Depression, stroke, and dementia in patients with myocardial infarction

Studies of risk and prognosis

Jens Sundbøll

This review has been accepted as a thesis together with four previously published papers by Aarhus University 24th of August 2017 and defended on 27th of September 2017

Tutors: Morten Schmidt, Poul Videbech, Hans Erik Bøtker, and Henrik Toft Sørensen

Official opponents: John-Bjarne Hansen, Rudi Westendorp, and Henrik Wiggers

Correspondence: Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, DK-8200, Aarhus N, Denmark

E-mail: jens.sundboll@clin.au.dk

Dan Med J 2018;65(4):B5423

THE FOUR ORIGINAL PAPERS ARE

I. Sundbøll J, Adelborg K, Munch T, Frøslev T, Sørensen HT, Bøtker HE, Schmidt M. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open* 2016;6:e012832
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. Higher Risk of Vascular Dementia in Myocardial Infarction Survivors. *Circulation* 2017 [Epub ahead of print].

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 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 chapter includes a summary in English.

INTRODUCTION

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.

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 dec-

ades,[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.

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]

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]

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 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]

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] - *BMJ Open* - 2013	- ICD-10: I21 - IN - Primary diagnoses	- 2000–2009 - Medical record review - N=148 - PPV	- PPV = 100 (97.5–100) - NPV, sensitivity, and specificity not included
- Thygesen *et al.* [33] - *BMC Med Res Methodol* - 2011	- ICD-10: I21, I22, I23 - IN/OUT - Primary diagnoses	- 1998–2007 - Discharge summaries - N=50 - PPV	- PPV = 98.0 (89.5–99.7) - NPV, sensitivity, and specificity not included; review restricted to discharge summaries
- Joensen *et al.* [34] - *J Clin Epidemiol* - 2009	- ICD-8: 410; ICD-10: I21 - IN/OUT/ED - Primary and secondary diagnoses	- 1993–2003 - Medical record review, discharge summary, blood tests, ECG - N=1072 - PPV	- PPV(IN/OUT/ED) = 81.9 (79.5–84.1) - PPV(IN; primary and secondary diagnoses) = 92.4 (90.4–93.9) - PPV(IN; primary diagnoses) = 94.4 (92.6–95.7) - Only one reviewer; NPV, sensitivity, and specificity not included
- Madsen *et al.* [35] - *J Clin Epidemiol* - 2003	- ICD-8: 410, 427.24, 427.27, 427.91, 427.97 - IN/OUT - Primary and secondary diagnoses	- 1982–1991 - DANMONICA (definite or possible cases including cardiac arrest) - N= 5022 - PPV and sensitivity	- PPV(primary diagnoses) = 94.3 (93.6–94.9) - PPV(primary and secondary diagnoses) = 93.4 (92.6–94.0) - Sensitivity(primary diagnoses) = 62.8 (61.7–64.0) - Sensitivity(primary and secondary diagnoses) = 69.5 (68.4–70.6) - NPV and specificity not included
Diagnosis: Unstable angina pectoris			
- Joensen *et al.* [34] - *J Clin Epidemiol* - 2009	- ICD-10: I20.0 - IN/OUT/ED - Primary and secondary diagnoses	- 1993–2003 - Medical record review, discharge summary, blood tests, ECG - N=444 - PPV	- PPV(IN/OUT/ED) = 27.5 (23.5–31.8) - PPV(IN) = 42.0 (36.0–48.0) - Only one reviewer; NPV, sensitivity, and specificity not included
Diagnosis: Heart failure			
- Thygesen *et al.* [33] - *BMC Med Res Methodol* - 2011	- ICD-10: I50, I11.0, I13.0, I13.2 - IN/OUT - Primary diagnoses	- 1998–2007 - Discharge summaries - N=50 - PPV	- PPV = 100 (92.9–100) - NPV, sensitivity, and specificity not included; review restricted to discharge summaries
- Mard *et al.* [36] - *Clin Epidemiol* - 2010	- ICD-10: I11.0, I13.0, I13.2, I42.0, I42.6–9, I50.0–I50.1, I50.9 - IN/OUT - Primary and secondary diagnoses	- 2005–2007 - Medical record review - N=758 - PPV	- PPV(overall) = 84.0 (81.3–86.5) - PPV(first-time events) = 77.9 (74.1–81.6) - NPV, sensitivity, and specificity not included - Only patients at university hospital cardiac care unit
Diagnosis: Arterial hypertension			
- Schmidt *et al.* [37] - *BMJ Open* - 2013	- ICD-8: 400–404; ICD-10: I10–I15 (essential hypertension in males) - IN/OUT - Primary and secondary diagnoses	- 1977–2010 - Prescription registry - N=524 - PPV	- PPV = 88.2 (85.4–90.9) - NPV, sensitivity, and specificity not included; reference based on redeemed prescriptions for antihypertensive medications; only males included.

