerede vi ingen substantiel association med Alzheimer's sygdom (justeret hazard ratio = 0.92, 95% CI 0.88–0.95), eller andre typer demens (justeret hazard ratio = 0.98, 95% CI 0.95–1.01). Patienter med blodprop i hjertet havde dog øget risiko for udvikling af vaskulær demens (justeret hazard ratio = 1.35, 95% CI 1.28–1.43).

Vi konkluderer at forudgående depression var associeret med moderat øget mortalitet efter blodprop i hjertet og at blodprop i hjertet er associeret med øget risiko for slagtilfælde og vaskulær demens, men ikke demens af andre årsager.

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## 9. Appendices

**Appendix I**

Paper I

**Appendix II**

Paper II

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Paper III

**Appendix IV**

Paper IV

# Paper I

BMJ Open

# Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study

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## ABSTRACT

**Objective:** The majority of cardiovascular diagnoses in the Danish National Patient Registry (DNPR) remain to be validated despite extensive use in epidemiological research. We therefore examined the positive predictive value (PPV) of cardiovascular diagnoses in the DNPR.

**Design:** Population-based validation study.

**Setting:** 1 university hospital and 2 regional hospitals in the Central Denmark Region, 2010–2012.

**Participants:** For each cardiovascular diagnosis, up to 100 patients from participating hospitals were randomly sampled during the study period using the DNPR.

**Main outcome measure:** Using medical record review as the reference standard, we examined the PPV for cardiovascular diagnoses in the DNPR, coded according to the International Classification of Diseases, 10th Revision.

**Results:** A total of 2153 medical records (97% of the total sample) were available for review. The PPVs ranged from 64% to 100%, with a mean PPV of 88%. The PPVs were ≥90% for first-time myocardial infarction, stent thrombosis, stable angina pectoris, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, takotsubo cardiomyopathy, arterial hypertension, atrial fibrillation or flutter, cardiac arrest, mitral valve regurgitation or stenosis, aortic valve regurgitation or stenosis, pericarditis, hypercholesterolaemia, aortic dissection, aortic aneurysm/dilation and arterial claudication. The PPVs were between 80% and 90% for recurrent myocardial infarction, first-time unstable angina pectoris, pulmonary hypertension, bradycardia, ventricular tachycardia/fibrillation, endocarditis, cardiac tumours, first-time venous thromboembolism and between 70% and 80% for first-time and recurrent admission due to heart failure, first-time dilated cardiomyopathy, restrictive cardiomyopathy and recurrent venous thromboembolism. The PPV for first-time myocarditis was 64%. The PPVs were consistent within age, sex, calendar year and hospital categories.

**Conclusions:** The validity of cardiovascular diagnoses in the DNPR is overall high and sufficient for use in research since 2010.

## Strengths and limitations of this study

- This is the first validation study to include all major cardiovascular diagnoses in the Danish National Patient Registry.
- We sampled patients only from hospitals in the Central Denmark Region. However, our results are most likely generalisable to other parts of the country as the Danish healthcare system is homogeneous in structure and practice.
- We only validated patients diagnosed during 2010–2012 and therefore cannot extrapolate our results to previous periods.

## INTRODUCTION

Remarkable improvements have occurred in the prevention and treatment of cardiovascular diseases during recent decades.[1–4] Still, cardiovascular diseases remain a leading cause of death worldwide,[5] underscoring the need for further research. Registries constitute an important source of data for cardiovascular research in Denmark. The key registry is the Danish National Patient Registry (DNPR),[6] which contains long-term longitudinal data, prospectively collected since 1977. The registry has nationwide coverage of a homogeneous healthcare system with free and equal access and holds the possibility of individual-level data linkage with other registries.[7 8] However, the quality of registry-based research largely depends on the validity of the diagnostic codes used. Existing validation studies for cardiovascular diagnoses in the DNPR have been limited to relatively few diagnoses.[6] We therefore conducted a validation study to examine the positive predictive value (PPV) of diagnoses in the DNPR for all major cardiovascular diseases.

## METHODS

### Setting

Denmark is divided into five regions, each of which is representative of the Danish population with respect to demographic and socioeconomic characteristics as well as healthcare usage and medication use.[9] Each region typically has one major university hospital (including a high volume cardiac centre) and several smaller regional hospitals. The Danish National Health Service provides free universal tax-supported healthcare, guaranteeing unfettered access to general practitioners and hospitals.[6]

### Study population

We used the DNPR to randomly sample inpatient and outpatient hospital diagnoses from the Central Denmark Region between 1 January 2010 and 31 December 2012. The Central Denmark Region has a source population of 1.2 million inhabitants. Within the Central Denmark Region, we sampled specifically from the university hospital (Aarhus University Hospital) and two regional hospitals (Regional Hospitals of Randers and Herning).[8] The DNPR has recorded data on dates of admission and discharge from all Danish non-psychiatric hospitals since 1977 and on dates of emergency room and outpatient clinic visits since 1995.[6] Each hospital discharge or outpatient visit is recorded with one primary diagnosis and one or more secondary diagnoses classified according to the International Classification of Diseases, 8th Revision (ICD-8) until the end of 1993 and 10th Revision (ICD-10) thereafter.[6]

Our study population consisted of patients discharged with a primary or secondary first-time diagnosis from departments of cardiology, internal medicine, acute medicine and neurology in the three hospitals. For myocardial infarction, heart failure and venous thromboembolism, we also validated recurrent events. For most diseases, both inpatient and outpatient diagnoses were included (see online supplementary table S1). However, for diseases expected only to be diagnosed at inpatient admission (eg, myocardial infarction, aortic dissection, cardiac arrest), we only sampled inpatient diagnoses to avoid potential misclassification. Up to 100 patients were sampled from the DNPR for each of the diagnoses, which included first-time acute myocardial infarction (subsequently stratified by ST-elevation (STEMI) and non-ST-elevation myocardial infarction (NSTEMI)), recurrent myocardial infarction, stent thrombosis, stable angina pectoris, unstable angina pectoris, first-time heart failure, heart failure readmission, arterial hypertension, pulmonary hypertension, atrial fibrillation or flutter, bradycardia, ventricular tachycardia or fibrillation, cardiac arrest with indication for resuscitation, endocarditis, myocarditis, pericarditis, first-time venous thromboembolism (subsequently stratified by deep venous thrombosis and pulmonary embolism), recurrent venous thromboembolism (subsequently stratified by deep venous thrombosis and pulmonary embolism), arterial claudication, hypercholesterolaemia and cardiac tumours. We sampled up to 100 cases for cardiomyopathy (by sampling 20 diagnoses each for dilated, hypertrophic, restrictive, arrhythmogenic right ventricular and takotsubo cardiomyopathy), valvular heart disease (sampling 50 diagnoses each for mitral valve regurgitation or stenosis, and aortic valve regurgitation or stenosis) and aortic diseases (sampling 50 diagnoses each for aortic dissection and aneurysm/dilation).

Recurrent myocardial infarction and readmission due to heart failure were defined as the first readmission after the initial diagnosis. Sampling of first-time and recurrent events was independent. Hence, recurrent events could potentially include patients also included in the random sample for validation of first-time events. To avoid situations in which a transfer from one department to another was registered as a new diagnosis, we required that patients should be discharged for >24 hours before readmission could be registered as a true recurrent event. Bradycardia was defined as sinus node dysfunction or atrioventricular block. For venous thromboembolism, we defined recurrent events as admissions occurring >3 months after the initial diagnosis as guidelines recommend at least 3 months of anticoagulant therapy following venous thromboembolism.[10] All ICD codes used in the study are provided in online supplementary table S1. The patients were sampled using SAS V.9.2 (SAS Institute, Cary, North Carolina, USA).

### Medical record review

Medical record review was used as the reference standard. We did not have access to ECGs or other paraclinical recordings that supported the clinician's decision. However, descriptions of such recordings were available in the medical records and included in the review process. Three physicians (JS, KA and TM) reviewed the medical records and judged whether they confirmed the cardiovascular diagnosis coded in the DNPR. If the diagnosis was not described in the discharge summary or if the discharge summary was not available, the full medical record was reviewed to examine whether the diagnosis code could be confirmed. Review of the discharge summary/medical records began with confirmation of the Civil Personal Register number (unique personal identifier) and discharge date for each hospital contact retrieved from the DNPR. The diagnoses from the discharge summary and/or medical records were then compared with the diagnoses in the DNPR. Events coded in the DNPR as recurrent were considered correct if they were truly new events (for myocardial infarction and venous thromboembolism) and for heart failure if the readmission was due to a heart failure exacerbation. If the reviewing physician was uncertain whether the discharge summary or medical record agreed with the ICD-10 code, a second independent review was performed by one of the two other physicians. In case of disagreement, a consensus agreement was reached.

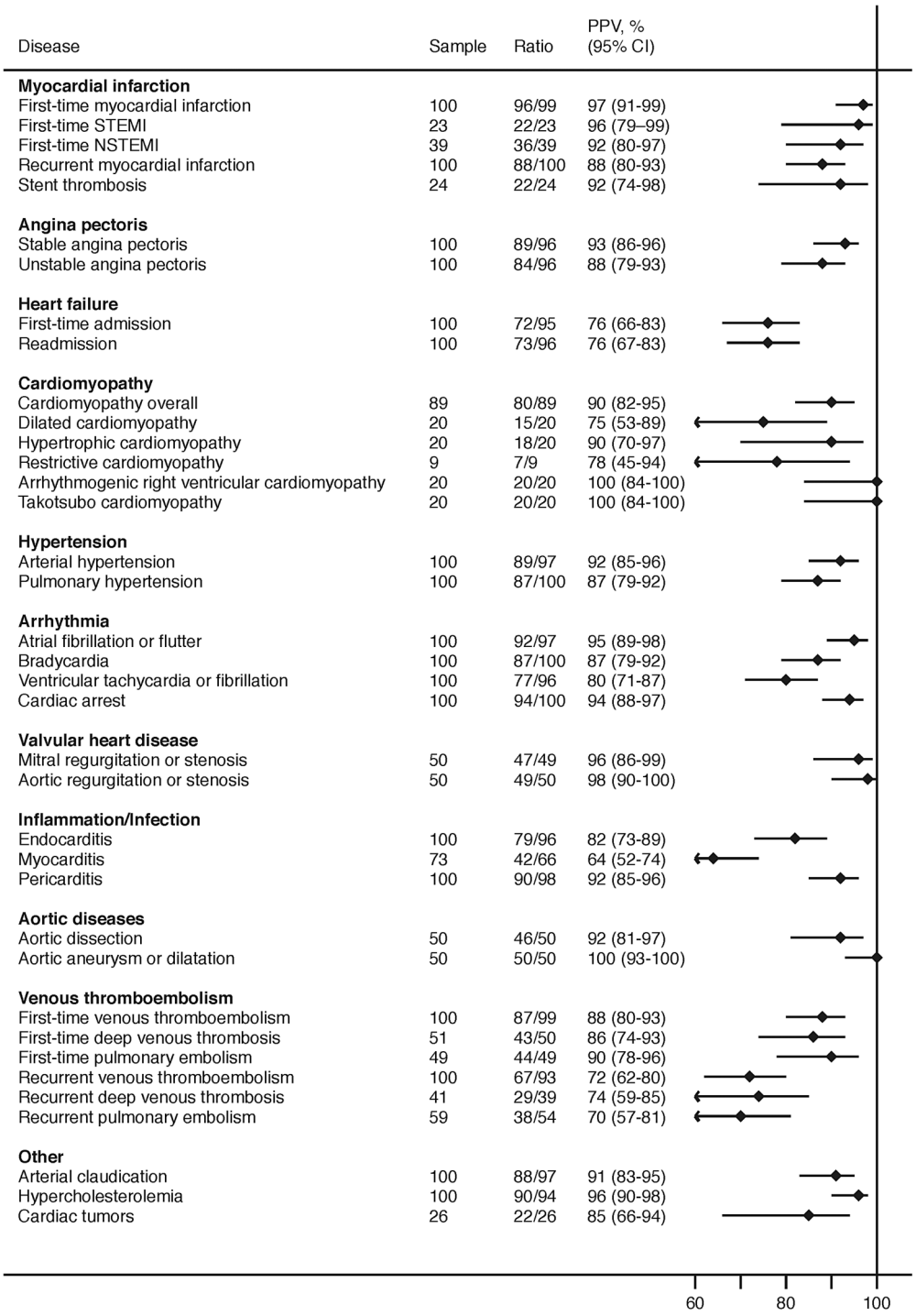


**Figure 1** Positive predictive values of cardiovascular diagnoses in the Danish National Patient Registry. Ratio, denotes confirmed diagnoses/available records; PPV, positive predictive value; STEMI, ST segment elevation myocardial infarction; NSTEMI, non-STEMI.

Data were entered into Epidata V.3.1 (EpiData Association, Odense, Denmark, http://www.epidata.dk) using a medical chart extraction form (see online supplementary table S2).

## Statistical analysis

For each diagnosis, we computed the PPV with 95% CIs according to the Wilson score method.[11] The PPV was computed as the proportion of diagnoses retrieved from the DNPR that could be confirmed in the discharge summary or medical record. For venous thromboembolism (including deep venous thrombosis and pulmonary embolism), we recalculated the PPVs for patients having an ultrasound and/or CT scan recorded in the registry during the index admission and for those who had neither of these registered. To calculate the mean PPV

Table 1 Positive predictive values of venous thromboembolism diagnoses in the Danish National Patient Registry, by diagnostic modalities during admission

| | Number of patients sampled | Confirmed diagnoses/ available records | Positive predictive value, % (95% CI) |
|---|---|---|---|
| First-time venous thromboembolism | 100 | 87/99 | 88 (80 to 93) |
| No ultrasound or CT scan during admission | 22 | 17/22 | 77 (57 to 90) |
| Ultrasound or CT scan during admission | 77 | 70/77 | 91 (82 to 96) |
| Ultrasound and CT scan during admission | 13 | 13/13 | 100 (77 to 100) |
| Recurrent venous thromboembolism | 100 | 67/93 | 72 (62 to 80) |
| No ultrasound or CT scan during admission | 25 | 11/25 | 44 (27 to 63) |
| Ultrasound or CT scan during admission | 72 | 56/68 | 82 (72 to 90) |
| Ultrasound and CT scan during admission | 7 | 5/7 | 71 (36 to 92) |

for all cardiovascular diseases, we divided the total number of correct cases by the total number of validated cases. We stratified the analyses by age group (<60 years, 60–80 years and >80 years), sex, calendar year (2010, 2011 and 2012), hospital type (regional or university hospital), type of diagnosis (primary or secondary) and type of hospital contact (inpatient or outpatient). Furthermore, we performed subgroup analyses for myocardial infarction (STEMI and NSTEMI diagnoses) and first-time and recurrent venous thromboembolism (deep venous thrombosis and pulmonary embolism diagnoses).

## RESULTS

We identified 2212 patients from the DNPR with cardiovascular diagnoses during 2010–2012. Medical records were available for 2153 patients (97% of the total sample). For the most common diseases, 100 patients were sampled; for rare diseases, fewer patients were available for sampling (figure 1). PPVs ranged between 64% and 100% with a mean PPV of 88%. PPVs were ≥90% for first-time myocardial infarction (including STEMI and NSTEMI), stent thrombosis, stable angina pectoris, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, takotsubo cardiomyopathy, arterial hypertension, atrial fibrillation or flutter, cardiac arrest with indication for resuscitation, mitral valve regurgitation or stenosis, aortic valve regurgitation or stenosis, pericarditis, hypercholesterolaemia, aortic dissection, aortic aneurysm/dilation and arterial claudication (figure 1). The distribution of cardiac arrest was 57% out of hospital, 30% inhospital and 13% undetermined. Apart from myocarditis (PPV=64%), the remaining PPVs were between 80% and 90% for recurrent myocardial infarction, unstable angina pectoris, pulmonary hypertension, bradycardia, ventricular tachycardia or fibrillation, endocarditis, cardiac tumours, first-time venous thromboembolism and between 70% and 80% for first-time and recurrent admission for heart failure, dilated cardiomyopathy, restrictive cardiomyopathy and recurrent venous thromboembolism. The PPV for venous thromboembolism improved when the following additional criteria were applied: receipt of CT or ultrasound scan during hospitalisation (PPV=91%), and receipt of both a CT and ultrasound scan during hospitalisation (PPV=100%; table 1).

The PPVs were consistent within age, sex, calendar year and hospital categories (tables 2 and 3). The stratified analyses by type of diagnosis and type of hospital contact revealed that the main results were driven by primary diagnoses from inpatient admissions. Thus, primary and inpatient diagnoses occurred most frequently, and the PPVs associated with these diagnosis types overall tended to be higher than for secondary and outpatient diagnoses (table 4).

## DISCUSSION

The DNPR accurately recorded diagnoses of the most common cardiovascular diseases during 2010–2012, with the PPV exceeding 90% for myocardial infarction, arterial hypertension, atrial fibrillation or flutter, valvular heart disease, aortic diseases and first-time venous thromboembolism. As an exception among the most frequent diseases, the PPV for heart failure was lower. For less common conditions, the PPV varied from 64% for myocarditis to 100% for takotsubo cardiomyopathy. The PPV for recurrent myocardial infarction was 88%, but somewhat lower for readmission for heart failure (76%) and recurrent venous thromboembolism (72%). The lower PPVs for recurrent events are most likely influenced by secondary recordings of the initial event as part of follow-up visits or during successive hospital contacts without the occurrence of a truly new event. The results were consistent in age, sex and calendar year categories.

This is the first validation study to include all major cardiovascular diagnoses in the DNPR. Comparing our results with previous Danish validation studies, it is apparent that the PPVs have improved over time for many cardiovascular diagnoses in the DNPR.[6] This may be explained by increased awareness of correct coding, implementation of clear guidelines and definitions of individual diseases, and improved availability of diagnostic modalities.[6] Thus, the PPV of coding has improved for myocardial infarction (PPV=100% during 1996–2009,[12] 98% during 1998–2007,[13] 92% during

**Table 2** Positive predictive values of cardiovascular diagnoses in the Danish National Patient Registry, by age groups and sex

| | <60 years | | 60–80 years | | >80 years | | Men | | Women | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Confirmed diagnoses/ available records | Positive predictive value, % (95% CI) | Confirmed diagnoses/ available records | Positive predictive value, % (95% CI) | Confirmed diagnoses/ available records | Positive predictive value, % (95% CI) | Confirmed diagnoses/ available records | Positive predictive value, % (95% CI) | Confirmed diagnoses/ available records | Positive predictive value, % (95% CI) |
| Myocardial infarction | | | | | | | | | | |
| First-time myocardial infarction | 29/30 | 97 (83 to 99) | 47/48 | 98 (89 to 100) | 20/21 | 95 (77 to 99) | 61/63 | 97 (89 to 99) | 35/36 | 97 (86 to 100) |
| Recurrent myocardial infarction | 17/19 | 89 (69 to 97) | 51/57 | 89 (79 to 95) | 20/24 | 83 (64 to 93) | 61/69 | 88 (79 to 94) | 27/31 | 87 (71 to 95) |
| Stent thrombosis | 9/9 | 100 (70 to 100) | 11/13 | 85 (58 to 96) | 2/2 | 100 (34 to 100) | 15/16 | 94 (72 to 99) | 7/8 | 88 (53 to 98) |
| Angina pectoris | | | | | | | | | | |
| Stable angina pectoris | 25/29 | 86 (69 to 95) | 51/54 | 94 (85 to 98) | 13/13 | 100 (77 to 100) | 63/69 | 91 (82 to 96) | 26/27 | 96 (82 to 99) |
| Unstable angina pectoris | 24/28 | 86 (69 to 94) | 51/57 | 89 (79 to 95) | 9/11 | 82 (52 to 95) | 48/55 | 87 (76 to 94) | 36/41 | 88 (74 to 95) |
| Heart failure | | | | | | | | | | |
| First-time heart failure | 13/13 | 100 (77 to 100) | 37/50 | 74 (60 to 84) | 22/32 | 69 (51 to 82) | 50/60 | 83 (72 to 91) | 22/35 | 63 (46 to 77) |
| Readmission for heart failure | 7/14 | 50 (27 to 73) | 42/50 | 84 (71 to 92) | 24/32 | 75 (58 to 87) | 45/56 | 80 (68 to 89) | 28/40 | 70 (55 to 82) |
| Cardiomyopathy | | | | | | | | | | |
| Cardiomyopathy overall | 32/33 | 97 (85 to 99) | 40/44 | 91 (79 to 96) | 8/12 | 67 (39 to 86) | 38/44 | 86 (73 to 94) | 42/45 | 93 (82 to 98) |
| Dilated cardiomyopathy | 3/3 | 100 (44 to 100) | 11/13 | 85 (58 to 96) | 1/4 | 25 (5 to 70) | 6/10 | 60 (31 to 83) | 9/10 | 90 (60 to 98) |
| Hypertrophic cardiomyopathy | 5/5 | 100 (57 to 100) | 9/10 | 90 (60 to 98) | 4/5 | 80 (38 to 96) | 12/13 | 92 (67 to 99) | 6/7 | 86 (49 to 97) |
| Restrictive cardiomyopathy | 2/3 | 67 (21 to 94) | 5/6 | 83 (44 to 97) | 0/0 | N/A | 4/5 | 80 (38 to 96) | 3/4 | 75 (30 to 95) |
| Arrhythmogenic right ventricular cardiomyopathy | 14/14 | 100 (78 to 100) | 6/6 | 100 (61 to 100) | 0/0 | N/A | 14/14 | 100 (78 to 100) | 6/6 | 100 (61 to 100) |
| Takotsubo cardiomyopathy | 8/8 | 100 (68 to 100) | 9/9 | 100 (70 to 100) | 3/3 | 100 (44 to 100) | 2/2 | 100 (34 to 100) | 18/18 | 100 (82 to 100) |
| Hypertension | | | | | | | | | | |
| Arterial hypertension | 20/24 | 83 (64 to 93) | 52/55 | 95 (85 to 98) | 17/18 | 94 (74 to 99) | 48/55 | 87 (76 to 94) | 41/42 | 98 (88 to 100) |
| Pulmonary hypertension | 24/28 | 86 (69 to 94) | 41/50 | 82 (69 to 90) | 22/22 | 100 (85 to 100) | 36/41 | 88 (74 to 95) | 51/59 | 86 (75 to 93) |
| Cardiac arrhythmias | | | | | | | | | | |
| Atrial fibrillation or flutter | 14/15 | 93 (70 to 99) | 49/53 | 92 (82 to 97) | 29/29 | 100 (88 to 100) | 50/53 | 94 (85 to 98) | 42/44 | 95 (85 to 99) |
| Bradycardia | 14/14 | 100 (78 to 100) | 35/40 | 88 (74 to 95) | 38/46 | 83 (69 to 91) | 49/55 | 89 (78 to 95) | 38/45 | 84 (71 to 92) |
| Ventricular tachycardia or fibrillation | 27/31 | 87 (71 to 95) | 37/51 | 73 (59 to 83) | 13/14 | 93 (69 to 99) | 50/60 | 83 (72 to 91) | 27/36 | 75 (59 to 86) |
| Cardiac arrest | 31/31 | 100 (89 to 100) | 43/45 | 96 (85 to 99) | 20/24 | 83 (64 to 93) | 69/73 | 95 (87 to 98) | 25/27 | 93 (77 to 98) |
| Valvular heart disease | | | | | | | | | | |
| Mitral regurgitation or stenosis | 8/9 | 89 (57 to 98) | 22/23 | 96 (79 to 99) | 17/17 | 100 (82 to 100) | 20/22 | 91 (72 to 97) | 27/27 | 100 (88 to 100) |
| Aortic regurgitation or stenosis | 6/6 | 100 (61 to 100) | 22/23 | 96 (79 to 99) | 21/21 | 100 (85 to 100) | 21/22 | 95 (78 to 99) | 28/28 | 100 (88 to 100) |
| Inflammation/infection | | | | | | | | | | |
| Endocarditis | 21/24 | 88 (69 to 96) | 40/47 | 85 (72 to 93) | 18/25 | 72 (52 to 86) | 62/75 | 83 (73 to 90) | 17/21 | 81 (60 to 92) |
| Myocarditis | 33/39 | 85 (70 to 93) | 8/18 | 44 (25 to 66) | 1/9 | 11 (2 to 44) | 30/43 | 70 (55 to 81) | 12/23 | 52 (33 to 71) |

Continued

**Table 2** Continued

| | <60 years | | 60–80 years | | >80 years | | Men | | Women | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Confirmed diagnoses/ available records | Positive predictive value, % (95% CI) | Confirmed diagnoses/ available records | Positive predictive value, % (95% CI) | Confirmed diagnoses/ available records | Positive predictive value, % (95% CI) | Confirmed diagnoses/ available records | Positive predictive value, % (95% CI) | Confirmed diagnoses/ available records | Positive predictive value, % (95% CI) |
| Pericarditis | 50/55 | 91 (80 to 96) | 36/39 | 92 (80 to 97) | 4/4 | 100 (51 to 100) | 59/65 | 91 (81 to 96) | 31/33 | 94 (80 to 98) |
| Aortic diseases | | | | | | | | | | |
| Aortic dissection | 18/19 | 95 (75 to 99) | 24/27 | 89 (72 to 96) | 4/4 | 100 (51 to 100) | 30/31 | 97 (84 to 99) | 16/19 | 84 (62 to 94) |
| Aortic aneurysm/dilation | 4/4 | 100 (51 to 100) | 34/34 | 100 (90 to 100) | 12/12 | 100 (76 to 100) | 31/31 | 100 (89 to 100) | 19/19 | 100 (83 to 100) |
| Venous thromboembolism | | | | | | | | | | |
| First-time venous thromboembolism | 25/29 | 86 (69 to 95) | 47/51 | 92 (82 to 97) | 15/19 | 79 (57 to 91) | 36/42 | 86 (72 to 93) | 51/57 | 89 (79 to 95) |
| First-time deep venous thrombosis | 16/19 | 84 (62 to 94) | 22/24 | 92 (74 to 98) | 5/7 | 71 (36 to 92) | 21/23 | 91 (73 to 98) | 22/27 | 81 (63 to 92) |
| First-time pulmonary embolism | 9/10 | 90 (60 to 98) | 25/27 | 93 (77 to 98) | 10/12 | 83 (55 to 95) | 15/19 | 79 (57 to 91) | 29/30 | 97 (83 to 99) |
| Recurrent venous thromboembolism | 18/26 | 69 (50 to 84) | 31/42 | 74 (59 to 85) | 18/25 | 72 (52 to 86) | 40/53 | 75 (62 to 85) | 27/40 | 68 (52 to 80) |
| Recurrent deep venous thrombosis | 12/16 | 75 (51 to 90) | 12/17 | 71 (47 to 87) | 5/6 | 83 (44 to 97) | 18/24 | 75 (55 to 88) | 11/15 | 73 (48 to 89) |
| Recurrent pulmonary embolism | 6/10 | 60 (31 to 83) | 19/25 | 76 (57 to 89) | 13/19 | 68 (46 to 85) | 22/29 | 76 (58 to 88) | 16/25 | 64 (45 to 80) |
| Other | | | | | | | | | | |
| Arterial claudication | 10/10 | 100 (72 to 100) | 63/70 | 90 (81 to 95) | 15/17 | 88 (66 to 97) | 49/57 | 86 (75 to 93) | 39/40 | 98 (87 to 100) |
| Hypercholesterolaemia | 35/37 | 95 (82 to 99) | 44/46 | 96 (85 to 99) | 11/11 | 100 (74 to 100) | 55/58 | 95 (86 to 98) | 35/36 | 97 (86 to 100) |
| Cardiac tumours | 11/11 | 100 (74 to 100) | 10/13 | 77 (50 to 92) | 1/2 | 50 (9 to 91) | 9/11 | 82 (52 to 95) | 13/15 | 87 (62 to 96) |

**Table 3** Positive predictive values of cardiovascular diagnoses in the Danish National Patient Registry, by calendar year and type of hospital

| | 2010 | | 2011 | | 2012 | | University hospital | | Regional hospital | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Confirmed diagnoses/ available records | Positive predictive value, % (95% CI) | Confirmed diagnoses/ available records | Positive predictive value, % (95% CI) | Confirmed diagnoses/ available records | Positive predictive value, % (95% CI) | Confirmed diagnoses/ available records | Positive predictive value, % (95% CI) | Confirmed diagnoses/ available records | Positive predictive value, % (95% CI) |
| Myocardial infarction | | | | | | | | | | |
| First-time myocardial infarction | 34/35 | 97 (85 to 99) | 28/29 | 97 (83 to 99) | 34/35 | 97 (85 to 99) | 59/61 | 97 (89 to 99) | 37/38 | 97 (87 to 100) |
| Recurrent myocardial infarction | 28/33 | 85 (69 to 93) | 35/38 | 92 (79 to 97) | 25/29 | 86 (69 to 95) | 47/51 | 92 (82 to 97) | 41/49 | 84 (71 to 91) |
| Stent thrombosis | 6/6 | 100 (61 to 100) | 7/9 | 78 (45 to 94) | 9/9 | 100 (70 to 100) | 20/21 | 95 (77 to 99) | 2/3 | 67 (21 to 94) |
| Angina pectoris | | | | | | | | | | |
| Stable angina pectoris | 32/35 | 91 (78 to 97) | 27/29 | 93 (78 to 98) | 30/32 | 94 (80 to 98) | 63/68 | 93 (84 to 97) | 26/28 | 93 (77 to 98) |
| Unstable angina pectoris | 26/29 | 90 (74 to 96) | 31/36 | 86 (71 to 94) | 27/31 | 87 (71 to 95) | 40/46 | 87 (74 to 94) | 44/50 | 88 (76 to 94) |
| Heart failure | | | | | | | | | | |
| First-time heart failure | 25/31 | 81 (64 to 91) | 27/38 | 71 (55 to 83) | 20/26 | 77 (58 to 89) | 29/40 | 73 (57 to 84) | 43/55 | 78 (66 to 87) |
| Readmission for heart failure | 21/28 | 75 (57 to 87) | 30/38 | 79 (64 to 89) | 22/30 | 73 (56 to 86) | 27/37 | 73 (57 to 85) | 46/59 | 78 (66 to 87) |
| Cardiomyopathy | | | | | | | | | | |
| Cardiomyopathy overall | 22/25 | 88 (70 to 96) | 22/24 | 92 (74 to 98) | 36/40 | 90 (77 to 96) | 61/66 | 92 (83 to 97) | 19/23 | 83 (63 to 93) |
| Dilated cardiomyopathy | 1/2 | 50 (9 to 91) | 6/7 | 86 (49 to 97) | 8/11 | 72 (43 to 90) | 6/8 | 75 (41 to 93) | 9/12 | 75 (47 to 91) |
| Hypertrophic cardiomyopathy | 4/5 | 80 (38 to 96) | 5/5 | 100 (57 to 100) | 9/10 | 90 (60 to 98) | 11/12 | 92 (65 to 99) | 7/8 | 88 (53 to 98) |
| Restrictive cardiomyopathy | 3/4 | 75 (30 to 95) | 1/2 | 50 (9 to 91) | 3/3 | 100 (44 to 100) | 7/9 | 78 (45 to 94) | 0/0 | N/A |
| Arrhythmogenic right ventricular cardiomyopathy | 8/8 | 100 (68 to 100) | 7/7 | 100 (65 to 100) | 5/5 | 100 (57 to 100) | 20/20 | 100 (84 to 100) | 0/0 | N/A |
| Takotsubo cardiomyopathy | 6/6 | 100 (61 to 100) | 3/3 | 100 (44 to 100) | 11/11 | 100 (74 to 100) | 17/17 | 100 (82 to 100) | 3/3 | 100 (44 to 100) |
| Hypertension | | | | | | | | | | |
| Arterial hypertension | 14/15 | 93 (70 to 99) | 39/43 | 91 (78 to 96) | 36/39 | 92 (80 to 97) | 35/41 | 85 (72 to 93) | 54/56 | 96 (88 to 99) |
| Pulmonary hypertension | 24/28 | 86 (69 to 94) | 26/31 | 84 (67 to 93) | 37/41 | 90 (77 to 96) | 49/60 | 82 (70 to 89) | 38/40 | 95 (84 to 99) |
| Cardiac arrhythmias | | | | | | | | | | |
| Atrial fibrillation or flutter | 27/29 | 93 (78 to 98) | 30/32 | 94 (80 to 98) | 35/36 | 97 (86 to 100) | 30/33 | 91 (76 to 97) | 62/64 | 97 (89 to 99) |
| Bradycardia | 24/26 | 92 (76 to 98) | 28/35 | 80 (64 to 90) | 35/39 | 90 (76 to 96) | 61/71 | 86 (76 to 92) | 26/29 | 90 (74 to 96) |
| Ventricular tachycardia or fibrillation | 23/30 | 77 (59 to 88) | 21/27 | 78 (59 to 89) | 33/39 | 85 (70 to 93) | 49/63 | 78 (66 to 86) | 28/33 | 85 (69 to 93) |
| Cardiac arrest | 29/32 | 91 (76 to 97) | 26/26 | 100 (87 to 100) | 39/42 | 93 (81 to 98) | 72/75 | 96 (89 to 99) | 22/25 | 88 (70 to 96) |
| Valvular heart disease | | | | | | | | | | |
| Mitral regurgitation or stenosis | 9/10 | 90 (60 to 98) | 15/16 | 94 (72 to 99) | 23/23 | 100 (86 to 100) | 30/32 | 94 (80 to 98) | 17/17 | 100 (82 to 100) |
| Aortic regurgitation or stenosis | 13/13 | 100 (77 to 100) | 16/16 | 100 (81 to 100) | 20/21 | 95 (77 to 99) | 29/29 | 100 (88 to 100) | 20/21 | 95 (77 to 99) |
| Inflammation/infection | | | | | | | | | | |
| Endocarditis | 25/29 | 86 (69 to 95) | 26/29 | 90 (74 to 96) | 28/38 | 74 (58 to 85) | 49/59 | 83 (72 to 91) | 30/37 | 81 (66 to 91) |
| Myocarditis | 14/21 | 67 (45 to 83) | 14/24 | 58 (39 to 76) | 14/21 | 67 (45 to 83) | 33/49 | 67 (53 to 79) | 9/17 | 53 (31 to 74) |

Continued

**Table 3** Continued

| | 2010 | | 2011 | | 2012 | | University hospital | | Regional hospital | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Confirmed diagnoses/ available records | Positive predictive value, % (95% CI) | Confirmed diagnoses/ available records | Positive predictive value, % (95% CI) | Confirmed diagnoses/ available records | Positive predictive value, % (95% CI) | Confirmed diagnoses/ available records | Positive predictive value, % (95% CI) | Confirmed diagnoses/ available records | Positive predictive value, % (95% CI) |
| Pericarditis | 31/36 | 86 (71 to 94) | 30/31 | 97 (84 to 99) | 29/31 | 93 (79 to 98) | 60/67 | 90 (80 to 95) | 30/31 | 97 (84 to 99) |
| Aortic diseases | | | | | | | | | | |
| Aortic dissection | 11/14 | 79 (52 to 92) | 16/16 | 100 (81 to 100) | 19/20 | 95 (76 to 99) | 32/36 | 89 (75 to 96) | 14/14 | 100 (78 to 100) |
| Aortic aneurysm/dilation | 13/13 | 100 (77 to 100) | 23/23 | 100 (86 to 100) | 14/14 | 100 (78 to 100) | 36/36 | 100 (90 to 100) | 14/14 | 100 (78 to 100) |
| Venous thromboembolism | | | | | | | | | | |
| First-time venous thromboembolism | 25/28 | 89 (73 to 96) | 30/33 | 91 (76 to 97) | 32/38 | 84 (70 to 93) | 28/34 | 82 (66 to 92) | 59/65 | 91 (81 to 96) |
| First-time deep venous thrombosis | 13/15 | 87 (62 to 96) | 13/14 | 93 (69 to 99) | 17/21 | 81 (60 to 92) | 13/16 | 81 (57 to 93) | 30/34 | 88 (73 to 95) |
| First-time pulmonary embolism | 12/13 | 92 (67 to 99) | 17/19 | 89 (69 to 97) | 15/17 | 88 (66 to 97) | 15/18 | 83 (61 to 94) | 29/31 | 94 (79 to 98) |
| Recurrent venous thromboembolism | 22/27 | 81 (63 to 92) | 20/29 | 69 (51 to 83) | 25/37 | 68 (51 to 80) | 25/39 | 64 (48 to 77) | 42/54 | 78 (65 to 87) |
| Recurrent deep venous thrombosis | 9/11 | 82 (52 to 95) | 9/13 | 69 (42 to 87) | 11/15 | 73 (48 to 89) | 6/10 | 60 (31 to 83) | 23/29 | 79 (62 to 90) |
| Recurrent pulmonary embolism | 13/16 | 81 (57 to 93) | 11/16 | 69 (44 to 86) | 14/22 | 64 (43 to 80) | 19/29 | 66 (47 to 80) | 19/25 | 76 (57 to 89) |
| Other | | | | | | | | | | |
| Arterial claudication | 18/20 | 90 (70 to 97) | 33/37 | 89 (75 to 96) | 37/40 | 93 (80 to 97) | 86/95 | 91 (83 to 95) | 2/2 | 100 (34 to 100) |
| Hypercholesterolaemia | 27/30 | 90 (74 to 97) | 30/31 | 97 (84 to 99) | 33/33 | 100 (90 to 100) | 48/51 | 94 (84 to 98) | 42/43 | 98 (88 to 100) |
| Cardiac tumours | 2/3 | 67 (21 to 94) | 9/11 | 82 (52 to 95) | 11/12 | 92 (65 to 99) | 17/18 | 94 (74 to 99) | 5/8 | 63 (31 to 86) |

**Table 4** Positive predictive values of cardiovascular diagnoses in the Danish National Patient Registry, by type of diagnosis

| | Primary diagnosis | | Secondary diagnosis | | Inpatient diagnosis | | Outpatient diagnosis | |
|---|---|---|---|---|---|---|---|---|
| | Confirmed diagnoses/ available records | Positive predictive value, % (95% CI) | Confirmed diagnoses/ available records | Positive predictive value, % (95% CI) | Confirmed diagnoses/ available records | Positive predictive value, % (95% CI) | Confirmed diagnoses/ available records | Positive predictive value, % (95% CI) |
| Myocardial infarction | | | | | | | | |
| First-time myocardial infarction | 88/89 | 99 (94 to 100) | 8/10 | 80 (49 to 94) | – | – | – | – |
| Recurrent myocardial infarction | 88/100 | 88 (80 to 93) | 0/0 | – | – | – | – | – |
| Stent thrombosis | 14/15 | 93 (70 to 99) | 8/9 | 89 (57 to 98) | – | – | – | – |
| Angina pectoris | | | | | | | | |
| Stable angina pectoris | 68/73 | 93 (85 to 97) | 21/23 | 91 (73 to 98) | – | – | – | – |
| Unstable angina pectoris | 80/90 | 89 (81 to 94) | 4/6 | 67 (30 to 90) | – | – | – | – |
| Heart failure | | | | | | | | |
| First-time heart failure | 31/39 | 79 (64 to 89) | 41/56 | 73 (60 to 83) | – | – | – | – |
| Readmission for heart failure | 73/96 | 76 (67 to 83) | 0/0 | – | – | – | – | – |
| Cardiomyopathy | | | | | | | | |
| Cardiomyopathy overall | 56/61 | 92 (82 to 96) | 24/37 | 65 (49 to 78) | 34/41 | 83 (69 to 91) | 26/27 | 96 (82 to 99) |
| Dilated cardiomyopathy | 8/10 | 80 (49 to 94) | 7/10 | 70 (40 to 89) | 11/15 | 73 (48 to 89) | 4/5 | 80 (38 to 96) |
| Hypertrophic cardiomyopathy | 11/12 | 92 (65 to 99) | 7/8 | 88 (53 to 98) | 8/10 | 80 (49 to 94) | 10/10 | 100 (72 to 100) |
| Restrictive cardiomyopathy | 6/8 | 75 (41 to 93) | 1/1 | 100 (21 to 100) | 7/8 | 88 (53 to 98) | 0/1 | 0 (0 to 79) |
| Arrhythmogenic right ventricular cardiomyopathy | 11/11 | 100 (74 to 100) | 9/9 | 100 (70 to 100) | 8/8 | 100 (68 to 100) | 12/12 | 100 (76 to 100) |
| Takotsubo cardiomyopathy | 20/20 | 100 (84 to 100) | 0/0 | – | – | – | – | – |
| Hypertension | | | | | | | | |
| Arterial hypertension | 30/33 | 91 (76 to 97) | 59/64 | 92 (83 to 97) | 49/53 | 92 (82 to 97) | 40/44 | 91 (79 to 96) |
| Pulmonary hypertension | 54/61 | 89 (78 to 94) | 33/39 | 85 (70 to 93) | 58/60 | 97 (89 to 99) | 29/40 | 73 (57 to 84) |
| Cardiac arrhythmias | | | | | | | | |
| Atrial fibrillation or flutter | 55/58 | 95 (86 to 98) | 37/39 | 95 (83 to 99) | 75/75 | 100 (95 to 100) | 17/22 | 77 (57 to 90) |
| Bradycardia | 75/79 | 95 (88 to 98) | 12/21 | 57 (37 to 76) | 78/85 | 92 (84 to 96) | 9/15 | 60 (36 to 80) |
| Ventricular tachycardia or fibrillation | 46/58 | 79 (67 to 88) | 31/38 | 82 (67 to 91) | 70/77 | 91 (82 to 96) | 7/19 | 37 (19 to 59) |
| Cardiac arrest | 66/67 | 99 (92 to 100) | 28/33 | 85 (69 to 93) | – | – | – | – |
| Valvular heart disease | | | | | | | | |
| Mitral regurgitation or stenosis | 19/20 | 95 (76 to 99) | 28/29 | 97 (83 to 99) | 21/21 | 100 (85 to 100) | 26/28 | 93 (77 to 98) |
| Aortic regurgitation or stenosis | 29/30 | 97 (83 to 99) | 20/20 | 100 (84 to 100) | 31/31 | 100 (89 to 100) | 18/19 | 95 (75 to 99) |
| Inflammation/infection | | | | | | | | |
| Endocarditis | 73/86 | 85 (76 to 91) | 6/10 | 60 (31 to 83) | 75/90 | 83 (74 to 90) | 4/6 | 67 (30 to 90) |
| Myocarditis | 33/41 | 80 (66 to 90) | 9/25 | 36 (20 to 55) | 37/59 | 63 (50 to 74) | 5/7 | 71 (36 to 92) |
| Pericarditis | 76/82 | 93 (85 to 97) | 14/16 | 88 (64 to 97) | 74/76 | 97 (91 to 99) | 16/22 | 73 (52 to 87) |
| Aortic diseases | | | | | | | | |
| Aortic dissection | 45/48 | 94 (83 to 98) | 1/2 | 50 (9 to 91) | – | – | – | – |
| Aortic aneurysm/dilation | 37/37 | 100 (91 to 100) | 13/13 | 100 (77 to 100) | 20/20 | 100 (84 to 100) | 30/30 | 100 (89 to 100) |
| Venous thromboembolism | | | | | | | | |
| First-time venous thromboembolism | 76/84 | 90 (82 to 95) | 11/15 | 73 (48 to 89) | 81/90 | 90 (82 to 95) | 6/9 | 67 (35 to 88) |

Continued

Table 4 Continued

| | Primary diagnosis | | Secondary diagnosis | | Inpatient diagnosis | | Outpatient diagnosis | |
|---|---|---|---|---|---|---|---|---|
| | Confirmed diagnoses/ available records | Positive predictive value, % (95% CI) | Confirmed diagnoses/ available records | Positive predictive value, % (95% CI) | Confirmed diagnoses/ available records | Positive predictive value, % (95% CI) | Confirmed diagnoses/ available records | Positive predictive value, % (95% CI) |
| First-time deep venous thrombosis | 38/44 | 86 (73 to 94) | 5/6 | 83 (44 to 97) | 38/43 | 88 (76 to 95) | 5/7 | 71 (36 to 92) |
| First-time pulmonary embolism | 38/40 | 95 (84 to 99) | 6/9 | 67 (35 to 88) | 43/47 | 91 (80 to 97) | 1/2 | 50 (9 to 91) |
| Recurrent venous thromboembolism | 65/77 | 84 (75 to 91) | 2/16 | 13 (4 to 36) | – | – | – | – |
| Recurrent deep venous thrombosis | 29/36 | 81 (65 to 90) | 0/3 | 0 (0 to 56) | – | – | – | – |
| Recurrent pulmonary embolism | 36/41 | 88 (74 to 95) | 2/13 | 15 (4 to 42) | – | – | – | – |
| Other | | | | | | | | |
| Arterial claudication | 83/92 | 90 (82 to 44) | 5/5 | 100 (57 to 100) | 15/17 | 88 (66 to 97) | 73/80 | 91 (83 to 96) |
| Hypercholesterolaemia | 17/17 | 100 (82 to 100) | 73/77 | 95 (87 to 98) | 62/64 | 97 (89 to 99) | 28/30 | 93 (79 to 98) |
| Cardiac tumours | 16/18 | 89 (67 to 97) | 6/8 | 75 (41 to 93) | 19/23 | 83 (63 to 93) | 3/3 | 100 (44 to 100) |

1993–2003[14] and 93% during 1982–1991,[15]) arterial hypertension (PPV=88% during 1977–2010[16] and ≈50% during 1990–1993[17]) and first-time venous thromboembolism (PPV=90% during 2004–2012[18] and 75% during 1994–2006[19]). The PPVs were overall in line with previous studies for heart failure (PPV=78% during 2005–2007[20] and 100% during 1998–2007[13]), atrial fibrillation or flutter (PPV=94% during 1993–2009,[21] 99% during 1980–2002[22] and 97% during 1980–2002[23]) and recurrent venous thromboembolism (PPV=79% during 2004–2012 with CT or ultrasound scan during admission and anticoagulant treatment 30 days after admission[18]). Previous studies reported markedly lower PPVs than our findings for unstable angina pectoris (PPV=42% during 1993–2003[14]) and cardiac arrest (PPV=50% during 1993–2003[14]). The finding of lower PPV for cardiac arrest in the previous study[14] may be explained by a small sample size (n=42) and their inclusion of emergency department and outpatient diagnoses, whereas we restricted to inpatient diagnoses. Moreover, the previous study is more than 10 years old and changes in coding practice may also account for part of the difference. For unstable angina pectoris,[14] the study period of the previous study ended in 2003, that is, shortly after the redefinition of myocardial infarction in 2000, which included troponin release as an absolute criterion.[24] This made the discrimination between unstable angina pectoris and myocardial infarction easier and most likely explains the higher PPV found in our study. To the best of our knowledge, the validity of the remaining diagnoses included in our study has not been assessed before.

Several limitations should be considered. Cautious interpretation of the PPV is warranted for diagnoses with sample sizes below 100. These include subgroups of an overall diagnosis and rare diagnoses with less than 100 cases diagnosed during the study period. Original recordings from diagnostic modalities such as ECG and echocardiography were not available. Therefore, the confirmation of the diagnoses was based solely on descriptions of such recordings included in the discharge summary or medical record. This limits the rigorousness of case validation and also could potentially lead to different interpretations between reviewers. We examined patients admitted to hospitals only in the Central Denmark Region. However, our results are most likely generalisable to other parts of the country as the Danish healthcare system is homogeneous in structure and practice.[9] Although some diagnoses (eg, myocardial infarction) have shown consistently high validity across countries despite different registry types and coding systems,[6 12 25] it should be noted that our findings may not per se be generalisable to all countries where coding systems, coding practice, disease definitions and diagnostics differ.

In this study, we chose the PPV as the measure of validity. The PPV is correlated with disease prevalence and is dependent on specificity. However, sensitivity, specificity and negative predictive value could not be calculated because the data were sampled from the codes pertinent

to the diagnosis of interest. The importance of the different measures of data quality depends on the study question and thus the design. A high PPV is important, for example, when identifying patient cohorts in prognosis studies, but cannot stand alone, for example, when identifying disease incidence. Future studies identifying cardiovascular diseases from diagnoses in the DNPR should consider the possibility that differential misclassification may occur between exposure groups (eg, if the exposure is diabetes, these patients may be more prone to have a given outcome registered due to detection bias and hence have a falsely increased risk of the outcome). Also, since diagnoses were only validated during 2010–2012, we cannot necessarily extrapolate our results to previous periods due to potential temporal differences in PPVs as exemplified above.

## CONCLUSION

The validity of cardiovascular diagnoses in the DNPR is overall high, and for the vast majority of diseases it is sufficient for use in research since 2010.

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**Contributors** MS, HTS, JS and KA conceived the study idea and designed the study. TF sampled the patients. JS, KA and TM reviewed all medical records. JS performed the statistical analysis. All authors analysed and interpreted the data. JS wrote the initial draft. All authors critically revised the manuscript for important intellectual content and approved the final version.

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**Competing interests** None declared.

**Ethics approval** In accordance with Danish law governing analysis of registry data, no Ethics Committee approval was required. The study was approved by the Danish Data Protection Agency (record number: 1-16-02-1-08) and the chief physicians of participating departments, as part of quality control.

**Data sharing statement** No additional data are available.



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# Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study

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# SUPPLEMENTAL MATERIAL

## Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study

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Contents

**Supplementary Table 1**. ICD-8 and ICD-10 codes for cardiovascular diagnoses.

| | ICD-8 code[a] | ICD-10 code | Location of admission |
|---|---|---|---|
| **Myocardial infarction** | | | |
| First-time myocardial infarction | 410 | I21 | Inpatient |
| STEMI | N/A | I211B, I210B, I213 | Inpatient |
| NSTEMI | | I211A, I210A, I214 | Inpatient |
| Recurrent myocardial infarction | 410 | I21 | Inpatient |
| Stent thrombosis | N/A | T823D, T823E | Inpatient |
| **Angina pectoris** | | | |
| Stable angina pectoris | 413 | I20 (without I200), I251, I259 | Inpatient |
| Unstable angina pectoris | 411 | I200 | Inpatient |
| **Heart failure** | | | |
| First-time heart failure | 42709, 42710, 42711, 42719, 42899, 78249 | I500, I501, I502, I503, I508, I509, I110, I130, I132, I420, I426, I427, I428, I429 | Inpatient |
| Readmission for heart failure | 42709, 42710, 42711, 42719, 42899, 78249 | I500, I501, I502, I503, I508, I509, I110, I130, I132, I420, I426, I427, I428, I429 | Inpatient |
| **Cardiomyopathy** | 425 | | |
| Dilated cardiomyopathy | N/A | I420 | Inpatient or outpatient |
| Hypertrophic cardiomyopathy | N/A | I421, I422 | Inpatient or outpatient |
| Restrictive cardiomyopathy | N/A | I425 | Inpatient or outpatient |
| ARVC | N/A | I428A | Inpatient or outpatient |
| Takotsubo cardiomyopathy | N/A | I428B | Inpatient |
| **Hypertension** | | | |
| Arterial hypertension | 400–404 | I10-I15 | Inpatient or outpatient |
| Pulmonary hypertension | 426 | I27 | Inpatient or outpatient |
| **Cardiac arrhythmias** | | | |
| Atrial fibrillation or flutter | 42793, 42794 | I48 | Inpatient or outpatient |
| Bradycardia | 42720, 42721, 42722, 42723 | I440, I441, I442, I443, I455A, I455B, I455C, I455G | Inpatient or outpatient |
| VT or VF | 42797, 42791 | I470, I472, I490 | Inpatient or outpatient |
| Cardiac arrest | 42727, 42797 | I46 | Inpatient |
| **Valvular heart disease** | | | |
| Mitral regurgitation or stenosis | 394 | I05, I34, I390, I511A | Inpatient or outpatient |
| Aortic regurgitation or stenosis | 395 | I06, I35, I391 | Inpatient or outpatient |
| **Inflammation/Infection** | | | |
| Endocarditis | 421 | I33, I38, I398 | Inpatient or outpatient |
| Myocarditis | 422 | I40, I41, I090, I514 | Inpatient or outpatient |
| Pericarditis | 39109, 393, 420, 423 | I30-132 | Inpatient or outpatient |
| **Aortic diseases** | | | |
| Aortic dissection | 44109 | I710 | Inpatient |
| Aortic aneurysm/dilatation | 44110, 44111, 44119, 44120, 44121, 44129, 44199 | I711-I716, I718-I719 | Inpatient or outpatient |
| **VTE** | | | |
| First-time VTE | 45100, 45108, 45109, 45099 | I801-I803, I26 | Inpatient or outpatient |
| First-time DVT | 45100, 45108, 45109 | I801-3 | Inpatient or outpatient |
| First-time PE | 45099 | I26 | Inpatient or outpatient |
| Recurrent VTE | 45100, 45108, 45109, 45099 | I801-I803, I26 | Inpatient |
| Recurrent DVT | 45100, 45108, 45109 | I801-3 | Inpatient |
| Recurrent PE | 45099 | I26 | Inpatient |
| **Other** | | | |
| Arterial claudication | 44389-44399 | I739A | Inpatient or outpatient |
| Hypercholesterolemia | 27200 | E780 | Inpatient or outpatient |
| Cardiac tumors | N/A | C38, C380, C388, D151, D487A, C380X, ZM88400 | Inpatient or outpatient |
| **Diagnostic modalities** | | | |
| CT scan | N/A | UXCA | N/A |
| Ultra sound scan | N/A | UXUG | N/A |

[a]ICD-8 codes were used to identify first-time and recurrent ICD-10 diagnoses.

Abbreviations: ICD, international classification of diseases; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; ARVC, arrhythmogenic right ventricular cardiomyopathy; VT or VF, ventricular tachycardia or ventricular fibrillation; VTE, venous thromboembolism; DVT, deep venous thrombosis; PE, pulmonary embolism; CT, computed tomography.

**Supplementary Table 2**. Medical chart extraction form

| Variables | Explanation |
|---|---|
| **Date** | Date of the medical record review |
| **Initials** | Initials of the investigator |
| **CPR number** | Unique 10-digit Civil Personal Register number |
| **CPR number (check)** | Confirmation of the CPR number |
| **SKS code** | ICD-10 code of the diagnosis |
| **Name of disease** | An abbreviation of the diagnosis |
| **Date of discharge** | The date the patient was examined/discharged |
| **Correct diagnosis** | 0=No, 1=Yes |
| **Correct diagnosis for subgroups** | 0=No, 1=Yes |
| **Data source** | 1=Discharge summary<br>2=Other medical record<br>3=Both 1+2 |
| **Algorithm** | 1=One investigator made the decision<br>2=A second independent reviewer agreed with the first reviewer<br>3=Consensus agreement |
| **Comments** | Any relevant comments |

# Paper II

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# Impact of pre-admission depression on mortality following myocardial infarction

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**Background**
The prognostic impact of previous depression on myocardial infarction survival remains poorly understood.

**Aims**
To examine the association between depression and all-cause mortality following myocardial infarction.

**Method**
Using Danish medical registries, we conducted a nationwide population-based cohort study. We included all patients with first-time myocardial infarction (1995–2014) and identified previous depression as either a depression diagnosis or use of antidepressants. We used Cox regression to compute adjusted mortality rate ratios (aMRRs) with 95% confidence intervals.

**Results**
We identified 170 771 patients with first-time myocardial infarction. Patients with myocardial infarction and a previous depression diagnosis had higher 19-year mortality risks (87% *v.* 78%). The overall aMRR was 1.11 (95% CI 1.07–1.15) increasing to 1.22 (95% CI 1.17–1.27) when including use of antidepressants in the depression definition.

**Conclusions**
A history of depression was associated with a moderately increased all-cause mortality following myocardial infarction.

**Declaration of interest**
None.



Despite remarkable advances in prevention and prognosis,[1,2] myocardial infarction remains a common life-threatening event and an enormous burden on Western healthcare systems.[2] While the incidence of first-time myocardial infarction has decreased by nearly 50% during the past 25 years,[1] the prevalence of myocardial infarction survivors has increased.[1,3] Patients with depression have an increased risk of myocardial infarction, but the prognostic impact of a history of depression on myocardial infarction remains to be established.[4] However, depression is associated with several factors that could worsen the prognosis following myocardial infarction. These include poor adherence to recommended lifestyle changes and advice relating to secondary prophylactic medications after myocardial infarction,[5] poor social support,[6] low heart rate variability[7] and increased levels of inflammatory markers.[8] Numerous studies have examined the impact of post-admission depression on myocardial infarction mortality, reporting adjusted hazard ratios ranging from 1.33 to 1.53.[4,9] Only two studies have examined the impact of pre-admission depression on myocardial infarction survival.[10,11] Reporting no association with mortality, these two studies had small sample sizes ($<600$ patients) and relied on patients' anamnesis to confirm previous depression. Trials have shown that antidepressive treatment after myocardial infarction improves survival only for a subgroup of patients with treatment-resistant depression,[12] but not for all patients with depression.[13,14] However, if depression only moderately increases mortality risk, the statistical power of these trials ($n<2500$) may have introduced a type 2 error. We therefore undertook a population-based cohort study to examine how a history of depression influences the mortality of an acute myocardial infarction.

## Method

### Setting and design

The study period for this nationwide population-based cohort study was 1 July 1995 to 1 February 2014. The Danish National Health Service provides free and universal tax-supported healthcare, guaranteeing unfettered access to general practitioners and hospitals. We linked medical registries using the unique central personal registry number assigned to each Danish citizen at birth and to residents upon immigration.[15] The study was approved by the Danish Data Protection Agency (Record number: 1-16-02-268-14). No approval from an ethics committee or patient informed consent is required for registry-based studies conducted in Denmark.

### Patients with myocardial infarction

In Denmark, care for patients with myocardial infarction and other medical emergencies is provided by public hospitals. We used the Danish National Patient Registry (DNPR), covering all Danish hospitals,[16] to identify all patients with a first-time in-patient admission for myocardial infarction during the study period, including registered ST-segment elevation myocardial infarction (STEMI) and non-STEMI. The DNPR contains data on admission and discharge dates and discharge diagnoses from all Danish non-psychiatric hospitals since 1977 and from emergency room and out-patient clinic visits since 1995.[16] Each hospital discharge is assigned one primary diagnosis and up to 19 secondary diagnoses classified according to the ICD-8[17] until the end of 1993 and ICD-10[18] thereafter.[16] We used both primary and secondary diagnoses to identify patients with myocardial infarction.

### Depression

We used the DNPR[16] and the Danish Psychiatric Central Research Register (DPCR)[19] to identify all diagnoses of depression prior to admission for myocardial infarction. The DPCR is a nationwide registry with records of all psychiatric admissions and, from 1995, also out-patient treatment at psychiatric departments in Denmark. All diagnoses in the DPCR are registered by

psychiatrists. Furthermore, we obtained information on depression severity (classified as mild, moderate or severe) using ICD-10 codes.[18] Patients with more than one severity code were assigned the most severe code. The positive predictive values of data in the DPCR have been reported previously and found to be high for severe depression (83%) but somewhat lower for moderate (76%) and mild depression (65%).[20] Because many patients with depression are managed in primary care only and hence not included in hospital registries, we sought to increase completeness of the depression diagnosis by including redeemed prescriptions for antidepressants in our analyses. We grouped patients into six categories based on depression diagnoses and antidepressant use: (a) no diagnosis of depression and $\leqslant 1$ redeemed prescription for antidepressants before the myocardial infarction/index date (reference group), (b) no diagnosis of depression, $>1$ redeemed prescription with former use of the antidepressant, (c) no diagnosis of depression, $>1$ redeemed prescription with current use of the antidepressant, (d) a prior depression diagnosis and $\leqslant 1$ redeemed prescription, (e) a prior depression diagnosis, $>1$ redeemed prescription with former use of the antidepressant, and (f) a prior depression diagnosis, $>1$ redeemed prescription with current use of the antidepressant. We defined 'current users' as patients having redeemed a prescription for antidepressants within 90 days before the index date. 'Former users' redeemed their last prescription more than 90 days before the myocardial infarction/index date.

### Patient characteristics

We used the complete medical history available in the DNPR[16] to ascertain the presence of non-psychiatric comorbidities and the DPCR[19] to identify psychiatric comorbidity. Both in-patient and out-patient diagnoses were used to identify comorbidity. Information on use of medications $<90$ days prior to myocardial infarction/index date was retrieved from the Danish Registry of Medicinal Product Statistics,[21] which has recorded all prescriptions redeemed in community pharmacies, according to the Anatomical Therapeutic Chemical (ATC) classification system, since 1995.[21] The following medications were included: antidepressants, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), anxiolytics/hypnotics, antipsychotics, statins, low-dose aspirin, angiotensin-converting enzyme inhibitors/angiotensin II receptor antagonists, beta blockers, diuretics and non-steroidal anti-inflammatory drugs. Data on socioeconomic variables (income, employment and education) were retrieved from the Integrated Database for Labour Market Research.[22] ICD and ATC codes used in the study are provided in online Table DS1.

### Outcome

We used the Danish Civil Registration System to obtain information on all-cause mortality.[15] This registry has recorded all changes in vital status and migration for the entire Danish population since 1968, with daily electronic updates.[15] We also examined immediate causes of deaths using data from the Danish Register of Causes of Death[23] (data available through 31 December 2012). We estimated cardiovascular and non-cardiovascular mortality in myocardial infarction patients with and without depression (defined as any diagnosis or $>1$ prescription of antidepressant before the index date). Moreover, we specifically examined deaths caused by arrhythmia, venous thromboembolism, stroke, myocardial infarction and heart failure.

### Statistical analysis

We characterised the myocardial infarction cohort according to age group, gender, calendar year interval, individual comorbidities, use of medication and socioeconomic status. We followed all patients from hospital admission date until death, emigration, or 1 September 2014, whichever came first. We used the Kaplan–Meier estimator to visually present the cumulative mortality during follow-up and to compute mortality risks at 1 year, 5 years, 10 years, 15 years and 19 years after myocardial infarction for patients with and without a pre-myocardial infarction depression diagnosis. We used Cox proportional hazards regression models to compute hazard ratios as a measure of the mortality rate ratio (MRR) comparing patients with myocardial infarction with and without a depression diagnosis from the DNPR or DPCR. Use of antidepressants was not included in this analysis. To increase the sensitivity of depression, we also conducted several analyses combining depression diagnoses and use of antidepressants. In the models, we adjusted for gender, age group, income, employment, calendar year interval and the individual comorbidities listed in Table 1 and online Table DS2. The proportional hazard assumption was assessed using log–log plots and found valid. We repeated the analysis on depression diagnoses stratifying by gender, age group, myocardial infarction type (STEMI or non-STEMI), comorbidity (cardiovascular and other), medication use and socioeconomic factors.

### Sensitivity analyses

We performed a variety of sensitivity analyses to test the robustness of the estimates. First, we analysed patients according to the registry in which the first diagnosis of depression was recorded (DNPR or DPCR), as the depression diagnosis has been validated only in the DPCR. Second, we restricted our analysis to depression diagnoses made 90 days and 1, 2, and 3 years before the index date to detect any temporal effect of the timing of first depression diagnosis. Third, we fitted five additional multivariable models as follows: (a) additional adjustment for education as these data were not available for all patients; (b) additional adjustment for use of anxiolytics/hypnotics and (c) antipsychotics as these drugs may in part serve as a proxy for depression, (d) additional adjustment for cardiovascular diseases and drugs that may represent intermediate steps between depression and post-myocardial infarction mortality,[24] and (d) omitting diabetes, stroke and hypertension from the model, as these covariates potentially could also represent intermediate steps in the association examined. Finally, to detect any temporal changes in the impact of depression, we analysed each calendar year interval separately. All analyses were performed using Stata, version 14.

## Results

### Patient characteristics

Overall, 171 200 patients with a first-time myocardial infarction were identified during the study period. We excluded 138 patients with no follow-up time, 11 patients with missing data on age, and 280 patients with missing data on income and employment. After these exclusions, 170 771 patients with myocardial infarction were available for analysis, of which 6015 (3.5%) had a previous depression diagnosis. Median follow-up time was 1460 days (25–75th percentiles: 283–3251 days) for patients without a depression diagnosis and 855 days (25–75th percentiles: 88–2215 days) for patients with a previous diagnosis. Median age was 71 years for patients without a previous depression diagnosis and 72 years for patients with a previous depression diagnosis. All comorbidities and use of medication were more common among patients with myocardial infarction with a previous depression diagnosis and among current users of antidepressants (Table 1 and online Table DS2).

**Table 1** Characteristics of myocardial infarction patients with and without a prior depression diagnosis

| | *n* (%) | |
|---|---|---|
| | No depression 164 756 (96.5) | Previous depression 6015 (3.5) |
| Age, years | | |
| <40 | 2624 (1.6) | 86 (1.4) |
| 40–59 | 36 211 (22.0) | 1225 (20.4) |
| 60–79 | 83 043 (50.4) | 3000 (49.9) |
| ⩾80 | 42 878 (26.0) | 1704 (28.3) |
| Women | 61 170 (37.1) | 3375 (56.1) |
| Calendar year interval | | |
| 1995–1999 | 41 759 (25.4) | 1075 (17.9) |
| 2000–2004 | 49 930 (30.3) | 1739 (28.9) |
| 2005–2009 | 42 159 (25.6) | 1735 (28.8) |
| 2010–2014 | 30 908 (18.8) | 1466 (24.4) |
| Comorbidity | | |
| Hypertension | 33 474 (20.3) | 1717 (28.6) |
| Atrial fibrillation/atrial flutter | 13 909 (8.4) | 633 (10.5) |
| Stroke | 13 766 (8.4) | 840 (14.0) |
| Cancer | 19 058 (11.6) | 893 (14.9) |
| Obesity | 6094 (3.7) | 447 (7.4) |
| Diabetes | 18 235 (11.1) | 909 (15.1) |
| Chronic pulmonary disease | 17 147 (10.4) | 1131 (18.8) |
| Chronic kidney disease | 5981 (3.6) | 320 (5.3) |
| Peptic ulcer | 10 983 (6.7) | 751 (12.5) |
| Illicit drug/alcohol/smoking abuse | 6764 (4.1) | 1470 (24.4) |
| Dementia | 3390 (2.1) | 618 (10.3) |
| Medication <90 days prior to MI/index date | | |
| Antidepressants | 14 140 (8.6) | 3190 (53.0) |
| SSRIs | 9415 (5.7) | 1799 (29.9) |
| TCAs | 2500 (1.5) | 597 (9.9) |
| Anxiolytics/hypnotics | 28 677 (17.4) | 2585 (43.0) |
| Antipsychotics | 4153 (2.5) | 1220 (20.3) |
| Statins | 20 033 (12.2) | 861 (14.3) |
| Low-dose aspirin | 36 396 (22.1) | 1630 (27.1) |
| ACE/ARBs | 34 370 (20.9) | 1318 (21.9) |
| Beta blockers | 26 121 (15.9) | 1028 (17.1) |
| Diuretics | 44 760 (27.2) | 2051 (34.1) |
| NSAIDs | 23 162 (14.1) | 949 (15.8) |
| Income | | |
| Low | 39 263 (23.8) | 1438 (23.9) |
| Intermediate | 41 782 (25.4) | 1886 (31.4) |
| High | 41 057 (24.9) | 1743 (29.0) |
| Very high | 42 654 (25.9) | 948 (15.7) |
| Employment | | |
| Employed | 43 637 (26.5) | 719 (12.0) |
| Early retirement: receiving sickness, disability or early retirement benefits | 4147 (2.5) | 168 (2.8) |
| Unemployed | 21 040 (12.8) | 1276 (21.2) |
| State pensioner | 95 932 (58.2) | 3852 (64.0) |
| Education | | |
| Basic education, primary school | 65 947 (40.0) | 2811 (46.7) |
| Youth education, high school or similar | 48 043 (29.2) | 1512 (25.1) |
| Higher education | 17 034 (10.3) | 599 (10.0) |
| Unknown | 33 732 (20.5) | 1093 (18.2) |

MI, myocardial infarction; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants, ACE/ARBs, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; NSAIDs, non-steroidal anti-inflammatory drugs.

## Mortality

Throughout the follow-up period, the mortality risks were higher among patients with myocardial infarction with a previous depression diagnosis than among those without a previous depression diagnosis (33% *v.* 26% at 1 year and 87% *v.* 78% at 19 years, Fig. 1 and online Table DS3). Adjusted MRRs (aMMRs) were increased for depression diagnoses overall (1.11, 95% CI 1.07–1.15). Consistent with this overall finding but without any trend, aMMRs were increased for mild (1.11, 95% CI 1.02–1.21), moderate (1.14, 95% CI 1.07–1.21) and severe previous depression diagnoses (1.15, 95% CI 1.05–1.26) (Table 2). Using patients without a previous depression diagnosis and without antidepressant use as the reference, the aMRR was 1.29 (95% CI 1.26–1.32) for current users of antidepressants without a depression diagnosis (no difference between TCA users and SSRI users) and 1.22 (95% CI 1.17–1.27) for current users with a previous depression diagnosis (slightly higher risk for TCA users compared with SSRI users) (Table 3).

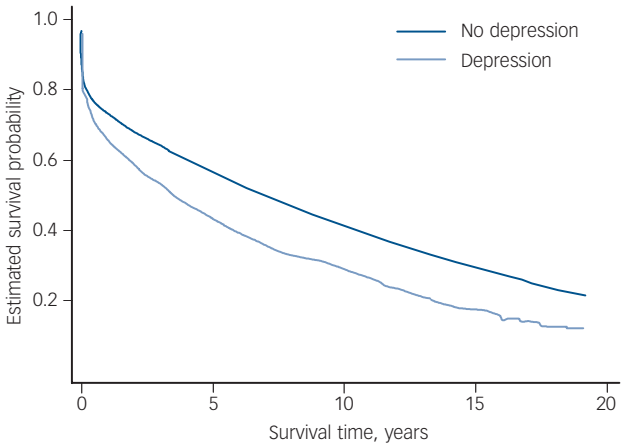


**Fig. 1** Kaplan–Meier survival curve for patients with myocardial infarction with and without a depression diagnosis.

We identified no notable modification of the effect found in the overall results on depression diagnoses (hazard ratio = 1.11) within strata of myocardial infarction type, age group, gender, comorbidity, medication use, income, employment and education (Table 4 and online Figs DS1–5). However, the effect of depression was not present in a few strata (SSRI use, antipsychotic use, illicit drug use, dementia and unemployed). In cause-specific analyses, patients with myocardial infarction with previous depression had higher non-cardiovascular mortality and moderately higher cardiovascular mortality than patients without previous depression (Table 5).

## Sensitivity analyses

The results were robust in the analysis restricted to patients registered in the DNPR and the DPCR, respectively. When the analysis was restricted to patients with a recent depression diagnosis (90 days, 1, 2, and 3 years prior to the myocardial infarction/index date), the association was stronger than the overall estimates (online Table DS4). In an analysis restricted to patients with either STEMI or non-STEMI, the results were consistent with the overall estimates (Table 4). When the model was extended to also adjust for education, use of anxiolytics/hypnotics, use of antipsychotics and cardiovascular diseases and drugs, the results were robust. Omitting diabetes, stroke and hypertension from the multivariate model did not change the results (online Table DS4). Finally, results were robust when stratifying by calendar year interval (online Table DS5).

## Discussion

In this nationwide cohort study of patients with first-time myocardial infarction, previously diagnosed depression was an

**Table 2** Nineteen-year mortality estimates in patients with myocardial infarction with and without a prior depression diagnosis, overall and by depression severity

| | Mortality rate per 1000 person-years (95% CI) | Crude mortality rate ratio (95% CI) | Adjusted mortality rate ratio (95% CI)[a] |
|---|---|---|---|
| No depression | 104.2 (103.6–104.9) | 1.0 (reference) | 1.0 (reference) |
| Depression overall[b] ($n = 6015$) | 168.1 (162.9–173.5) | 1.43 (1.38–1.47) | 1.11 (1.07–1.15) |
| Mild depression[c] ($n = 798$) | 209.2 (192.2–227.6) | 1.63 (1.50–1.77) | 1.11 (1.02–1.21) |
| Moderate depression[c] ($n = 1778$) | 170.3 (160.4–180.9) | 1.37 (1.29–1.46) | 1.14 (1.07–1.21) |
| Severe depression[c] ($n = 768$) | 179.2 (163.9–196.0) | 1.45 (1.32–1.58) | 1.15 (1.05–1.26) |

a. Adjusted for age group, gender, hypertension, atrial fibrillation/atrial flutter, stroke, cancer, obesity, diabetes, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking misuse, dementia, income, employment and calendar year interval.
b. Including all ICD codes for depression.
c. Specific ICD-10 codes provided in online Table DS1.

**Table 3** Nineteen-year mortality rate ratios in patients with myocardial infarction according to presence of a depression diagnosis and use of antidepressants before the index date

| | Crude mortality rate ratio (95% CI) | Adjusted mortality rate ratio (95% CI)[a] |
|---|---|---|
| No prior depression diagnosis | | |
| No use ($n = 138\,405$) | 1.0 (reference) | 1.0 (reference) |
| Former use ($n = 13\,184$) | 1.14 (1.11–1.17) | 1.06 (1.04–1.09) |
| Current use ($n = 13\,167$) | 1.79 (1.76–1.83) | 1.29 (1.26–1.32) |
| Selective serotonin reuptake inhibitors ($n = 8782$) | 1.91 (1.86–1.96) | 1.30 (1.27–1.33) |
| Tricyclic antidepressants ($n = 2348$) | 1.59 (1.52–1.67) | 1.27 (1.21–1.33) |
| Prior depression diagnosis | | |
| No use ($n = 1348$) | 1.28 (1.19–1.36) | 1.01 (0.95–1.08) |
| Former use ($n = 1522$) | 1.17 (1.10–1.26) | 1.10 (1.02–1.18) |
| Current use ($n = 3145$) | 1.83 (1.76–1.91) | 1.22 (1.17–1.27) |
| Selective serotonin reuptake inhibitors ($n = 1771$) | 1.93 (1.82–2.04) | 1.17 (1.11–1.24) |
| Tricyclic antidepressants ($n = 592$) | 1.78 (1.62–1.95) | 1.34 (1.22–1.47) |

a. Adjusted for age group, gender, hypertension, atrial fibrillation/atrial flutter, stroke, cancer, obesity, diabetes, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking misuse, dementia, income, employment and calendar year interval.

**Table 4** Nineteen-year mortality rate ratios in patients with myocardial infarction with and without a prior depression diagnosis, by type of myocardial infarction

| | Crude mortality rate ratio (95% CI) | Adjusted mortality rate ratio (95% CI)[a] |
|---|---|---|
| Non-ST segment elevation myocardial infarction | | |
| No depression ($n = 46\,349$) | 1.0 (reference) | 1.0 (reference) |
| Depression overall[b] ($n = 1774$) | 1.50 (1.41–1.59) | 1.15 (1.08–1.23) |
| Mild depression[c] ($n = 250$) | 1.81 (1.54–2.12) | 1.20 (1.02–1.40) |
| Moderate depression[c] ($n = 585$) | 1.36 (1.21–1.52) | 1.16 (1.03–1.30) |
| Severe depression[c] ($n = 235$) | 1.50 (1.26–1.78) | 1.16 (0.97–1.38) |
| ST-segment elevation myocardial infarction | | |
| No depression ($n = 20\,295$) | 1.0 (reference) | 1.0 (reference) |
| Depression overall[b] ($n = 728$) | 1.49 (1.33–1.67) | 1.08 (0.96–1.21) |
| Mild depression[c] ($n = 108$) | 1.89 (1.44–2.47) | 1.12 (0.85–1.47) |
| Moderate depression[c] ($n = 252$) | 1.36 (1.12–1.66) | 1.07 (0.87–1.30) |
| Severe depression[c] ($n = 108$) | 1.24 (0.90–1.70) | 1.01 (0.74–1.39) |

a. Adjusted for age group, gender, hypertension, atrial fibrillation/atrial flutter, stroke, cancer, obesity, diabetes, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking misuse, dementia, income, employment, and calendar year interval.
b. Including all ICD codes for depression.
c. Specific ICD-10 codes provided in online Table DS1.

adverse prognostic factor for all-cause mortality, independent of depression severity and type of myocardial infarction. The association was strongest for recent depression and for current users of antidepressants, indicating that active depression exacerbates its adverse prognostic influence on post-myocardial infarction mortality. The association was overall consistent with the analysis on depression diagnoses in the strata of age, gender, comorbidity, medication use, or socioeconomic status.

Only two studies have examined the effect of pre-admission depression on mortality following myocardial infarction.[10,11] Neither of these studies reported any association with mortality. However, one study had only 4 months of follow-up,[11] and both studies had small sample sizes, selective inclusion of patients from specific hospitals, and assessed depression by self-report questionnaires and medical chart review. Other studies on the association between depression and mortality following myocardial infarction have focused on post-myocardial infarction depression (i.e. detecting the depression after admission for myocardial infarction). Two recent meta-analyses with post-myocardial infarction depression as the exposure reported

**Table 5** Cardiovascular and non-cardiovascular mortality in patients with myocardial infarction with and without previous depression, 1995–2012

| | Mortality rate per 1000 person-years (95% CI) | | Adjusted mortality rate ratio (95% CI)[b] |
|---|---|---|---|
| | No depression ($n = 138\,405$) | Depression[a] ($n = 32\,366$) | |
| All-cause mortality | 110.3 (109.5–111.1) | 193.5 (190.8–196.2) | 1.19 (1.17–1.21) |
| Cardiovascular mortality | 41.0 (40.5–41.5) | 71.1 (69.4–72.7) | 1.15 (1.11–1.18) |
| Arrhythmia | 3.7 (3.5–3.8) | 6.1 (5.6–6.6) | 1.12 (1.02–1.23) |
| Venous thromboembolism | 0.7 (0.7–0.8) | 1.3 (1.1–1.5) | 1.19 (0.96–1.46) |
| Myocardial infarction | 12.0 (11.7–12.2) | 25.8 (24.9–26.9) | 1.15 (1.10–1.21) |
| Stroke | 3.5 (3.3–3.6) | 6.3 (5.8–6.8) | 1.16 (1.05–1.27) |
| Heart failure | 7.2 (7.0–7.4) | 13.0 (12.3–13.7) | 1.19 (1.11–1.27) |
| Non-cardiovascular mortality | 48.2 (47.7–48.7) | 91.2 (89.4–93.1) | 1.25 (1.22–1.29) |

a. Including all patients with ICD codes for depression or more than one prescription of an antidepressant before the index date.
b. Adjusted for age group, gender, hypertension, atrial fibrillation/atrial flutter, stroke, cancer, obesity, diabetes, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking misuse, dementia, income, employment and calendar year interval.

increased relative risks for all-cause mortality (1.23, 95% CI 1.15–1.31[9] and 1.80, 95% CI 1.50–2.15[4]). Thus, these studies generally found higher estimates compared with our study. This may be explained by lack of adjustment for essential covariates included in our study (for example alcohol misuse and socioeconomic status). Furthermore, the stronger association in studies of post-myocardial infarction depression may be confounded by severity of myocardial infarction, i.e., the likelihood of detecting important depressive symptoms (for example fatigue, disturbed sleep and poor appetite) may be higher after severe cases of myocardial infarction and hence would lead to stronger association with mortality. In post-myocardial infarction depression studies that did adjust for myocardial infarction severity (Killip class or left ventricular ejection fraction), the association with mortality was attenuated by 25% after adjustment,[9] further supporting this notion. By contrast, we based our depression exposure on physician-diagnosed depression prior to admission for myocardial infarction. This strict definition of depression explains the discrepancy between depression prevalence in our cohort (3.5%) and that of previously reported studies (approximately 20%).[25] However, when we also included use of antidepressants in the definition, the prevalence increased to 19% (Table 3).

Several underlying pathophysiological mechanisms have been suggested to link depression to increased mortality in patients with myocardial infarction, and the causality is likely to be multifactorial. Evidence for a biological pathway suggests that depression is associated with hyperactivity of the hypothalamic–pituitary–adrenocortical axis with increased cortisol levels,[26] which can lead to elevation of blood pressure, increased plasma volume, hyperinsulinaemia, hyperglycaemia, insulin resistance and dyslipidaemia.[27] It is unlikely that the increased mortality can be attributed to the antidepressive treatment itself as treatment with SSRIs has been shown to lower cortisol and insulin resistance.[28] Moreover, clinical trials have shown no[13,14] or a slightly positive effect[12] of SSRI treatment on mortality. Depression has also been associated with disturbances in cardiac autonomic tone including elevated heart rate and low heart rate variability.[29] These factors may exacerbate heart failure in the course of myocardial infarction and are associated with post-myocardial infarction mortality.[30] A behavioural pathway suggests that patients with a depression diagnosis are less likely to adopt a healthy lifestyle (for example, regarding physical activity and smoking) and dietary recommendations, and are less likely to adhere to recommended secondary prophylactic medication than patients without depression.[5] Clinical pathways may include metabolic syndrome[31] leading to increased risk of cardiovascular diseases such as stroke and heart failure.[24]

## Limitations

Several issues should be considered when interpreting our results. This is the first nationwide study of the association between pre-admission depression and all-cause mortality following myocardial infarction. Its main strength is its large population-based design within a tax-supported, uniformly organised healthcare system with independently and prospectively recorded hospital and prescription history, and with complete follow-up for all patients. This setting reduces the risk of selection biases.[32] One study limitation is reliance on routine hospital discharge diagnoses, which may contain coding errors. However, the positive predictive value of myocardial infarction diagnoses in the DNPR has been examined previously and found to exceed 95%.[16,33]

Misclassification because of underreporting of depression diagnoses from primary care has most likely biased the estimates based only on depression diagnoses towards the null. This is supported by the increased mortality in analyses including anti-depressants in the depression definition. In these analyses, however, increased mortality may be because of prescribing of antidepressants for more severe conditions than depression (such as cancer pain). Another concern is that the depression diagnosis has been validated only in the DPCR;[20] however, we obtained similar results when we separately analysed individuals with depression identified from the DNPR and from the DPCR. The observational nature of our study renders it vulnerable to unmeasured confounding. Specifically, we lacked information on smoking. However, we did adjust for chronic pulmonary disease as a proxy for smoking and for socioeconomic status and alcohol misuse, which are likely to mimic the distribution of smoking.

## Implications

We found that depression diagnosed prior to myocardial infarction was an adverse prognostic factor for post-myocardial infarction mortality. The association was stronger in patients with recent depression or current use of antidepressants, but was not influenced by depression severity or type of myocardial infarction. Our findings merit clinical attention to myocardial infarction patients with a previous depression diagnosis or with current use of antidepressants. The clinical pathways responsible for increased mortality in these patients need further clarification to allow prevention of specific high-risk conditions.

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EXTRA CONTENT ONLINE

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## Supplemental tables

**Table DS1.** *International Classification of Diseases* codes and Anatomical Theurapeutic Classification codes used in the study.

| | ICD-8 | ICD-10 | ATC codes |
|---|---|---|---|
| **Myocardial infarction** | 410 | I21 | N/A |
| **Depression** | 29609, 29629, 29809, 30049 | F32-F33 | |
| Mild depression | N/A | F320, F3200, F3201, F330, F3300, F3301 | N/A |
| Moderate depression | N/A | F321, F3210, F3211, F331, F3310, F3311 | |
| Severe depression | N/A | F322, F323, F3230, F3231, F332, F333, F3330, F3331 | |
| **Cardiac comorbidities** | | | |
| Heart failure | 42709, 42710, 42711, 42719, 42899, 78249 | I110, I130, I132, I420, I426, I427, I428, I429, I500, I501, I502, I503, I508, I509 | N/A |
| Heart valve disease | 394-397 | I05-I08, I098, I34-I37 | |
| Myocarditis | 422, 39129 | I40-I41, I090, I514 | |
| Hypertension | 400-404 | DI10-DI15 | N/A |
| Angina pectoris | 411, 413 | I20, I251, I259 | |
| Atrial fibrillation/atrial flutter | 42793, 42794 | I48 | |
| Cardiomyopathy | 425 | I42-I43 | N/A |
| **Non-cardiac comorbidities** | | | |
| Stroke | 430-434 | I60-I61, I63-I64 | N/A |
| Cancer | 140-209 | C00-C96 | N/A |
| Obesity | 277 | E65-E66 | N/A |
| Diabetes | 24900-24909 (excluding 24902), 25000-25009 (excluding 25002) | E10 (excluding E102), E11 (excluding E112), E14 (excluding E142) | N/A |
| Chronic pulmonary disease | 490-493, 515-518 | J40-J47, J60-J67, J684, J701, J703, J841, J920, J961, J982-J983 | N/A |
| Chronic kidney disease | 24902, 25002, 75310-75319, 582-584, 59009, 59320, 792 | E102, E112, E142, N03, N05, N110, N14, N16, N18-N19, N269, Q611-Q614 | N/A |
| Peptic ulcer | 53091, 53098, 531-534 | K221, K25-K28 | N/A |
| Illicit drug/alcohol/smoking abuse[a] | 303-304 | F10-F19 | N/A |
| Dementia[a] | 29009-29019, 29309 | F00-F03, G30 | N/A |
| **Medication prescription <90 days prior to MI/index date** | | | |

| | | | |
|---|---|---|---|
| Antidepressants | N/A | N/A | N06A |
| SSRIs | N/A | N/A | N06AB |
| TCAs | N/A | N/A | N06AA |
| Anxiolytics/hypnotics | N/A | N/A | N05B, N05C |
| Antipsychotics | N/A | N/A | N05A |
| Statins | N/A | N/A | C10AA, C10B |
| Low-dose aspirin | N/A | N/A | B01AC06, N02BA01 |
| ACE/ARBs | N/A | N/A | C09A, C09B, C09C, C09D |
| Beta blockers | N/A | N/A | C07 |
| Diuretics | N/A | N/A | C03 |
| NSAIDs | N/A | N/A | M01A |

Abbreviations: SSRIs, Selective serotonin inhibitors; TCAs, Tricyclic antidepressants; ACE/ARBs, Angiotensin receptor antagonist/Angiotensin II receptor blockers; NSAIDs, Nonsteroidal anti-inflammatory drugs.
[a]Data from the Danish National Patient Registry and the Danish Psychiatric Central Research Register.

**Table DS2.** Descriptive data for myocardial infarction patients, by prior depression diagnosis and use of antidepressants.

| | No diagnosed depression | | | | Diagnosed depression | | | |
|---|---|---|---|---|---|---|---|---|
| | Total n=164,756 (96.5%) | Use of antidepressants | | | Total n=6,015 (3.5%) | Use of antidepressants | | |
| | | No use n=138,405 (81.1%) | Former use n=13,184 (7.7%) | Current use n=13,167 (7.7%) | | No use n=1348 (0.8%) | Former use n=1522 (0.9%) | Current use n=3145 (1.8%) |
| **Age, years** | | | | | | | | |
| <40 | 2624 (1.6) | 2292 (1.7) | 205 (1.6) | 127 (1.0) | 86 (1.4) | 12 (0.9) | 33 (2.2) | 41 (1.3) |
| 40–59 | 36211 (22.0) | 31123 (22.5) | 3149 (23.9) | 1939 (14.7) | 1225 (20.4) | 285 (21.1) | 447 (29.4) | 493 (15.7) |
| 60–79 | 83043 (50.4) | 70534 (51.0) | 6340 (48.1) | 6169 (46.9) | 3000 (49.9) | 792 (58.8) | 742 (48.8) | 1466 (46.6) |
| ≥80 | 42878 (26.0) | 34456 (24.9) | 3490 (26.5) | 4932 (37.5) | 1704 (28.3) | 259 (19.2) | 300 (19.7) | 1145 (36.4) |
| **Women** | 61,170 (37.1) | 47775 (34.5) | 6246 (47.4) | 7149 (54.3) | 3375 (56.1) | 665 (49.3) | 712 (46.8) | 1998 (63.5) |
| **Calendar year interval** | | | | | | | | |
| 1995–1999 | 41,759 (25.4) | 38505 (27.8) | 1222 (9.3) | 2032 (15.4) | 1,075 (17.9) | 470 (34.9) | 158 (10.4) | 447 (14.2) |
| 2000–2004 | 49,930 (30.3) | 42457 (30.7) | 3500 (26.6) | 3973 (30.2) | 1,739 (28.9) | 425 (31.5) | 400 (26.3) | 914 (29.1) |
| 2005–2009 | 42,159 (25.6) | 33719 (24.4) | 4336 (32.9) | 4104 (31.2) | 1,735 (28.8) | 277 (20.6) | 461 (30.3) | 997 (31.7) |
| 2010–2014 | 30,908 (18.8) | 23724 (17.1) | 4126 (31.3) | 3058 (23.2) | 1,466 (24.4) | 176 (13.1) | 503 (33.1) | 787 (25.0) |
| **Comorbidity** | | | | | | | | |
| Hypertension | 33,474 (20.3) | 25470 (18.4) | 3831 (29.1) | 4173 (31.7) | 1717 (28.6) | 281 (20.9) | 453 (29.8) | 983 (31.3) |
| Atrial fibrillation/atrial flutter | 13909 (8.4) | 10827 (7.8) | 1402 (10.6) | 1680 (12.8) | 633 (10.5) | 116 (8.61) | 153 (10.1) | 364 (11.6) |
| Stroke | 13,766 (8.4) | 9505 (6.9) | 1755 (13.3) | 2506 (19.0) | 840 (14.0) | 135 (10.0) | 174 (11.4) | 531 (16.9) |
| Cancer | 19,058 (11.6) | 15018 (10.9) | 1882 (14.3) | 2158 (16.4) | 893 (14.9) | 173 (12.8) | 211 (13.9) | 509 (16.2) |
| Obesity | 6094 (3.7) | 4500 (3.3) | 795 (6.0) | 799 (6.1) | 447 (7.4) | 100 (7.4) | 114 (7.5) | 233 (7.4) |
| Diabetes | 18,235 (11.1) | 14001 (10.1) | 1987 (15.1) | 2247 (17.1) | 909 (15.1) | 175 (13.0) | 226 (14.9) | 508 (16.2) |
| Chronic pulmonary disease | 17,147 (10.4) | 12553 (9.1) | 2171 (16.5) | 2423 (18.4) | 1131 (18.8) | 218 (16.2) | 263 (17.3) | 650 (20.7) |
| Chronic kidney disease | 5981 (3.6) | 4506 (3.3) | 715 (5.4) | 760 (5.8) | 320 (5.3) | 54 (4.0) | 86 (5.7) | 180 (5.7) |
| Peptic ulcer | 10,983 (6.7) | 8227 (5.9) | 1239 (9.4) | 1517 (11.5) | 751 (12.5) | 155 (11.5) | 177 (11.6) | 419 (13.3) |
| Illicit drug/alcohol misuse | 6764 (4.1) | 4282 (3.1) | 1266 (9.6) | 1216 (9.2) | 1470 (24.4) | 344 (25.5) | 429 (28.2) | 697 (22.2) |
| Dementia | 3390 (2.1) | 1731 (1.3) | 516 (3.9) | 1143 (8.7) | 618 (10.3) | 55 (4.1) | 124 (8.2) | 439 (14.0) |
| **Medication <90 days prior to myocardial infarction/index date** | | | | | | | | |
| Antidepressants | 14,140 (8.6) | 973 (0.7) | 0 (0.0) | 13167 (100.0) | 3190 (53.0) | 45 (3.3) | 0 (0.0) | 3145 (100.0) |
| SSRIs | 9415 (5.7) | 633 (0.5) | 0 (0.0) | 8782 (66.7) | 1799 (29.9) | 28 (2.1) | 0 (0.0) | 1771 (56.3) |
| TCAs | 2500 (1.5) | 152 (0.1) | 0 (0.0) | 2348 (17.8) | 597 (9.9) | 5 (0.4) | 0 (0.0) | 592 (18.8) |
| Anxiolytics/hypnotics | 28,677 (17.4) | 19428 (14.0) | 3890 (29.5) | 5359 (40.7) | 2585 (43.0) | 433 (32.1) | 496 (32.6) | 1656 (52.7) |
| Antipsychotics | 4153 (2.5) | 2282 (1.7) | 662 (5.0) | 1209 (9.2) | 1220 (20.3) | 169 (12.5) | 227 (14.9) | 824 (26.2) |
| Statins | 20,033 (12.2) | 15490 (11.2) | 2251 (17.1) | 2292 (17.4) | 861 (14.3) | 123 (9.1) | 227 (14.9) | 511 (16.3) |
| Low-dose aspirin | 36,396 (22.1) | 28627 (20.7) | 3366 (25.5) | 4403 (33.4) | 1630 (27.1) | 285 (21.1) | 338 (22.2) | 1007 (32.0) |
| ACE/ARBs | 34,370 (20.9) | 27506 (19.9) | 3303 (25.1) | 3561 (27.0) | 1318 (21.9) | 239 (17.7) | 323 (21.2) | 756 (24.0) |
| Beta blockers | 26,121 (15.9) | 21102 (15.3) | 2425 (18.4) | 2594 (19.7) | 1028 (17.1) | 220 (16.3) | 231 (15.2) | 577 (18.4) |
| Diuretics | 44,760 (27.2) | 35355(25.5) | 3921 (29.7) | 5484 (41.7) | 2051 (34.1) | 401 (29.8) | 387 (25.4) | 1263 (40.2) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| NSAIDs | 23,162 (14.1) | 18581 (13.4) | 2134 (16.2) | 2447 (18.6) | 949 (15.8) | 185 (13.7) | 200 (13.1) | 564 (17.9) |
| **Income** | | | | | | | | |
| Low | 39,263 (23.8) | 33854 (24.5) | 2373 (18.0) | 3036 (23.1) | 1438 (23.9) | 447 (33.2) | 278 (18.3) | 713 (22.7) |
| Intermediate | 41,782 (25.4) | 33608 (24.3) | 3765 (28.6) | 4409 (33.5) | 1886 (31.4) | 421 (31.2) | 430 (28.3) | 1035 (32.9) |
| High | 41,057 (24.9) | 33400 (24.1) | 3967 (30.1) | 3690 (28.0) | 1743 (29.0) | 305 (22.6) | 490 (32.2) | 948 (30.1) |
| Very high | 42,654 (25.9) | 37543 (27.1) | 3079 (23.3) | 2032 (15.4) | 948 (15.7) | 175 (13.0) | 324 (21.3) | 449 (14.3) |
| **Employment** | | | | | | | | |
| Employed | 43,637 (26.5) | 39505 (28.5) | 2652 (20.1) | 1480 (11.2) | 719 (12.0) | 218 (16.2) | 251 (16.5) | 250 (8.0) |
| Early retirement, receiving sickness/incapacity/early retirement | 4147 (2.5) | 3477 (2.5) | 406 (3.1) | 264 (2.0) | 168 (2.8) | 32 (2.4) | 64 (4.2) | 72 (2.3) |
| Unemployed | 21,040 (12.8) | 16683 (12.1) | 2444 (18.5) | 1913 (14.5) | 1276 (21.2) | 254 (18.8) | 449 (29.5) | 573 (18.2) |
| State pensioner | 95,932 (58.2) | 78740 (56.9) | 7682 (58.3) | 9510 (72.2) | 3852 (64.0) | 844 (62.6) | 758 (49.8) | 2250 (71.5) |
| **Education** | | | | | | | | |
| Basic education, primary school | 65,947 (40.0) | 54566 (39.4) | 5593 (42.4) | 5788 (44.0) | 2811 (46.7) | 680 (50.5) | 664 (43.6) | 1467 (46.7) |
| Youth education, high school or similar | 48,043 (29.2) | 40947 (29.6) | 3960 (30.0) | 3136 (23.8) | 1512 (25.1) | 341 (25.3) | 472 (31.0) | 699 (22.2) |
| Higher education | 17,034 (10.3) | 14450 (10.4) | 1501 (11.4) | 1083 (8.2) | 599 (10.0) | 101 (7.5) | 193 (12.7) | 305 (9.7) |
| Unknown | 33,732 (20.5) | 28442 (20.6) | 2130 (16.2) | 3160 (24.0) | 1093 (18.2) | 226 (16.8) | 193 (12.7) | 674 (21.4) |

Data are numbers (%).

Abbreviations: SSRIs, Selective serotonin inhibitors; TCAs, Tricyclic antidepressants; ACE/ARBs, Angiotensin receptor antagonist/Angiotensin II receptor blockers; NSAIDs, Non-steroidal anti-inflammatory drugs

**Table DS3** Mortality risks among myocardial infarction patients with and without previous depression.

| | Risk estimates, % (95% confidence intervals) | | | | |
|---|---|---|---|---|---|
| | **1-year** | **5-year** | **10-year** | **15-year** | **19-year** |
| No depression | 25.9 (25.7–26.1) | 43.4 (43.1–43.6) | 58.4 (58.2–58.7) | 70.3 (70.0–70.6) | 77.8 (77.3–78.3) |
| Depression | 33.4 (32.2–34.6) | 56.6 (55.3–58.0) | 72.0 (70.5–73.3) | 81.7 (80.2–83.3) | 87.4 (85.0–89.6) |

**Table DS4** 19-year mortality rate ratios comparing myocardial infarction patients with and without a prior depression diagnosis according to source of depression diagnosis, years since diagnosis, and extension of the model.

| | Crude mortality rate ratio (95% confidence intervals) | Adjusted mortality rate ratio[a] (95% confidence intervals) |
|---|---|---|
| **Registry providing first diagnosis of depression** | | |
| National Patient Registry (n= 1248) | 1.78 (1.67–1.90) | 1.14 (1.07–1.22) |
| Psychiatric Central Research Register (n= 4767) | 1.34 (1.30–1.39) | 1.09 (1.05–1.14) |
| **Years since first depression diagnosis** | | |
| 90 days (n=222) | 1.95 (1.68–2.25) | 1.17 (1.01–1.35) |
| 1 year (n= 573) | 1.75 (1.59–1.93) | 1.20 (1.09–1.32) |
| 2 years (n= 989) | 1.68 (1.56–1.81) | 1.21 (1.13–1.31) |
| 3 years (n= 1356) | 1.66 (1.56–1.77) | 1.22 (1.14–1.30) |
| **Additional adjustments[a]** | | |
| + education[b] (n= 4922) | 1.59 (1.53–1.65) | 1.14 (1.09–1.18) |
| + anxiolytics/hypnotics (n= 6015) | 1.43 (1.38–1.47) | 1.07 (1.03–1.10) |
| + antipsychotics (n= 6015) | 1.43 (1.38–1.47) | 1.05 (1.02–1.09) |
| + cardiovascular diseases and drugs[c] (n= 6015) | 1.43 (1.38–1.47) | 1.09 (1.06–1.13) |
| No adjustment for diabetes, stroke, hypertension (n=6015) | 1.43 (1.38–1.47) | 1.12 (1.08–1.16) |

The number of patients with depression is reported in parentheses.
[a]Adjusted for age groups, sex, hypertension, atrial fibrillation/atrial flutter, stroke, cancer, obesity, diabetes, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking abuse, dementia, income, employment, and calendar year interval.
[b]Analyses restricted to patients with complete data on all variables.
[c]Congestive heart failure, venous thromboembolism, heart valve disease, myocarditis, stabile angina pectoris, hypercholesterolemia, pulmonary hypertension, arterial claudication, statins, low-dose aspirin, angiotensin receptor antagonist/Angiotensin II receptor blockers, beta blockers, diuretics, and nonsteroidal anti-inflammatory drugs.

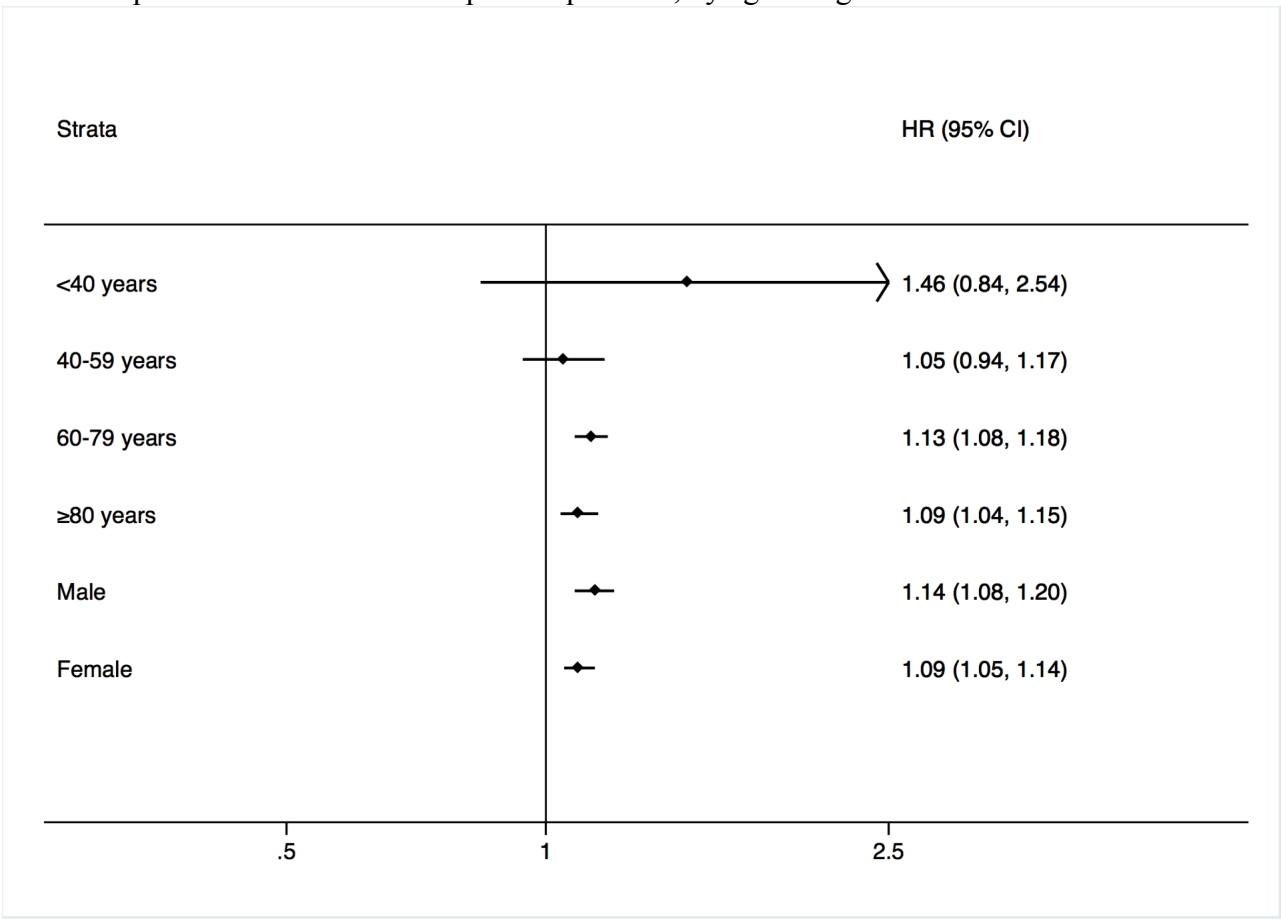
**Table DS5** Mortality estimates in myocardial infarction patients with and without a prior depression diagnosis, by calendar year interval.

| | Crude mortality rate ratio (95% confidence intervals) | Adjusted mortality rate ratio (95% confidence intervals)[a] |
|---|---|---|
| **1995–1999** | | |
| No depression diagnosis | 1.0 (reference) | 1.0 (reference) |
| Depression diagnosis | 1.39 (1.30–1.49) | 1.12 (1.05–1.20) |
| **2000–2004** | | |
| No depression diagnosis | 1.0 (reference) | 1.0 (reference) |
| Depression diagnosis | 1.46 (1.38–1.54) | 1.08 (1.02–1.14) |
| **2005–2009** | | |
| No depression diagnosis | 1.0 (reference) | 1.0 (reference) |
| Depression diagnosis | 1.52 (1.43–1.62) | 1.12 (1.05–1.19) |
| **2010–2014** | | |
| No depression diagnosis | 1.0 (reference) | 1.0 (reference) |
| Depression diagnosis | 1.52 (1.39–1.66) | 1.12 (1.03–1.23) |

[a]Adjusted for age groups, sex, hypertension, atrial fibrillation/atrial flutter, stroke, cancer, obesity, diabetes, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking abuse, dementia, income, employment, and calendar year interval.

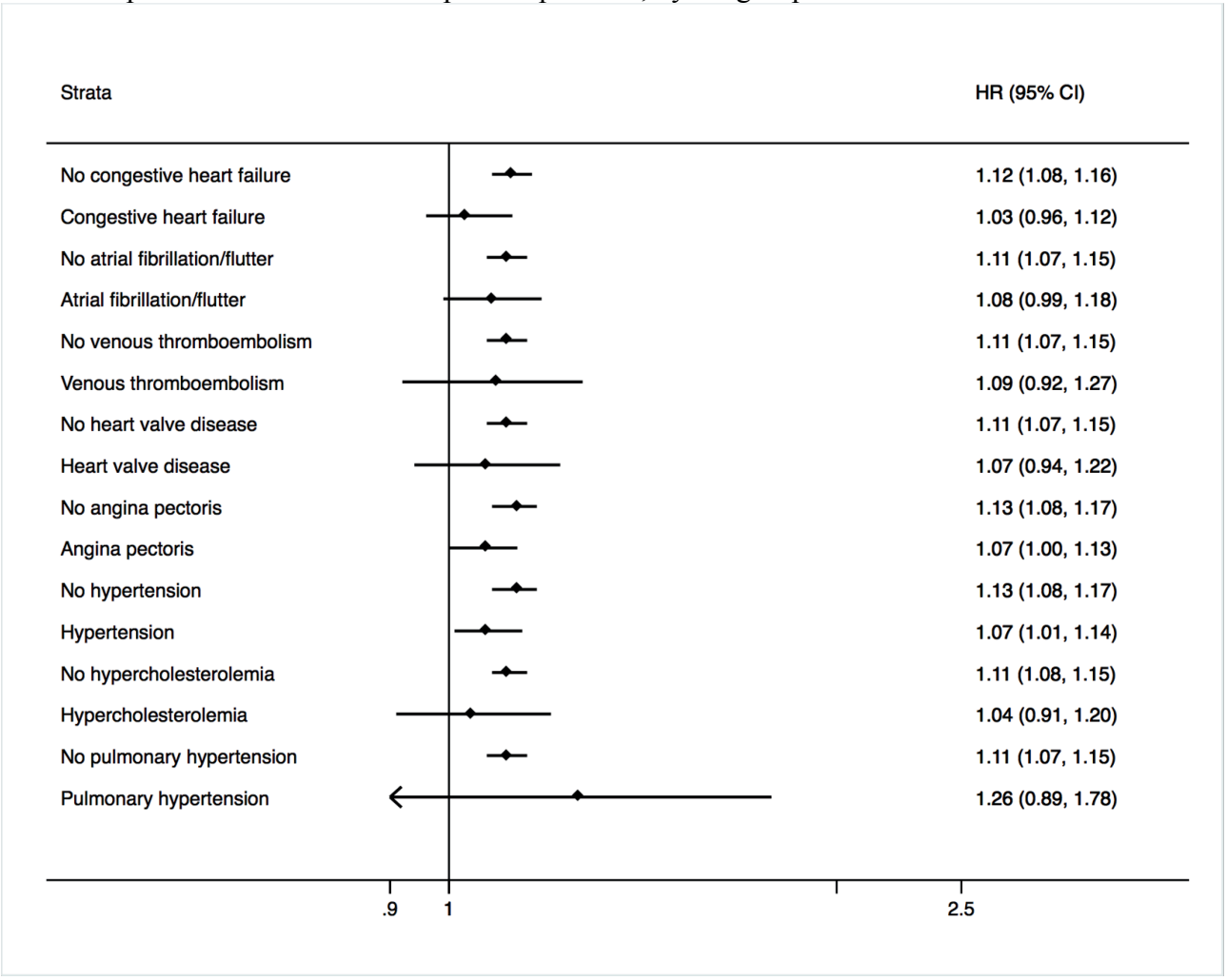
## Supplemental figures

**Figure DS1.** Adjusted[a] mortality rate ratios with 95% confidence intervals comparing myocardial infarction patients with and without prior depression, by age and gender



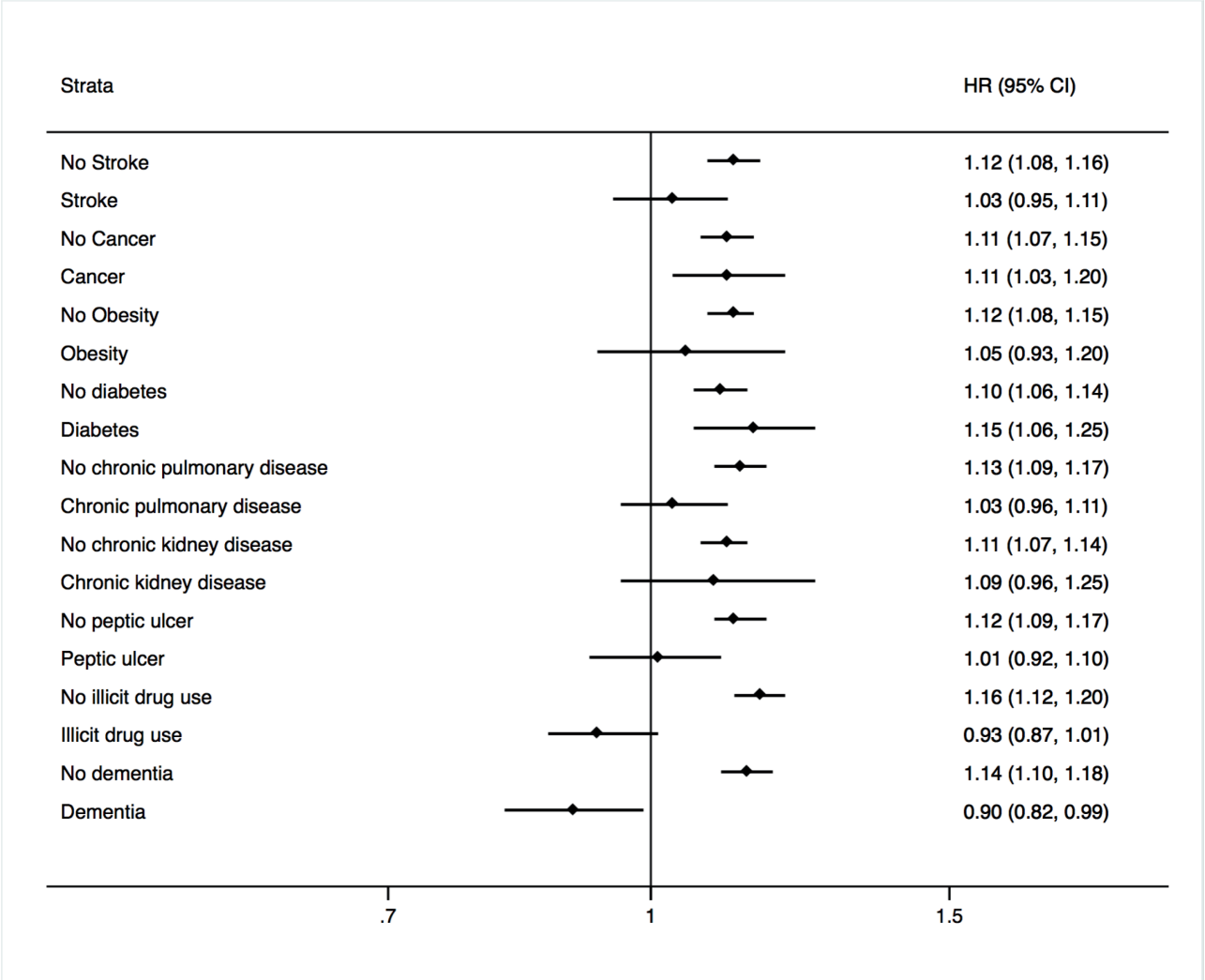

[a]Adjusted for age groups, gender, hypertension, atrial fibrillation/atrial flutter, stroke, cancer, obesity, diabetes, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking abuse, dementia, income, employment, and calendar year interval (not adjusted for gender in the gender-stratified analysis).

**Figure DS2.** Adjusted[a] mortality rate ratios with 95% confidence intervals comparing myocardial infarction patients with and without prior depression, by subgroups of cardiac diseases.



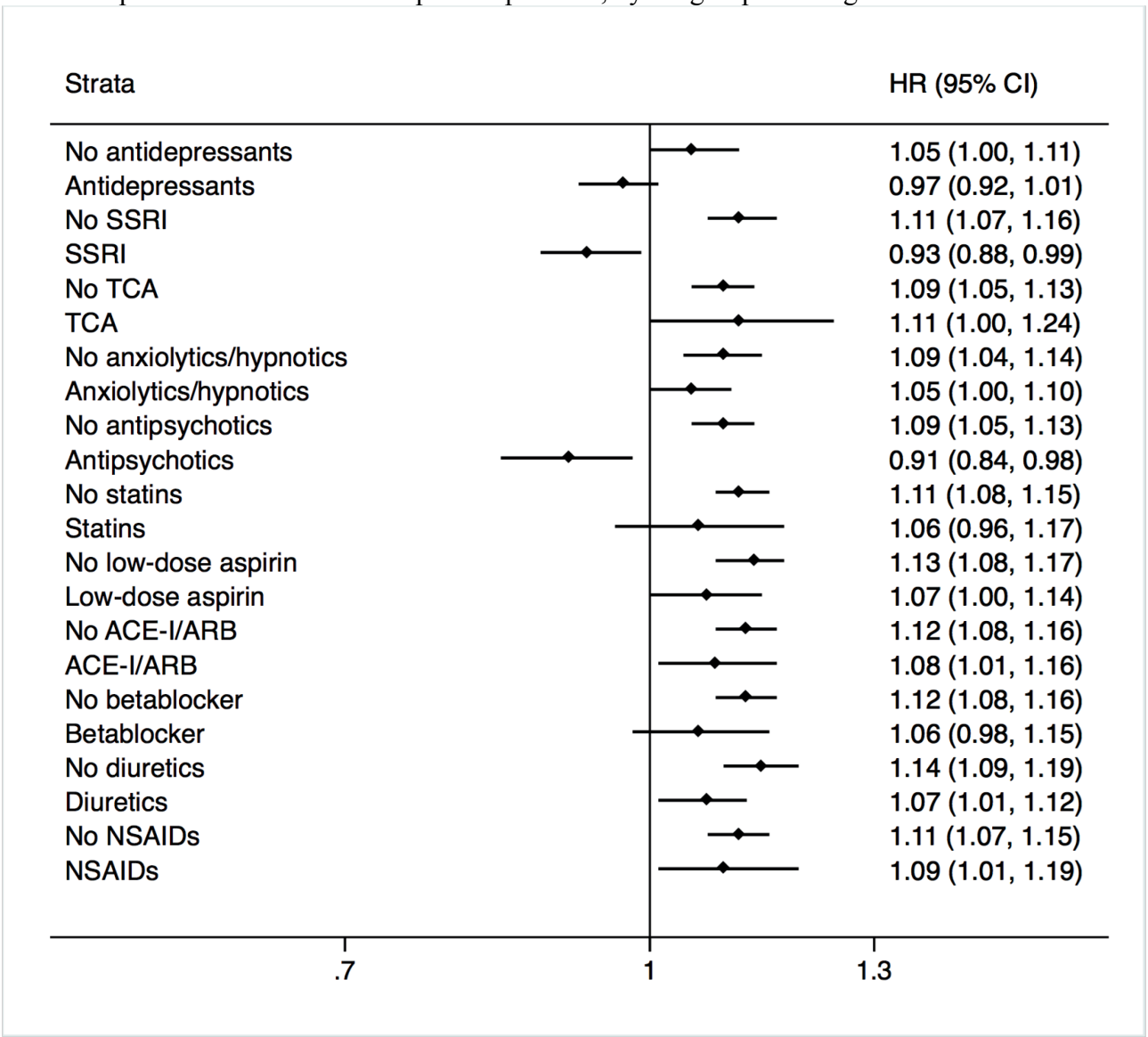

[a]Adjusted for age groups, gender, hypertension, atrial fibrillation/atrial flutter, stroke, cancer, obesity, diabetes, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking misuse, dementia, income, employment, and calendar year interval (except the stratifying variable).

**Figure DS3.** Adjusted[a] mortality rate ratios with 95% confidence intervals comparing myocardial infarction patients with and without prior depression, by subgroups of non-cardiac diseases.



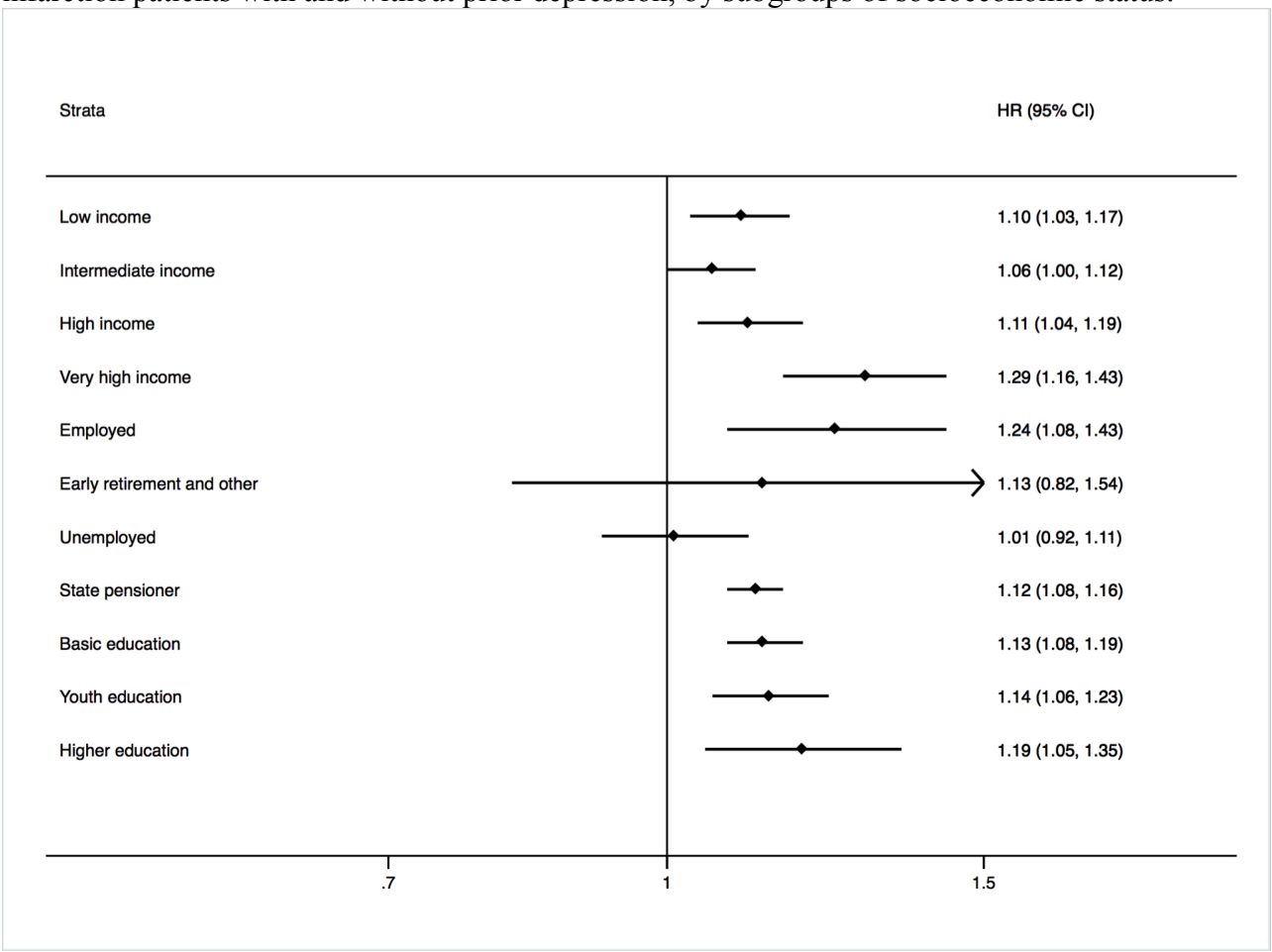

[a]Adjusted for age groups, gender, hypertension, atrial fibrillation/atrial flutter, stroke, cancer, obesity, diabetes, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking misuse, dementia, income, employment, and calendar year interval (except the stratifying variable).

**Figure DS4.** Adjusted[a] mortality rate ratios with 95% confidence intervals comparing myocardial infarction patients with and without prior depression, by subgroups of drugs.




[a]Adjusted for age groups, gender, hypertension, atrial fibrillation/atrial flutter, stroke, cancer, obesity, diabetes, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking misuse, dementia, income, employment, and calendar year interval (except the stratifying variable).

**Figure DS5.** Adjusted[a] mortality rate ratios with 95% confidence intervals comparing myocardial infarction patients with and without prior depression, by subgroups of socioeconomic status.




[a]Adjusted for age groups, gender, hypertension, atrial fibrillation/atrial flutter, stroke, cancer, obesity, diabetes, chronic kidney disease, peptic ulcer, chronic pulmonary disease, illicit drug/alcohol/smoking misuse, dementia, income, employment, and calendar year interval (except the stratifying variable).

# Impact of pre-admission depression on mortality following myocardial infarction

Jens Sundbøll, Morten Schmidt, Kasper Adelborg, Lars Pedersen, Hans Erik Bøtker, Poul Videbech and Henrik Toft Sørensen

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# Paper III

# Long-Term Risk of Stroke in Myocardial Infarction Survivors

## Thirty-Year Population-Based Cohort Study

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***Background and Purpose***—Improved survival after myocardial infarction (MI) has increased the number of patients at risk of post-MI stroke. We examined risks of ischemic stroke, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH) in patients with MI compared with the general population.

***Methods***—We conducted a nationwide population–based cohort study using Danish medical registries. During 1980 to 2009, we identified all patients with a first-time inpatient diagnosis of MI and formed a sex- and age-matched comparison cohort. We computed cumulative stroke risks and adjusted stroke rate ratios with 95% confidence intervals (CIs).

***Results***—We identified 258 806 patients with an MI and 1 244 773 individuals from the general population. For patients with MI, the cumulative stroke risks after 1 to 30 years were 12.6% for ischemic stroke, 1.2% for ICH, and 0.24% for SAH. During the first 30 days after MI, the adjusted stroke rate ratio was 30-fold increased for ischemic stroke (31.9; 95% CI, 28.4–35.8), 20-fold for ICH (21.8; 95% CI, 16.6–28.5), and 15-fold for SAH (16.6; 95% CI, 8.7–32.0). The adjusted stroke rate ratio remained increased during 31 to 365 days (3-fold for ischemic stroke, 2-fold for ICH, and 1.5-fold for SAH). During the ensuing 1 to 30 years, the risks remained increased for ischemic stroke (1.6; 95% CI, 1.6–1.6) but decreased to near unity for ICH (1.1; 95% CI, 1.0–1.2) and SAH (1.1; 95% CI, 0.94–1.2).

***Conclusions***—MI was a risk factor for all stroke subtypes during the first year of follow-up, but only for ischemic stroke thereafter. **(*Stroke*. 2016;47:1727-1733. DOI: 10.1161/STROKEAHA.116.013321.)**

**Key Words:** myocardial infarction ■ risk factor ■ stroke ■ subarachnoid hemorrhage



Stroke is a serious complication after myocardial infarction (MI)[1] with a 1-year risk of ischemic stroke ranging from 2% to 4%.[2,3] Despite an almost 50% decrease in the incidence of first-time MI during the past 25 years,[4] the prevalence of MI survivors actually has increased owing to a concomitant improved survival after MI.[4,5] With a current prevalence of nearly 8 million MI survivors in the United States alone,[6] the population at risk of MI-related stroke is substantial.

During the past 30 years, the introduction of aspirin, ADP receptor inhibitors, statins, β-blockers, and angiotensin-converting enzyme inhibitors has improved prognosis after MI.[4,7] As well, treatment of atrial fibrillation—a strong risk factor for post-MI stroke[8]—changed with the introduction of warfarin around 1990[9] and more recently with the availability of new target-specific oral anticoagulants.[10] These advances may have decreased the risk of ischemic stroke after MI, but at the potential cost of increased risk of hemorrhagic stroke. Previous studies of post-MI stroke had follow-up periods less than a year long[2,3,8,11–15] or focused solely on ischemic stroke.[8,15,16] No studies have examined the long-term risks of ischemic stroke, intracerebral hemorrhage (ICH), or subarachnoid hemorrhage (SAH) after MI.

To address this issue, we conducted a nationwide 30-year cohort study of patients with first-time MI to examine the long-term risk of ischemic stroke, ICH, and SAH after MI, compared with risks in the general population.

## Methods

### Setting

We conducted the study in Denmark, which had a cumulative population of 7 543 591 persons during 1980 to 2009. The Danish National Health Service provides government-funded universal health care guaranteeing unfettered access to general practitioners and hospital-based care.[17] Accurate linkage of all Danish registries

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**The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.116.013321/-/DC1.**

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at the individual level is possible using the unique Central Personal Registry number assigned to each Danish citizen at birth and to residents on immigration.[18]

## Myocardial Infarction

In Denmark, all care for patients with MI, stroke, and other medical emergencies is provided by public hospitals. We used the Danish National Patient Registry (DNPR), covering all Danish hospitals,[19] to identify all Danish-born patients with a first-time inpatient diagnosis of MI during the 30-year period from 1 January 1980 to 31 December 2009. The DNPR contains data on dates of admission and discharge from all Danish nonpsychiatric hospitals since 1977 and from emergency room and outpatient clinic visits since 1995.[19] Each hospital discharge or outpatient visit is recorded in the registry with 1 primary diagnosis and one or more secondary diagnoses classified according to the *International Classification of Diseases*, Eighth Revision until the end of 1993 and *International Classification of Diseases*, Tenth Revision thereafter.[19] We identified patients with MI using both primary and secondary diagnoses, excluding patients with a previous or concurrent inpatient or outpatient diagnosis of stroke or transient ischemic attack. Associated *International Classification of Diseases* codes are provided in Table I in the online-only Data Supplement.

## Comparison Cohort

We formed a population-based comparison cohort from the general population using the Danish Central Personal Registry.[20] For each patient with MI, we matched (on sex and age) ≤5 individuals from the general population who were alive on the date the corresponding patient was hospitalized with MI. Each comparison cohort member was assigned an index date corresponding to the admission date for the matched MI patient. We included only members of the general population without a hospital discharge diagnosis of MI, stroke, or transient ischemic attack before or on the index date. If a member of the comparison cohort subsequently experienced an MI, he or she joined the MI cohort at that point.

## Comorbidity

We obtained complete information on comorbid conditions before the index date from inpatient and outpatient hospital diagnoses recorded in the DNPR. We identified the following individual comorbidities of prognostic importance: congestive heart failure, stable angina pectoris, atrial fibrillation or flutter, valvular heart disease, intermittent claudication, venous thromboembolism, hypertension, obesity, diabetes mellitus, chronic kidney disease, and chronic pulmonary disease.

## Stroke

We obtained information from the DNPR[19] on all inpatient hospitalizations for ischemic stroke, ICH, and SAH after the MI admission/index date. Approximately one third of all stroke diagnoses in the DNPR has been coded as unspecified stroke.[21] Because more than two thirds of all unspecified strokes are known to be ischemic strokes,[22] we classified unspecified strokes as ischemic strokes. We identified incident strokes using both primary and secondary stroke diagnoses.

## Statistical Analysis

We characterized the MI and comparison cohort members according to sex, age group (<60, 60–69, 70–79, or ≥80 years), and the comorbidities listed in Table 1. We followed all patients with MI and comparison cohort members from the MI admission/index date until the occurrence of a hospitalization for stroke (ischemic stroke, ICH, or SAH) or until emigration, death, 31 December 2012, or 30 years of follow-up, whichever came first.

Using cumulative incidence functions with death as a competing risk,[23] we illustrated the cumulative stroke risk graphically for both cohorts. Cumulative risks at 30 days, 365 days, and 30 years were computed using the pseudovalue approach.[24]

For the 1 to 30 days, 31 to 365 days, and 1 to 30 years of follow-up periods, we computed the stroke rate and used stratified Cox proportional-hazards regression (ie, retaining matching by age and sex in the analysis) to compute unadjusted and adjusted hazard ratios as a measure of the stroke rate ratios (SRRs) between the MI and the comparison cohorts. In the regression model, we adjusted for the individual comorbidities listed in Table 1. For all estimates, we computed 95% confidence intervals (CIs). The proportional-hazards assumption was assessed graphically using log–log plots. Because the assumption was violated within the whole period, we examined SRRs separately within 1 to 30 days, 31 to 365 days, and 1 to 30 years of follow-up periods.[25]

To assess temporal changes in stroke risk during the study period, we stratified the regression analyses by the calendar periods listed in Table 1. In these analyses, a 1 to 5 years instead of a 1 to 30 years of follow-up period was used for long-term risk assessment, to allow for sufficient follow-up time in the last calendar period (2005–2009). In addition, we stratified the analyses by sex, age, and the individual comorbidities listed in Table 1 to detect whether cardiovascular diseases had any major influence on stroke risk. In all stratified analyses, we dissolved the matching and adjusted instead for the matching factors (age and sex) and the individual comorbidities.

In sensitivity analyses, we repeated the analyses separating ischemic stroke into specified ischemic stroke and unspecified stroke and extended the hypertension and diabetes mellitus definitions to also include medication, which was available in the last study period (2005–2009). For the temporal trends in stroke risk, we also computed the cumulative risks for each calendar period in addition to SRRs.

Because this study did not involve contact with patients or any intervention, approval from the Danish Scientific Ethical Committee and patient consent were not required. The study was approved by the Danish Data Protection Agency (record number 1-16-02-1-08).

# Results

A total of 258 806 patients with first-time MI were identified during the study period. The comparison cohort consisted of 1 244 773 sex- and age-matched persons from the general population without a previous MI. Comorbidities were more common among patients with MI than among comparison cohort members (Table 1).

## Ischemic Stroke

Cumulative risk functions for the MI and comparison cohorts during the 30-year follow-up period are presented in Figure 1 and corresponding cumulative risks after 1 to 30 days, 31 to 365 days, and 1 to 30 years are presented in Table 2. After 30 years of follow-up, the cumulative risk of ischemic stroke was 12.6% for the MI cohort and 11.9% for the comparison cohort. During 1 to 30 days of follow-up, the adjusted SRR was 31.9 (95% CI, 28.4–35.8), comparing the MI cohort with the matched general population comparison cohort. The adjusted SRR remained elevated during both the 31 to 365 days (3.1; 95% CI, 3.0–3.3) and 1 to 30 years of period (1.6; 95% CI, 1.6–1.6).

## ICH and SAH

After 30 years of follow-up, the cumulative risk of ICH was lower in the MI cohort (1.2%) than in the comparison cohort (1.6%) because of competing mortality in the MI cohort. The adjusted SRR was elevated during the first 1 to 30 days (21.8; 95% CI, 16.6–28.5) and 31 to 365 days (2.1; 95% CI, 1.9–2.5) and declined to near unity during the ensuing 1 to 30 years (1.1; 95% CI, 1.0–1.2).

**Table 1. Characteristics of Patients With a First-Time Hospitalization for Myocardial Infarction and Age- and Sex-Matched Comparison Cohort Members**

| | Myocardial Infarction Cohort, n (%) | Comparison Cohort, n (%) |
|---|---|---|
| Total | 258 806 (100) | 1 244 773 (100) |
| Sex (male) | 162 862 (62.9) | 784 141 (63.0) |
| Age, y | | |
| <60 | 60 074 (23.2) | 297 410 (23.9) |
| 60–69 | 66 496 (25.7) | 324 540 (26.1) |
| 70–79 | 78 553 (30.4) | 375 238 (30.2) |
| ≥80 | 53 683 (20.7) | 247 585 (19.9) |
| Median (interquartile range) | 70.4 (60.8–78.5) | 70.0 (60.5–78.2) |
| Year of diagnosis/index date | | |
| 1980–1984 | 57 725 (22.3) | 284 316 (22.8) |
| 1985–1989 | 53 054 (20.5) | 259 119 (20.8) |
| 1990–1994 | 46 174 (17.8) | 224 360 (18.0) |
| 1995–1999 | 33 177 (12.8) | 158 339 (12.7) |
| 2000–2004 | 36 477 (14.1) | 170 106 (13.7) |
| 2005–2009 | 32 199 (12.4) | 148 533 (11.9) |
| Comorbidities | | |
| Congestive heart failure | 15 610 (6.0) | 27 990 (2.3) |
| Angina pectoris | 24 356 (9.4) | 36 692 (3.0) |
| Atrial fibrillation or flutter | 10 692 (4.1) | 31 694 (2.6) |
| Heart valve disease | 4375 (1.7) | 8442 (0.7) |
| Intermittent claudication | 2984 (1.2) | 4207 (0.3) |
| Venous thromboembolism | 4632 (1.8) | 15 767 (1.3) |
| Hypertension | 25 068 (9.7) | 55 242 (4.4) |
| Obesity | 6337 (2.5) | 13 690 (1.1) |
| Diabetes mellitus | 19 091 (7.4) | 36 049 (2.9) |
| Chronic kidney disease | 5118 (2.0) | 7993 (0.6) |
| Chronic pulmonary disease | 16 973 (6.6) | 50 555 (4.1) |

The cumulative risk of SAH after 30 years of follow-up was low for both the MI (0.24%) and comparison cohort (0.29%). During the first 30 days of follow-up, the adjusted SRR was 16.6 (95% CI, 8.7–32.0). The adjusted SRR remained elevated during 31 to 365 days (1.5; 95% CI, 1.1–2.1) after which there was no difference in risk between the MI and the comparison cohorts (SRR, 1.1; 95% CI, 0.94–1.2).

### Temporal Trends in Stroke Risk

Changes in adjusted SRR during the 30-year study period are presented in Figure 2. For ischemic stroke, an abrupt decrease was observed for all 3 periods of follow-up during the first half of the study period. Thereafter, the adjusted SRR decreased only little.

For ICH, there was a modest drop in the 1- to 30-day adjusted SRR during the first half of the study period, after which it increased to ≈30 during 1995 to 1999 and settled at ≈12 during 2005 to 2009. During 31 to 365 days and 1 to 5 years of follow-up periods, a decline was observed in the first decade of the study period, after which the SRR increased marginally.

For SAH, a bimodal pattern was observed during the 1 to 30 days and 31 to 365 days of follow-up, with the SRR declining during the first 2 decades of the study period, followed by an abrupt increase in the last decade. During 1 to 5 years of follow-up, the SRRs remained close to unity throughout the study period apart from a peak during 1985 to 1989.

### Additional Analyses

In stratified analyses by sex and age, the adjusted SRR was slightly higher among females and younger age groups during the first 1 to 30 days and 31 to 365 days of follow-up. However, for SAH the adjusted SRR was higher for males than for females. No effect modification by sex or age was observed for the remaining 1 to 30 years of follow-up (Table II in the online-only Data Supplement).

Stratified analyses by individual comorbidities are presented in Table III in the online-only Data Supplement. In these analyses, adjusted SRRs were slightly higher for strata with no comorbidity. This was expected because of the lower absolute risk of stroke.

In the sensitivity analyses, results were unchanged when separating ischemic stroke into specified ischemic stroke and unspecified stroke (Table IV in the online-only Data Supplement). When including medication in the definition of hypertension and diabetes mellitus during 2005 to 2009, the prevalence of these diseases in the MI cohort increased from 20.6% to 35.7% for hypertension and from 9.7% to 12.7% for diabetes mellitus (Table V in the online-only Data Supplement). However, the SRRs were consistent with the primary results (Table VI in the online-only Data Supplement). Cumulative risks by calendar periods were continuously higher in the MI cohort compared with the comparison cohort (Table VII in the online-only Data Supplement).

## Discussion

MI was a strong risk factor for all stroke types during 1 to 30 days and 31 to 365 days of follow-up. During 1 to 30 years of follow-up, the risk remained elevated for ischemic stroke, but leveled out for ICH and SAH. Throughout the 30-year study period and for all 3 follow-up periods, a continuous decrease in stroke risk was observed for ischemic stroke, whereas risks of ICH and SAH decreased only during the first 2 decades after which a marginal increase was observed for SAH. The observed pattern of ischemic versus hemorrhagic stroke risk after MI may reflect secondary MI prevention strategies.[26] During the last study decade, guidelines recommended an aggressive antithrombotic regimen with dual antiplatelet therapy (DAPT) for 1 year after

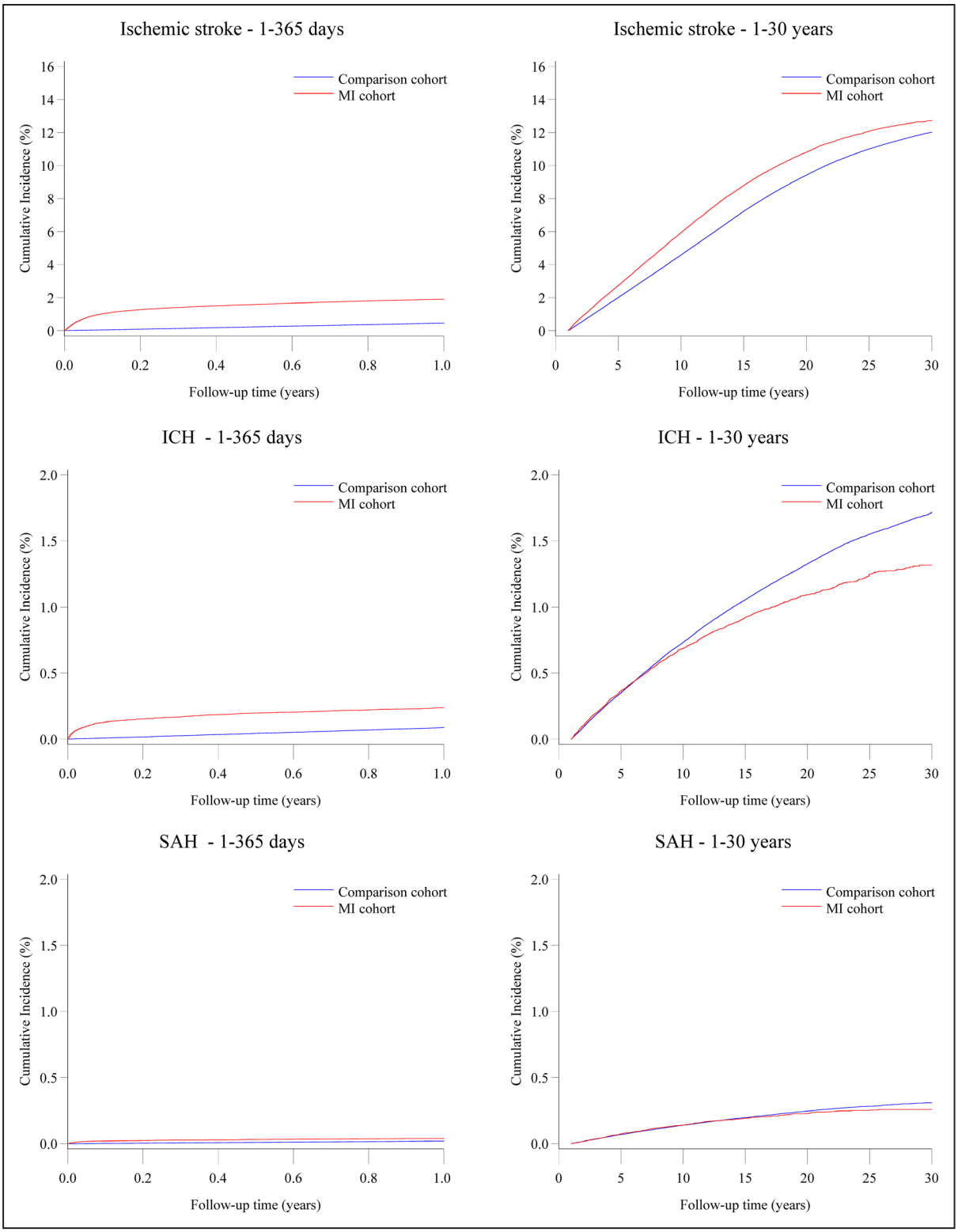


**Figure 1.** Cumulative risk of stroke after myocardial infarction (MI) during 1 to 365 days and 1 to 30 years of follow-up. ICH indicates intracerebral hemorrhage; and SAH, subarachnoid hemorrhage.

MI (ie, aspirin plus an ADP receptor inhibitor) followed by lifelong aspirin treatment.[26] This may explain, in part, why the risk of hemorrhagic stroke was elevated only during the first year after MI. Similarly, the introduction of DAPT in the beginning of the last study decade may explain why the initial decline in ICH and SAH risks was followed by a marginal increase toward the end of the study period.[27,28] The notable decrease in ischemic stroke risk between 1985 to 1989 and 1990 to 1994 coincides with the broad implementation of aspirin treatment for patients with MI in the early

**Table 2. Stroke Risk Estimates After MI**

| | Stroke Risk,* % (95% CI) | Stroke Rate† (95% CI) | Stroke Rate Ratio (95% CI) | |
|---|---|---|---|---|
| | | | Unadjusted | Adjusted‡ |
| Ischemic stroke | | | | |
| 1–30 d | | | | |
| Comparison cohort | 0.04 (0.03–0.04) | 4.6 (4.2–5.1) | 1 (reference) | 1 (reference) |
| MI cohort | 1.0 (0.92–1.0) | 146.0 (140.4–151.9) | 32.0 (28.6–35.7) | 31.9 (28.4–35.8) |
| 31–365 d | | | | |
| Comparison cohort | 0.43 (0.41–0.44) | 4.7 (4.6–4.9) | 1 (reference) | 1 (reference) |
| MI cohort | 1.3 (1.2–1.3) | 15.1 (14.5–15.7) | 3.3 (3.1–3.5) | 3.1 (3.0–3.3) |
| 1–30 y | | | | |
| Comparison cohort | 11.9 (11.8–12.0) | 7.9 (7.8–8.0) | 1 (reference) | 1 (reference) |
| MI cohort | 12.6 (12.4–12.8) | 10.8 (10.6–11.0) | 1.7 (1.6–1.7) | 1.6 (1.6–1.6) |
| ICH | | | | |
| 1–30 d | | | | |
| Comparison cohort | 0.01 (0.01–0.01) | 0.93 (0.76–1.1) | 1 (reference) | 1 (reference) |
| MI cohort | 0.12 (0.11–0.14) | 18.8 (16.8–21.0) | 21.6 (16.7–28.0) | 21.8 (16.6–28.5) |
| 31–365 d | | | | |
| Comparison cohort | 0.08 (0.08–0.09) | 0.89 (0.84–0.95) | 1 (reference) | 1 (reference) |
| MI cohort | 0.16 (0.13–0.17) | 1.8 (1.6–2.0) | 2.2 (2.0–2.6) | 2.1 (1.9–2.5) |
| 1–30 y | | | | |
| Comparison cohort | 1.6 (1.6–1.7) | 1.1 (1.1–1.1) | 1 (reference) | 1 (reference) |
| MI cohort | 1.2 (1.2–1.3) | 1.1 (1.0–1.1) | 1.1 (1.1–1.2) | 1.1 (1.0–1.2) |
| SAH | | | | |
| 1–30 d | | | | |
| Comparison cohort | 0.00 (0.00–0.00) | 0.19 (0.12–0.29) | 1 (reference) | 1 (reference) |
| MI cohort | 0.02 (0.01–0.02) | 2.8 (2.1–3.8) | 14.5 (8.2–25.5) | 16.6 (8.7–32.0) |
| 31–365 d | | | | |
| Comparison cohort | 0.02 (0.01–0.02) | 0.19 (0.17–0.22) | 1 (reference) | 1 (reference) |
| MI cohort | 0.03 (0.02–0.03) | 0.30 (0.23–0.40) | 1.5 (1.1–2.1) | 1.5 (1.1–2.1) |
| 1–30 y | | | | |
| Comparison cohort | 0.29 (0.28–0.30) | 0.20 (0.19–0.21) | 1 (reference) | 1 (reference) |
| MI cohort | 0.24 (0.21–0.27) | 0.22 (0.20–0.25) | 1.1 (0.97–1.3) | 1.1 (0.94–1.2) |

CI indicates confidence interval; ICH, intracerebral hemorrhage; MI, myocardial infarction; and SAH, subarachnoid hemorrhage.

*Treating death as a competing risk.

†Rates per 1000 person-years.

‡Adjusted for congestive heart failure, angina pectoris, atrial fibrillation or flutter, heart valve disease, intermittent arterial claudication, venous thromboembolism, hypertension, obesity, diabetes mellitus, chronic kidney disease, and chronic pulmonary disease.

1990s prompted by the Second International Study of Infarct Survival (ISIS-2) trial.[29]

Mechanisms underlying elevated risk of ischemic stroke for up to 30 years after MI likely include shared risk factors for atherosclerosis, which account for the mutual pathophysiological disarray underlying ischemic stroke and MI.[30] The extent to which MI itself is responsible for increased risk of ischemic stroke remains unclear. Cardioembolic stroke has been reported to account for 60% of in-hospital post-MI ischemic strokes.[13] As only about one fifth of all ischemic strokes is cardioembolic,[31] the high proportion of cardioembolic strokes among post-MI ischemic strokes may be because of complications of MI, such as atrial fibrillation or regional wall motion abnormality with formation of left ventricular thrombi. However, 3 large trials have shown no association between anticoagulation therapy in patients with MI and stroke occurrence, suggesting a minor role of cardioembolic stroke.[32–34]

Our findings merit increased awareness of both ischemic and hemorrhagic stroke during the first year after MI and attention to ischemic stroke thereafter. Prevention of

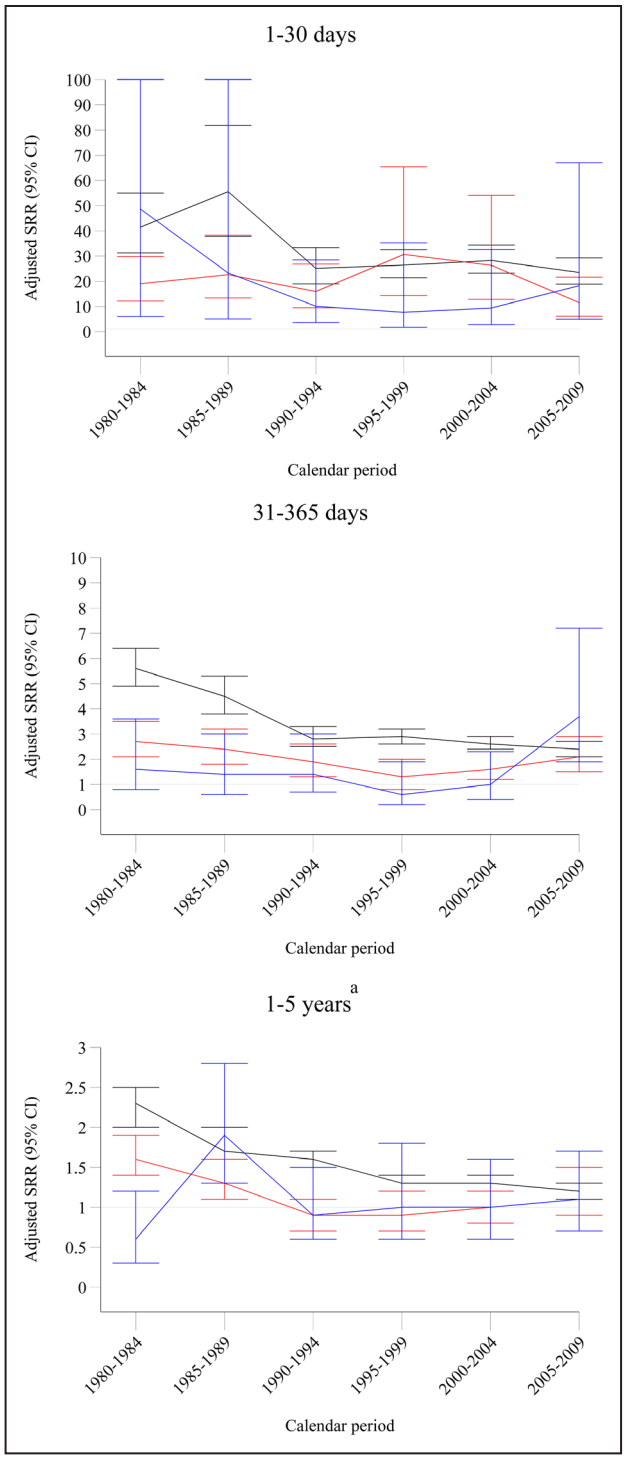


**Figure 2.** Short- and long-term temporal trends in the adjusted stroke rate ratio after myocardial infarction during 1980 to 2009, with 95% confidence intervals (CIs). All estimates were adjusted for congestive heart failure, angina pectoris, atrial fibrillation or flutter, heart valve disease, intermittent arterial claudication, venous thromboembolism, hypertension, obesity, diabetes mellitus, chronic kidney disease, and chronic pulmonary disease. [a]For long-term risk assessment, a 1 to 5 year instead of a 1- to 30-year follow-up period was used, to allow for follow-up during the last calendar period (ie, 2005–2009).

post-MI ischemic stroke should focus on established risk factors, including hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, and smoking.[8,13]

Antithrombotic therapy after MI follows current guidelines recommending 1 year of DAPT followed by lifelong aspirin therapy.[28] A recent trial found that continuation of the DAPT regimen beyond 1 year after MI[35] reduced 3-year stroke risk without a concomitant increase in serious bleeding events, including intracranial hemorrhage. Prolongation of DAPT after MI is intriguing in light of our finding that only the risk of ischemic stroke was increased beyond 1 year after MI. However, we cannot rule out that the increased risk of hemorrhagic stroke during the first year could be related to DAPT treatment itself, as supported by the increased 1- to 30-day and 31- to 365-day SRR for SAH during the 2000 to 2009 period where DAPT was implemented.

Several study strengths and limitations should be considered. We had sufficient sample size and follow-up time to examine short- and long-term risk of stroke after MI. The population-based design within a uniformly organized healthcare system limited the risk of selection biases because of inclusion of specific hospitals, health insurance systems, or age groups.[17] Follow-up was complete for all patients.[18] The positive predictive values of inpatient diagnoses in the DNPR have previously been validated and found to be 97% for ischemic stroke, 74% for ICH, 67% for SAH,[22] and >90% for MI.[36] Because we classified unspecified strokes as ischemic strokes, a few ICHs (≈6%) were almost certainly misclassified as ischemic strokes.[22] However, separate analyses of specified ischemic stroke and unspecified stroke did not change our main results. Although we adjusted for the most important potential confounders (eg, hypertension, obesity, diabetes mellitus, and chronic pulmonary disease as an indirect measure of smoking)[37,38] and in sensitivity analyses ruled out residual confounding by hypertension and diabetes mellitus, we cannot rule out unknown or unmeasured confounders (eg, physical activity and comedication).

In conclusion, we found that the risks of ischemic stroke, ICH, and SAH were increased in the first year after MI. During the ensuing 1 to 30 years of follow-up, the risk remained elevated for ischemic stroke, whereas the risks receded for ICH and SAH. We observed a declining trend in the risk of post-MI stroke. This was most pronounced during the first half of the study period, particularly for ischemic stroke. The increased risk of ischemic stroke beyond 1 year after MI merits continued clinical attention to this frequently disabling or fatal complication.

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## Disclosures

None.

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# Long-Term Risk of Stroke in Myocardial Infarction Survivors: Thirty-Year Population-Based Cohort Study

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**SUPPLEMENTAL MATERIAL**

# Long-term Risk of Stroke in Myocardial Infarction Survivors: A 30-year population-based cohort study

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Contents

**Supplemental Table I.** International Classification of Diseases codes

| | ICD-8 codes | ICD-10 codes |
|---|---|---|
| **Myocardial infarction** | 410 | I21 |
| **Stroke** | | |
| Unspecified stroke | 434 | I64 |
| Ischemic stroke | 433-434 | I63-I64 |
| Intracerebral hemorrhage | 431 | I61 |
| Subarachnoid hemorrhage | 430 | I60 |
| Transient ischemic attack | 435 | G45.9 |
| **Cardiovascular diseases** | | |
| Congestive 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 |
| Heart valve disease | 394-398 | I05, I06, I07, I08.0, I09.8, I34-I37, I39.0, I39.3, I51.1A, Q22 |
| Intermittent claudication | 443.89-443.99 | I73.9 |
| Venous thromboembolism | 450.99, 451.00 | I26, I80.1-3 |
| Hypertension | 400-404 | DI10-DI15, I67.4 |
| Hypertension (extended model) | A previous diagnosis of hypertension or a combination treatment of at least two redeemed prescriptions for different types of the following classes of antihypertensive drugs within 180 days prior to myocardial infarction: α adrenergic blockers, ATC: C02A, C02B, C02C, non-loop diuretics, ATC: C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C09BA, C09DA, C09XA52, vasodilators, ATC: C02DB, C02DD, C02DG, C04, C05, β-blockers, ATC: C07, calcium channel blockers, ATC: C07F, C08, C09BB, C09DB, and renin-angiotensin system inhibitors, ATC: C09. | |
| **Other diseases** | | |
| Obesity | 277 | E65-E68 |
| Diabetes | 249, 250 (excluding 249.02, 250.02) | E10, E11, H36.0 |
| Diabetes (extended model) | A previous diagnosis of diabetes or a claimed prescription for a glucose lowering drug within 180 days prior to myocardial infarction, ATC: A10. | |
| Chronic kidney disease | 249.02, 250.02, 753.10-753.19, 582, 583, 584, 590.09, 593.20, 792 | E10.2, E11.2, E14.2, N03, N05, N11.0, N14; N16, N18-N19, N26.9, Q61.1-Q61.4 |
| 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 |

Abbreviations: ICD, International Classification of Diseases; ATC, Anatomical Therapeutic Chemical classification system.

**Supplemental Table II.** Adjusted stroke rate ratio following myocardial infarction with 95% confidence intervals during 1980-2009, by sex and age.*

| | 1-30 days | 31–365 days | 1-30 years |
|---|---|---|---|
| **Ischemic stroke** | | | |
| Female | 34.2 (29.5–39.8) | 3.9 (3.6–4.2) | 1.6 (1.6–1.7) |
| Male | 27.5 (24.1–31.3) | 2.7 (2.6–2.9) | 1.5 (1.5–1.5) |
| Age, years | | | |
| <60 | 53.2 (35.2–80.4) | 4.9 (4.1–5.8) | 1.9 (1.9–2.0) |
| 60-69 | 39.3 (30.4–50.7) | 3.4 (3.1–3.9) | 1.5 (1.4–1.5) |
| 70-79 | 27.0 (23.0–31.6) | 3.0 (2.8–3.3) | 1.4 (1.3–1.4) |
| ≥80 | 27.2 (23.2–31.9) | 2.9 (2.7–3.1) | 1.3 (1.2–1.4) |
| **ICH** | | | |
| Female | 22.1 (15.7–31.2) | 2.4 (2.0–3.0) | 1.1 (1.0–1.2) |
| Male | 17.7 (12.9–24.3) | 1.9 (1.6–2.2) | 1.1 (1.0–1.1) |
| Age, years | | | |
| <60 | 48.6 (19.2–122.8) | 2.4 (1.6–3.8) | 1.1 (1.0–1.2) |
| 60-69 | 28.2 (14.7–54.0) | 2.1 (1.6–2.8) | 1.0 (0.94–1.1) |
| 70-79 | 14.9 (10.5–21.0) | 1.9 (1.5–2.4) | 1.1 (1.0–1.2) |
| ≥80 | 19.0 (12.7–28.4) | 2.1 (1.6–2.6) | 0.87 (0.73–1.0) |
| **SAH** | | | |
| Female | 12.6 (6.4–24.7) | 1.3 (0.76–2.2) | 1.2 (1.0–1.5) |
| Male | 20.2 (8.1–50.3) | 1.7 (1.1–2.5) | 1.0 (0.88–1.2) |
| Age, years | | | |
| <60 | 30.0 (6.6–136.1) | 1.7 (0.95–2.9) | 1.2 (0.96–1.4) |
| 60-69 | 13.9 (4.3–45.0) | 1.2 (0.66–2.3) | 1.0 (0.80–1.2) |
| 70-79 | 10.3 (4.5–23.9) | 1.1 (0.52–2.1) | 1.1 (0.84–1.4) |
| ≥80 | 18.8 (5.9–59.6) | 2.5 (1.2–4.9) | 1.0 (0.62–1.7) |

*Adjusted for congestive heart failure, angina pectoris, atrial fibrillation or flutter, heart valve disease, intermittent arterial claudication, venous thromboembolism, hypertension, obesity, diabetes, chronic kidney disease, and chronic pulmonary disease.

Abbreviations: ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage.

**Supplemental Table III.** Adjusted stroke rate ratio following myocardial infarction with 95% confidence intervals during 1980-2009, by comorbidity.*

| | 1-30 days | 31–365 days | 1-30 years |
|---|---|---|---|
| **Ischemic stroke** | | | |
| Congestive heart failure | 14.6 (10.3–20.7) | 2.3 (1.9–2.8) | 1.3 (1.1–1.4) |
| No congestive heart failure | 31.8 (28.7–35.3) | 3.2 (3.0–3.4) | 1.5 (1.5–1.6) |
| Previous angina | 15.0 (10.6–21.3) | 2.3 (2.0–2.7) | 1.3 (1.2–1.4) |
| No previous angina | 31.7 (28.6–35.2) | 3.3 (3.1–3.4) | 1.6 (1.5–1.6) |
| Atrial fibrillation or flutter | 16.8 (12.3–23.0) | 2.5 (2.1–2.9) | 1.3 (1.2–1.5) |
| No atrial fibrillation or flutter | 31.9 (28.7–35.4) | 3.2 (3.1–3.4) | 1.5 (1.5–1.6) |
| Heart valve disease | 14.9 (7.8–28.5) | 2.5 (1.8–3.5) | 1.3 (1.1–1.6) |
| No heart valve disease | 30.7 (27.8–34.0) | 3.2 (3.0–3.4) | 1.5 (1.5–1.6) |
| Intermittent claudication | 44.1 (10.7–182.2) | 2.1 (1.4–3.0) | 1.1 (0.9–1.4) |
| No intermittent claudication | 30.2 (27.4–33.4) | 3.2 (3.0–3.4) | 1.5 (1.5–1.6) |
| Venous thromboembolism | 18.1 (10.0–32.7) | 2.9 (2.1–3.9) | 1.4 (1.2–1.6) |
| No venous thromboembolism | 30.7 (27.8–34.0) | 3.2 (3.0–3.3) | 1.5 (1.5–1.6) |
| Hypertension | 16.5 (12.7–21.5) | 2.4 (2.1–2.7) | 1.2 (1.2–1.3) |
| No hypertension | 32.8 (29.5–36.5) | 3.3 (3.1–3.5) | 1.6 (1.5–1.6) |
| Obesity | 11.3 (6.1–20.9) | 2.3 (1.7–3.2) | 1.4 (1.2–1.6) |
| No obesity | 31.0 (28.0–34.3) | 3.2 (3.0–3.4) | 1.5 (1.5–1.6) |
| Diabetes | 13.8 (10.0–19.1) | 2.6 (2.2–3.0) | 1.4 (1.3–1.5) |
| No diabetes | 32.2 (29.0–35.7) | 3.2 (3.1–3.4) | 1.5 (1.5–1.6) |
| Chronic kidney disease | 16.2 (7.3–36.0) | 2.7 (1.9–3.7) | 1.5 (1.2–1.7) |
| No chronic kidney disease | 30.6 (27.7–33.8) | 3.2 (3.0–3.3) | 1.5 (1.5–1.6) |
| Chronic pulmonary disease | 29.0 (19.1–44.2) | 2.5 (2.1–3.0) | 1.5 (1.3–1.6) |
| No chronic pulmonary disease | 30.4 (27.4–33.7) | 3.2 (3.1–3.4) | 1.5 (1.5–1.6) |
| **ICH** | | | |
| Congestive heart failure | 15.3 (4.4–52.7) | 2.4 (1.3–4.3) | 1.2 (0.8–1.6) |
| No congestive heart failure | 19.8 (15.7–25.1) | 2.0 (1.8–2.3) | 1.1 (1.0–1.1) |
| Previous angina | 12.5 (4.4–35.9) | 1.4 (0.9–2.4) | 1.0 (0.8–1.3) |
| No previous angina | 20.0 (15.7–25.3) | 2.1 (1.8–2.4) | 1.1 (1.0–1.1) |
| Atrial fibrillation or flutter | 14.2 (5.2–39.0) | 1.6 (1.0–2.6) | 1.0 (0.8–1.4) |
| No atrial fibrillation or flutter | 19.9 (15.7–25.3) | 2.1 (1.8–2.4) | 1.1 (1.0–1.1) |
| Heart valve disease | 8.1 (1.5–43.2) | 1.6 (0.63–4.0) | 1.4 (0.9–2.1) |
| No heart valve disease | 19.9 (15.8–25.2) | 2.1 (1.8–2.4) | 1.1 (1.0–1.1) |
| Intermittent claudication | – | 1.4 (0.6–3.6) | 1.3 (0.7–2.5) |
| No intermittent claudication | 19.5 (15.5–24.6) | 2.1 (1.8–2.4) | 1.1 (1.0–1.1) |
| Venous thromboembolism | – | 2.0 (0.8–5.1) | 0.7 (0.4–1.1) |
| No venous thromboembolism | 19.4 (15.4–24.5) | 2.1 (1.8–2.4) | 1.1 (1.0–1.1) |
| Hypertension | 10.2 (5.3–19.6) | 1.4 (1.0–2.0) | 0.9 (0.7–1.0) |
| No hypertension | 21.1 (16.5–27.1) | 2.2 (1.9–2.5) | 1.1 (1.0–1.2) |
| Obesity | 11.2 (2.2–56.1) | 2.9 (1.2–6.8) | 0.8 (0.5–1.2) |
| No obesity | 19.8 (15.7–25.0) | 2.1 (1.8–2.3) | 1.1 (1.0–1.1) |
| Diabetes | 11.0 (4.8–25.2) | 2.0 (1.3–3.2) | 0.7 (0.6–1.0) |
| No diabetes | 20.4 (16.0–26.0) | 2.1 (1.8–2.4) | 1.1 (1.0–1.2) |
| Chronic kidney disease | – | 2.4 (1.1–5.4) | 0.9 (0.6–1.5) |
| No chronic kidney disease | 19.6 (15.5–24.7) | 2.0 (1.8–2.3) | 1.1 (1.0–1.1) |
| Chronic pulmonary disease | 5.6 (2.5–12.6) | 2.0 (1.2–3.4) | 0.9 (0.7–1.2) |
| No chronic pulmonary disease | 21.4 (16.8–27.2) | 2.1 (1.8–2.4) | 1.1 (1.0–1.1) |
| **SAH** | | | |
| Congestive heart failure | – | – | 0.9 (0.4–2.4) |
| No congestive heart failure | 14.3 (8.3–24.6) | 1.6 (1.1–2.1) | 1.1 (1.0–1.2) |
| Previous angina | 2.9 (0.2–47.7) | 1.5 (0.4–5.1) | 0.6 (0.4–1.1) |
| No previous angina | 15.7 (9.1–27.2) | 1.5 (1.1–2.1) | 1.1 (1.0–1.3) |
| Atrial fibrillation or flutter | 13.6 (1.5–124.9) | 0.6 (0.1–5.2) | 0.9 (0.4–2.0) |
| No atrial fibrillation or flutter | 15.2 (8.7–26.4) | 1.6 (1.1–2.1) | 1.1 (1.0–1.2) |
| Heart valve disease | 3.2 (0.2–51.9) | – | – |
| No heart valve disease | 15.8 (9.1–27.3) | 1.6 (1.1–2.1) | 1.1 (1.0–1.2) |

**Supplemental Table III.** Adjusted stroke rate ratio following myocardial infarction with 95% confidence intervals during 1980-2009, by comorbidity.*

| | | | |
|---|---|---|---|
| Intermittent claudication | – | 2.3 (0.1–36.6) | 0.3 (0.04–2.6) |
| No intermittent claudication | 14.5 (8.4–24.9) | 1.5 (1.1–2.1) | 1.1 (1.0–1.2) |
| Venous thromboembolism | – | 12.4 (1.2–126.4) | 0.3 (0.1–1.5) |
| No venous thromboembolism | 14.9 (8.7–25.5) | 1.4 (1.0–2.0) | 1.1 (1.0–1.2) |
| Hypertension | – | 1.0 (0.4–2.4) | 1.0 (0.6–1.5) |
| No hypertension | 13.8 (8.0–23.8) | 1.6 (1.2–2.3) | 1.1 (1.0–1.2) |
| Obesity | – | – | 0.4 (0.1–1.8) |
| No obesity | 14.9 (8.7–25.6) | 1.5 (1.1–2.0) | 1.1 (1.0–1.2) |
| Diabetes | 12.2 (1.4–107.3) | 2.6 (0.6–11.1) | 1.1 (0.6–2.2) |
| No diabetes | 15.2 (8.7–26.5) | 1.5 (1.1–2.1) | 1.1 (1.0–1.2) |
| Chronic kidney disease | – | 7.2 (0.6–87.1) | 0.7 (0.1–3.5) |
| No chronic kidney disease | 14.9 (8.7–25.5) | 1.5 (1.1–2.0) | 1.1 (1.0–1.2) |
| Chronic pulmonary disease | 1.4 (0.1–13.5) | 3.2 (1.1–9.5) | 0.7 (0.4–1.5) |
| No chronic pulmonary disease | 17.4 (9.8–30.9) | 1.4 (1.0–2.0) | 1.1 (1.0–1.2) |

*Adjusted for sex, age, congestive heart failure, angina pectoris, atrial fibrillation or flutter, heart valve disease, intermittent arterial claudication, venous thromboembolism, hypertension, obesity, diabetes, chronic kidney disease, and chronic pulmonary disease.
Abbreviations: ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage.

**Supplemental Table IV.** Sensitivity analysis: Ischemic stroke risk estimates following myocardial infarction (combined, specified, and unspecified).

| | **Stroke risk*** **% (95% CI)** | **Stroke rate†** **(95% CI)** | **Stroke rate ratio (95% CI)** | |
|---|---|---|---|---|
| | | | Unadjusted | Adjusted‡ |
| **Combined ischemic stroke, 1980–2009 (ICD8: 433, 434; ICD-10: I63, I64)** | | | | |
| 1-30 days | | | | |
| Comparison cohort | 0.04 (0.03–0.04) | 4.6 (4.2–5.1) | 1 (reference) | 1 (reference) |
| MI cohort | 1.0 (0.92–1.0) | 146.0 (140.4–151.9) | 32.0 (28.6–35.7) | 31.9 (28.4–35.8) |
| 31–365 days | | | | |
| Comparison cohort | 0.43 (0.41–0.44) | 4.7 (4.6–4.9) | 1 (reference) | 1 (reference) |
| MI cohort | 1.3 (1.2–1.3) | 15.1 (14.5–15.7) | 3.3 (3.1–3.5) | 3.1 (3.0–3.3) |
| 1-30 year | | | | |
| Comparison cohort | 11.9 (11.8–12.0) | 7.9 (7.8–8.0) | 1 (reference) | 1 (reference) |
| MI cohort | 12.6 (12.4–12.8) | 10.8 (10.6–11.0) | 1.7 (1.6–1.7) | 1.6 (1.6–1.6) |
| **Specified ischemic stroke, 1995–2009 (ICD-10: I63)** | | | | |
| 1-30 days | | | | |
| Comparison cohort | 0.03 (0.02–0.03) | 3.2 (2.7–3.8) | 1 (reference) | 1 (reference) |
| MI cohort | 0.5 (0.5–0.6) | 75.2 (69.1–81.9) | 23.3 (18.9–28.8) | 24.3 (19.5–30.4) |
| 31–365 days | | | | |
| Comparison cohort | 0.3 (0.3–0.3) | 3.4 (3.3–3.6) | 1 (reference) | 1 (reference) |
| MI cohort | 0.8 (0.7–0.8) | 9.0 (8.3–9.7) | 2.8 (2.5–3.1) | 2.7 (2.4–3.0) |
| 1-15 year | | | | |
| Comparison cohort | 5.7 (5.6–5.9) | 4.7 (4.6–4.7) | 1 (reference) | 1 (reference) |
| MI cohort | 6.6 (6.2–7.0) | 5.7 (5.5–5.9) | 1.4 (1.4–1.5) | 1.4 (1.3–1.4) |
| **Unspecified stroke, 1995–2009 (ICD-10: I64)** | | | | |
| 1-30 days | | | | |
| Comparison cohort | 0.04 (0.04–0.05) | 5.4 (4.7–6.1) | 1 (reference) | 1 (reference) |
| MI cohort | 1.1 (1.0–1.1) | 149.6 (140.9–158.9) | 29.0 (24.7–34.1) | 29.2 (24.6–34.6) |
| 31–365 days | | | | |
| Comparison cohort | 0.5 (0.4–0.5) | 5.1 (4.9–5.4) | 1 (reference) | 1 (reference) |
| MI cohort | 1.1 (1.1–1.2) | 13.2 (12.4–14.1) | 2.9 (2.6–3.1) | 2.7 (2.5–2.9) |
| 1-15 year | | | | |
| Comparison cohort | 4.5 (4.4–4.6) | 4.3 (4.3–4.4) | 1 (reference) | 1 (reference) |
| MI cohort | 5.1 (4.9–5.4) | 5.3 (5.1–5.6) | 1.5 (1.4–1.6) | 1.4 (1.3–1.5) |

*Treating death as competing risk.

†Rates per 1000 person-years.

‡Adjusted for congestive heart failure, angina pectoris, atrial fibrillation or flutter, heart valve disease, intermittent arterial claudication, venous thromboembolism, hypertension, obesity, diabetes, chronic kidney disease, and chronic pulmonary disease.

Abbreviations: CI, confidence interval; MI, myocardial infarction; ICD, International Classification of Diseases.

**Supplemental Table V.** Characteristics of patients with a first-time hospitalization for myocardial infarction and age- and sex-matched comparison cohort members, according to definition of hypertension and diabetes, during 2005-2009.

| | Myocardial infarction cohort, n (%) | Comparison cohort, n (%) |
|---|---|---|
| **Hypertension*** | | |
| Only diagnosis | 6,646 (20.6) | 17,426 (11.7) |
| Diagnosis + medication | 11,498 (35.7) | 36,532 (24.6) |
| **Diabetes†** | | |
| Only diagnosis | 3,131 (9.7) | 7,059 (4.8) |
| Diagnosis + medication | 4,077 (12.7) | 10,463 (7.0) |

*Defined by either a previous diagnosis of hypertension or a claimed prescription for a glucose lowering drug within 180 days prior to myocardial infarction.

†Defined by either a previous diagnosis of diabetes or combination treatment of at least two redeemed prescriptions for different of antihypertensive drugs within 180 days prior to myocardial infarction.

**Supplemental Table VI.** Stroke risk estimates following myocardial infarction with extended model including medication to more completely identify hypertension and diabetes, during 2005-2009.

| | Stroke rate† (95% CI) | Stroke rate ratio (95% CI) | | |
|---|---|---|---|---|
| | | Unadjusted | Adjusted (exsisting model)‡ | Adjusted (extended model)§ |
| **Ischemic stroke** | | | | |
| 1–30 days | | | | |
| Comparison cohort | 8.1 (6.6–9.8) | 1 (reference) | 1 (reference) | 1 (reference) |
| MI cohort | 196.0 (178.9–214.8) | 25.2 (19.9–31.9) | 26.2 (20.4–33.8) | 25.8 (20.1–33.1) |
| 31–365 days | | | | |
| Comparison cohort | 7.7 (7.2–8.2) | 1 (reference) | 1 (reference) | 1 (reference) |
| MI cohort | 18.1 (16.4–19.9) | 2.5 (2.2–2.9) | 2.4 (2.1–2.7) | 2.4 (2.1–2.8) |
| 1–5 years | | | | |
| Comparison cohort | 7.3 (7.1–7.5) | 1 (reference) | 1 (reference) | 1 (reference) |
| MI cohort | 8.4 (7.9–9.0) | 1.3 (1.2–1.4) | 1.2 (1.1–1.3) | 1.2 (1.1–1.3) |
| **ICH** | | | | |
| 1–30 days | | | | |
| Comparison cohort | 1.2 (0.7–1.9) | 1 (reference) | 1 (reference) | 1 (reference) |
| MI cohort | 15.3 (11.0–21.2) | 12.3 (6.5–23.2) | 15.7 (6.9–36.0) | 14.5 (6.6–31.6) |
| 31–365 days | | | | |
| Comparison cohort | 1.0 (0.8–1.1) | 1 (reference) | 1 (reference) | 1 (reference) |
| MI cohort | 2.0 (1.5–2.7) | 2.4 (1.7–3.5) | 2.1 (1.4–3.1) | 2.0 (1.4–3.0) |
| 1–5 years | | | | |
| Comparison cohort | 1.0 (0.9–1.1) | 1 (reference) | 1 (reference) | 1 (reference) |
| MI cohort | 1.1 (0.9–1.3) | 1.3 (1.0–1.6) | 1.2 (1.0–1.6) | 1.3 (1.0–1.6) |
| **SAH** | | | | |
| 1–365 days | | | | |
| Comparison cohort | 0.3 (0.1–0.8) | 1 (reference) | 1 (reference) | 1 (reference) |
| MI cohort | 4.3 (2.3–7.9) | 14.8 (4.1–53.9) | 19.9 (2.4–163.5) | 21.7 (2.2–216.6) |
| 31–365 days | | | | |
| Comparison cohort | 0.2 (0.1–0.3) | 1 (reference) | 1 (reference) | 1 (reference) |
| MI cohort | 0.6 (0.4–1.0) | 3.1 (1.6–6.2) | 3.5 (1.6–7.6) | 3.6 (1.7–7.8) |
| 1–5 years | | | | |
| Comparison cohort | 0.3 (0.2–0.3) | 1 (reference) | 1 (reference) | 1 (reference) |
| MI cohort | 0.2 (0.2–0.36) | 0.9 (0.6–1.4) | 0.9 (0.5–1.4) | 0.9 (0.5–1.4) |

†Rates per 1000 person-years.

‡Adjusted for congestive heart failure, angina pectoris, atrial fibrillation or flutter, heart valve disease, intermittent arterial claudication, venous thromboembolism, hypertension, obesity, diabetes, chronic kidney disease, and chronic pulmonary disease.

§Adjusted for congestive heart failure, angina pectoris, atrial fibrillation or flutter, heart valve disease, intermittent arterial claudication, venous thromboembolism, hypertension (defined by either a previous diagnosis of hypertension or a claimed prescription for a glucose lowering drug within 180 days prior to myocardial infarction), obesity, diabetes (defined by either a previous diagnosis of diabetes or combination treatment of at least two redeemed prescriptions for different of antihypertensive drugs within 180 days prior to myocardial infarction), chronic kidney disease, and chronic pulmonary disease.

Abbreviations: CI, confidence interval; MI, myocardial infarction; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage.

**Supplemental Table VII.** Cumulative stroke risks, by calendar periods.

| | Cumulative incidence, % (95% CI) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Ischemic stroke | | | ICH | | | SAH | | |
| | 1-30 days | 31–365 days | 1-5 years | 1-30 days | 31–365 days | 1-5 years | 1-30 days | 31–365 days | 1-5 years |
| **1980–1984** | | | | | | | | | |
| CC cohort | 0.02 (0.01–0.02) | 0.20 (0.18–0.22) | 0.79 (0.76–0.83) | 0.01 (0.01–0.01) | 0.08 (0.07–0.09) | 0.33 (0.31–0.35) | 0.00 (0.00–0.00) | 0.01 (0.01–0.02) | 0.05 (0.04–0.06) |
| MI cohort | 0.63 (0.56–0.69) | 0.98 (0.89–1.1) | 1.6 (1.4–1.7) | 0.13 (0.10–0.16) | 0.19 (0.14–0.23) | 0.45 (0.37–0.52) | 0.01 (0.00–0.02) | 0.02 (0.01–0.03) | 0.03 (0.01–0.05) |
| **1985–1989** | | | | | | | | | |
| CC cohort | 0.01 (0.01–0.02) | 0.15 (0.13–0.16) | 0.74 (0.71–0.78) | 0.01 (0.00–0.01) | 0.07 (0.06–0.08) | 0.33 (0.31–0.35) | 0.00 (0.00–0.00) | 0.02 (0.01–0.02) | 0.06 (0.05–0.07) |
| MI cohort | 0.48 (0.42–0.54) | 0.61 (0.53-0.69) | 1.2 (1.0–1.3) | 0.12 (0.09–0.15) | 0.16 (0.12–0.20) | 0.39 (0.32–0.46) | 0.02 (0.01–0.03) | 0.02 (0.01–0.03) | 0.11 (0.07–0.14) |
| **1990–1994** | | | | | | | | | |
| CC cohort | 0.03 (0.02–0.03) | 0.32 (0.29–0.34) | 2.6 (2.5–2.7) | 0.01 (0.01–0.01) | 0.07 (0.06–0.08) | 0.33 (0.31–0.36) | 0.00 (0.00–0.00) | 0.02 (0.01–0.02) | 0.07 (0.05–0.08) |
| MI cohort | 0.55 (0.48–0.62) | 0.84 (0.74–0.93) | 3.5 (3.3–3.8) | 0.12 (0.09–0.15) | 0.13 (0.09–0.16) | 0.27 (0.21–0.33) | 0.02 (0.01–0.03) | 0.03 (0.01–0.04) | 0.06 (0.03–0.09) |
| **1995–1999** | | | | | | | | | |
| CC cohort | 0.07 (0.06–0.08) | 0.76 (0.72–0.80) | 3.5 (3.4–3.6) | 0.01 (0.00–0.01) | 0.08 (0.07–0.09) | 0.37 (0.33–0.40) | 0.00 (0.00–0.00) | 0.02 (0.01–0.03) | 0.07 (0.05–0.08) |
| MI cohort | 1.5 (1.4–1.6) | 2.0 (1.8–2.2) | 4.2 (3.9–4.4) | 0.13 (0.09–0.17) | 0.10 (0.06–0.14) | 0.30 (0.23–0.37) | 0.01 (0.00–0.02) | 0.01 (0.00–0.02) | 0.07 (0.03–0.10) |
| **2000–2004** | | | | | | | | | |
| CC cohort | 0.07 (0.06–0.08) | 0.84 (0.79–0.88) | 3.3 (3.2–3.4) | 0.01 (0.00–0.01) | 0.09 (0.08–0.11) | 0.40 (0.37–0.43) | 0.00 (0.00–0.00) | 0.02 (0.02–0.03) | 0.08 (0.07–0.10) |
| MI cohort | 1.8 (1.6–1.9) | 2.0 (1.9–2.2) | 3.9 (3.7–4.1) | 0.12 (0.09–0.16) | 0.14 (0.10–0.18) | 0.36 (0.28–0.43) | 0.02 (0.00–0.03) | 0.02 (0.01–0.04) | 0.08 (0.05–0.12) |
| **2005–2009** | | | | | | | | | |
| CC cohort | 0.07 (0.05–0.08) | 0.69 (0.65–0.73) | 2.7 (2.6–2.7) | 0.01 (0.00–0.01) | 0.09 (0.07–0.10) | 0.35 (0.32–0.39) | 0.00 (0.00–0.00) | 0.01 (0.01–0.02) | 0.09 (0.08–0.11) |
| MI cohort | 1.4 (1.3–1.6) | 1.5 (1.4–1.7) | 2.9 (2.6–3.1) | 0.11 (0.08–0.15) | 0.17 (0.12–0.22) | 0.37 (0.29–0.45) | 0.03 (0.01–0.05) | 0.05 (0.02–0.08) | 0.10 (0.06–0.15) |

Abbreviations: CI, confidence interval; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; CC, comparison cohort; MI, myocardial infarction

# Paper IV

# Long-term Risk of Dementia in Myocardial Infarction Survivors

**Short 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 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 increased risk of vascular dementia (aHR = 1.35, 95% CI: 1.28–1.43), which was substantially amplified for patients experiencing stroke after MI (aHR = 4.48, 95% CI: 3.29–6.12).

***Conclusions***—MI was not associated with all-cause dementia, but the risk of vascular dementia was increased in MI patients throughout follow-up and was intensified in patients suffering stroke.

## INTRODUCTION

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 tertiary 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, 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 increased 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

### 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 (Table 1). 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.

Using cumulative incidence functions with death as a competing risk, we calculated dementia risks during 1-35 years of follow-up. Hazard ratios (HRs) with 95% confidence intervals (CIs) were computed using multivariable stratified Cox proportional hazards regression models, 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 Tables 1 and 2 in the online-only Data Supplement.

**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 occuring between MI and start of follow-up 1 year later. 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.[16] As a higher cognitive reserve may modify any association between MI and dementia,[17] we examined the impact of socioeconomic status (income, employment, and education). In the stratified analyses by underlying preadmission comorbidity, modified CCI scores and socioeconomic status, the matching was dissolved and HRs additionally adjusted for matching variables.

**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 (Figure 1). 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. 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 decreased (adjusted HR = 0.92, 95% CI: 0.88–0.95), whereas risk of vascular dementia was significantly increased (adjusted HR = 1.35, 95% CI: 1.28–1.43).

**Additional analyses**

The increase in 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). 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). The risk of vascular dementia was not modified by percutaneous coronary intervention during the MI admission or development of heart failure during the first year after MI.

In age-stratified analyses, a positive association was observed for 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]. The results for other age groups were consistent with the main analysis. No difference was observed between men and women (Table 3 in the online-only Data Supplement). Results remained robust in subgroup analyses of cardiac and non-cardiac comorbidity and CCI levels (Table 4 in the online-only Data Supplement). We observed no temporal difference in the association observed during early (1980–1994) *vs*. late

(1995–2012) time periods (Table 5 in the online-only Data Supplement). In analyses stratified by primary *vs*. secondary diagnoses of MI, the risks of all-cause and vascular dementia were slightly increased for secondary diagnoses (Table 5 in the online-only Data Supplement). Across levels of income, employment status, and education, results agreed with those of the main analysis (Table 6 in the online-only Data Supplement).

**Sensitivity analyses**

Results of the sensitivity analyses are presented in Table 7 in the online-only Data Supplement. 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 no association with all-cause dementia. The risk of Alzheimer's disease was marginally decreased, whereas we found a significantly increased risk of vascular dementia, which was potentiated in MI patients who experienced stroke during the first year after MI.

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 increased 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%,[18,19] 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,[20] while vascular dementia has a cerebrovascular pathology, characterized by strategically located infarctions and hemorrhages.[21]

Our finding of increased 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 increased in our study. MI has been associated with increased risk of both ischemic stroke and hemorrhagic stroke,[5] which in turn have been associated with increased 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 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.[22]

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 atherosclerosis involving the left main stem, which indicates 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[23] plausibly increasing risk of dementia. However, it remains controversial whether CABG itself increases the risk of long-term dementia.[24]

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.[11,16,25,26] 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.[27]

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.

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[28] and dementia.[29] 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[30,31] 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 increased risk of vascular dementia. The lack of an association with all-cause dementia, Alzheimer's disease, and other dementias indicates that shared risk factors (*e.g.*, atherosclerosis) combined with post-MI procedures and complications leading to stroke were the driving mechanisms behind the association with vascular dementia.

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## DISCLOSURES

None.

## AFFILIATIONS

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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) |
| Osteoartrhitis | 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, 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 performed during hospitalization for MI and stroke and heart failure during the first year after myocardial infarction.

| | Adjusted hazard ratio (95% CI)* | | | |
|---|---|---|---|---|
| | All-cause dementia | Alzheimer's disease | Vascular dementia | Other dementias |
| **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) |
| **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) |

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.

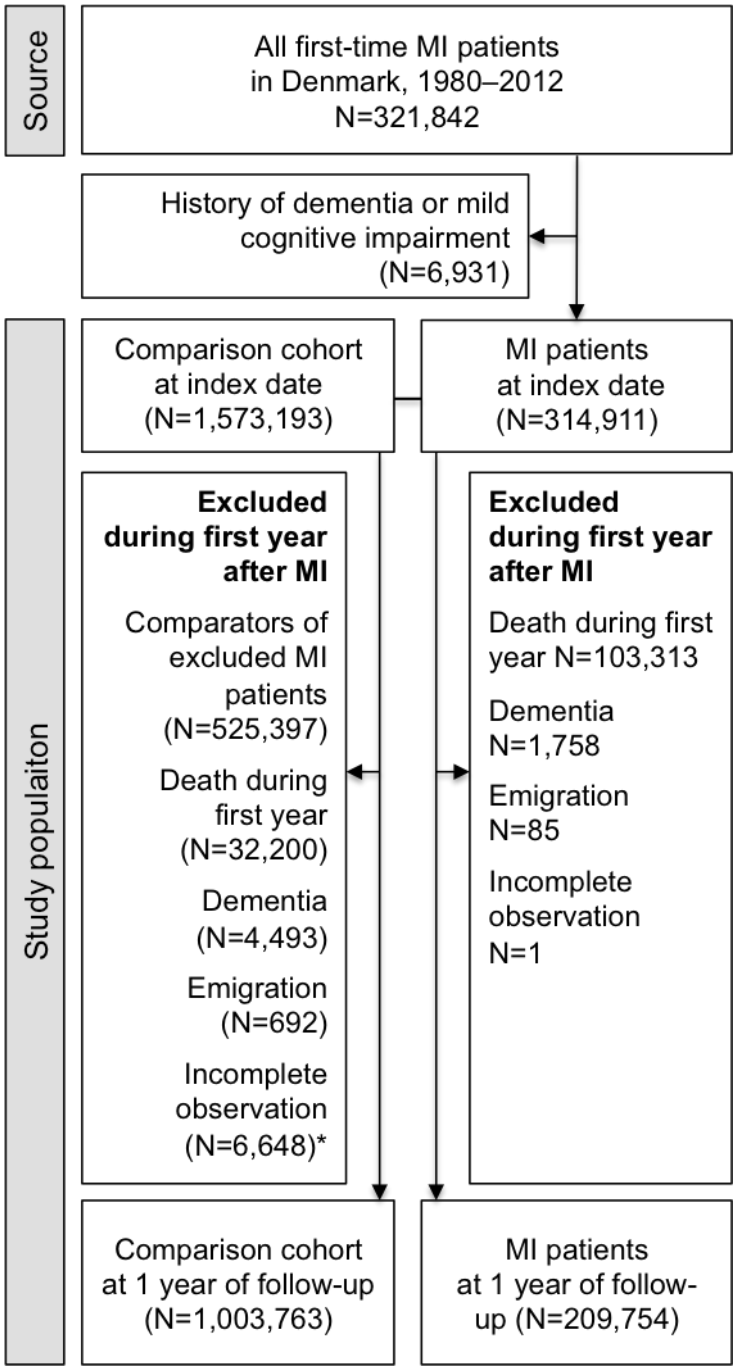


**Figure 1.** Study flowchart. Population of first-time myocardial infarction survivors and members of the matched general population comparison cohort. *6,625 patients out of these 6,648 were censored because they had a myocardial infarction during the first year of follow-up, while the remainder were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

MI indicates myocardial infarction.

# SUPPLEMENTAL MATERIAL

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

| | ICD-8 codes | ICD-10 codes | Procedure 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 | |
| **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 |

**Supplementary 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 |

**Supplementary Table 3.** 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.

**Supplementary Table 4**. 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 (0.84–0.96) | 0.83 (0.74–0.94) | 1.09 (0.93–1.29) | 0.89 (0.81–0.98) |
| No | 1.01 (0.99–1.03) | 0.93 (0.90–0.97) | 1.31 (1.24–1.37) | 0.98 (0.95–1.01) |
| **Atrial fibrillation or flutter** | | | | |
| Yes | 0.96 (0.87–1.05) | 0.80 (0.66–0.96) | 1.07 (0.86–1.33) | 1.01 (0.89–1.16) |
| No | 1.00 (0.98–1.02) | 0.93 (0.90–0.96) | 1.30 (1.24–1.37) | 0.97 (0.94–1.00) |
| **Valvular heart disease** | | | | |
| Yes | 1.05 (0.88–1.25) | 0.96 (0.71–1.31) | 1.22 (0.82–1.79) | 1.05 (0.82–1.35) |
| No | 1.00 (0.98–1.02) | 0.92 (0.89–0.96) | 1.29 (1.23–1.36) | 0.97 (0.95–1.00) |
| **Hypertension** | | | | |
| Yes | 0.94 (0.88–1.00) | 0.79 (0.69–0.90) | 1.10 (0.96–1.27) | 0.96 (0.87–1.05) |
| No | 1.01 (0.99–1.03) | 0.94 (0.90–0.97) | 1.31 (1.25–1.38) | 0.97 (0.94–1.00) |
| **Hypercholesterolemia** | | | | |
| Yes | 0.92 (0.77–1.10) | 0.93 (0.68–1.26) | 0.77 (0.49–1.21) | 0.97 (0.74–1.26) |
| No | 1.00 (0.98–1.02) | 0.92 (0.89–0.96) | 1.30 (1.24–1.36) | 0.97 (0.95–1.00) |
| **Obesity** | | | | |
| Yes | 0.90 (0.77–1.06) | 0.75 (0.56–1.01) | 0.99 (0.71–1.39) | 0.97 (0.78–1.21) |
| No | 1.00 (0.98–1.02) | 0.93 (0.89–0.96) | 1.30 (1.24–1.36) | 0.97 (0.95–1.00) |
| **Diabetes mellitus** | | | | |
| Yes | 1.08 (0.99–1.17) | 0.89 (0.76–1.06) | 1.34 (1.12–1.60) | 1.08 (0.96–1.22) |
| No | 1.00 (0.98–1.02) | 0.93 (0.89–0.96) | 1.29 (1.22–1.35) | 0.97 (0.94–1.00) |
| **Chronic pulmonary disease** | | | | |
| Yes | 1.01 (0.92–1.11) | 0.93 (0.79–1.11) | 1.46 (1.16–1.83) | 0.95 (0.83–1.08) |
| No | 1.00 (0.98–1.02) | 0.92 (0.89–0.96) | 1.29 (1.22–1.35) | 0.98 (0.95–1.00) |
| **Myxedema** | | | | |
| Yes | 0.90 (0.71–1.15) | 0.87 (0.56–1.35) | 0.99 (0.52–1.86) | 0.90 (0.65–1.24) |
| No | 1.00 (0.98–1.02) | 0.92 (0.89–0.96) | 1.29 (1.23–1.36) | 0.97 (0.95–1.00) |
| **Alcoholism-related disease** | | | | |
| Yes | 0.96 (0.82–1.14) | 0.82 (0.53–1.25) | 1.03 (0.69–1.53) | 0.98 (0.80–1.21) |
| No | 1.00 (0.98–1.02) | 0.93 (0.89–0.96) | 1.30 (1.24–1.36) | 0.97 (0.95–1.00) |
| **Head trauma** | | | | |
| Yes | 0.97 (0.91–1.03) | 0.94 (0.83–1.05) | 1.25 (1.07–1.45) | 0.91 (0.83–0.99) |
| No | 1.01 (0.99–1.03) | 0.92 (0.89–0.96) | 1.30 (1.23–1.36) | 0.98 (0.95–1.01) |
| **Osteoarthritis** | | | | |
| Yes | 0.93 (0.87–0.99) | 0.85 (0.76–0.96) | 1.10 (0.93–1.30) | 0.93 (0.85–1.02) |
| No | 1.01 (0.99–1.03) | 0.93 (0.90–0.97) | 1.31 (1.25–1.38) | 0.98 (0.95–1.01) |
| **Anemia** | | | | |
| Yes | 1.09 (0.95–1.25) | 0.94 (0.71–1.25) | 1.44 (1.06–1.97) | 1.06 (0.88–1.26) |
| No | 1.00 (0.98–1.02) | 0.92 (0.89–0.96) | 1.29 (1.23–1.35) | 0.97 (0.94–1.00) |
| **Chronic kidney disease** | | | | |
| Yes | 0.93 (0.75–1.15) | 1.23 (0.82–1.87) | 0.95 (0.58–1.56) | 0.81 (0.60–1.08) |
| No | 1.00 (0.98–1.02) | 0.92 (0.89–0.96) | 1.30 (1.24–1.36) | 0.98 (0.95–1.00) |
| **Modified CCI score** | | | | |
| Normal | 1.01 (0.99–1.03) | 0.94 (0.90–0.97) | 1.28 (1.21–1.35) | 0.98 (0.95–1.01) |
| Moderate | 0.98 (0.92–1.05) | 0.87 (0.76–0.99) | 1.39 (1.20–1.61) | 0.92 (0.84–1.01) |
| Severe | 0.94 (0.86–1.02) | 0.82 (0.70–0.96) | 1.22 (0.99–1.50) | 0.94 (0.84–1.06) |
| Very severe | 0.98 (0.82–1.17) | 0.82 (0.58–1.16) | 1.57 (1.05–2.34) | 0.92 (0.73–1.17) |

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).

**Supplementary Table 5**. 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.

**Supplementary Table 6**. 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 (1.21–1.48) | 0.94 (0.89–1.00) |
| Intermediate | 0.98 (0.94–1.01) | 0.90 (0.85–0.96) | 1.25 (1.15–1.36) | 0.95 (0.91–1.00) |
| High | 1.01 (0.97–1.05) | 0.93 (0.87–1.00) | 1.23 (1.12–1.35) | 0.99 (0.94–1.05) |
| Very high | 1.07 (1.02–1.12) | 1.00 (0.92–1.08) | 1.36 (1.22–1.53) | 1.03 (0.97–1.11) |
| **Employment** | | | | |
| Employed | 1.11 (1.06–1.16) | 1.04 (0.96–1.12) | 1.41 (1.28–1.56) | 1.07 (1.00–1.14) |
| Early retirement | 1.06 (1.00–1.12) | 0.94 (0.84–1.05) | 1.27 (1.10–1.46) | 1.07 (0.98–1.17) |
| Unemployed | 1.02 (0.87–1.20) | 0.96 (0.70–1.31) | 1.52 (1.07–2.18) | 0.92 (0.73–1.15) |
| State pensioner | 0.96 (0.94–0.98) | 0.88 (0.84–0.92) | 1.24 (1.17–1.32) | 0.94 (0.90–0.97) |
| **Education** | | | | |
| Basic education, primary school | 1.00 (0.97–1.04) | 0.91 (0.86–0.97) | 1.24 (1.15–1.34) | 0.99 (0.94–1.04) |
| Youth education, high school or similar education | 1.07 (1.02–1.12) | 0.95 (0.87–1.03) | 1.41 (1.27–1.57) | 1.05 (0.98–1.12) |
| Higher education | 1.02 (0.94–1.10) | 0.85 (0.74–0.97) | 1.42 (1.17–1.71) | 1.04 (0.93–1.17) |
| Unknown | 0.97 (0.94–1.00) | 0.91 (0.87–0.97) | 1.26 (1.16–1.37) | 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).

**Supplementary Table 7**. 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.

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