- **Nielsen *et al.***[38] - *Ugeskr Laeg* - 1996	- ICD-8: 401.99 - IN - Primary diagnoses	- 1983–1990 - Medical record review - N=310 - PPV	- PPV = 40 (26–55) to 60 (49–70) - Restricted to inpatients and primary diagnoses; NPV, sensitivity, and specificity not included
Diagnosis: Atrial fibrillation or flutter			
- **Rix *et al.***[39] - *Scand Cardiovasc J* - 2012	- ICD-8: 427.93, 427.94; ICD-10: I48 - IN/OUT/ED - Primary and secondary diagnoses	- 1993–2009 - Medical record and heart rhythm documentation - N=284 - PPV	- PPV(All) = 92.3 (88.6–94.8) - PPV(IN/OUT) = 94.0 (90.5–96.3) (independent of diagnosis type and department specialty) - PPV(ED) = 64.7 (41.3–82.7) - 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] - *Am J Med* - 2007	- ICD-8: 427.93, 427.94; ICD-10: I48 - N/A - N/A	- 1980–2002 - Medical record and heart rhythm documentation - N=174 - PPV	- PPV = 98.9 (95.9–99.7) - 13% of the sampled medical records could not be retrieved; NPV, sensitivity, and specificity not included
- **Frost *et al.***[41] - *Arch Intern Med* - 2004	- ICD-8: 427.93, 427.94; ICD-10: I48 - N/A - N/A	- 1980–2002 - Medical record and heart rhythm documentation - N=116 - PPV	- PPV = 96.6 (91.5–98.7) - Only one reviewer; NPV, sensitivity, and specificity not included
Diagnosis: Cardiac arrest			
- **Joensen *et al.***[34] - *J Clin Epidemiol* - 2009	- ICD-8: 427.27; ICD-10: I46 - IN/OUT/ED - Primary and secondary diagnoses	- 1993–2003 - Medical record review, discharge summary, blood tests, ECG - N=42 - PPV	- PPV(IN/OUT/ED) = 50.0 (35.5–64.5) - PPV(IN) = 53.1 (36.5–69.1) - Only one reviewer; NPV, sensitivity, and specificity not included
Diagnosis: Venous thromboembolism			
- **Schmidt *et al.***[42] - *J Thromb Haemost* - 2014	- ICD-10: I80.1–3, I26 + prescriptions for anticoagulants ≤ 30 days after diagnosis - IN/OUT - Primary and secondary diagnoses	- 2004–2012 - Medical record review - N=20 - PPV	- PPV=90.0 (69.9–97.2) - NPV, sensitivity, and specificity not included
- **Severinsen *et al.***[43] - *J Clin Epidemiol* - 2010	- ICD-8: 450.99, 451.00, 451.08, 451.09, 451.99; ICD-10: I26, I80.1–I80.9 - IN/OUT/ED - Primary and secondary diagnoses	- 1994–2006 - Medical record review, discharge summary, blood tests, ultrasound, venography, echo, ventilation-perfusion lung scan, CT scan - N=1100 - PPV	- PPV(All) = 58.5 (55.5–61.3) - PPV(IN/OUT) = 75.0 (71.9–77.8) - PPV(ED) = 31.3 (27.2–35.7) - PPV(primary diagnosis) = 77.0 (73.7–80.0) - NPV, sensitivity, and specificity not included
Diagnosis: Recurrent venous thromboembolism			
- **Schmidt *et al.***[42] - *J Thromb Haemost* - 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 - IN/OUT - Primary and secondary diagnoses	- 2004–2012 - Medical record review - N=90 - 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) - 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] - *Circ Cardiovasc Qual Outcomes* - 2009	- Cohort study - Registry-based - Veterans Health Administration hospitals across the US (2004–2006)	- MI patients (n=21,745) - Psychiatric comorbidity (1) secondary inpatient diagnosis during MI admission, 2) diagnoses from prior outpatient visits - Reference: no psychiatric comorbidity using both methods - 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 - 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) - Older male (98%) population with unique benefits → selection bias and hampered generalizability; broad exposure definition; unknown data quality
Dickens *et al.*[45] - *J Am Coll Cardiol* - 2007	- Cohort study - Questionnaire, interview, population records - Manchester, UK (1997–1999)	- MI patients (n=588) - Depression immediately preceding MI and 12 months after MI - 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) - Small sample size, questionnaire for depression assessment
Bush *et al.*[46] - *Am J Cardiol* - 2001	- Cohort study - Clinical interview - US, Single-center study (Jul 1995 – Dec 1996)	- MI patients (n=266) - History of depression - 4-month all-cause mortality	- RR = 1.0 (p=1.0) - 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] - *Circulation* - 2017	- Cohort study - SRQ - US, 24 hospitals (data from the TRIUMPH study) (2005–2008)	- MI patients ≥18 years (n=4,062) - Depression during admission ('treated' [discharge diagnosis / medication / referral for counseling], or 'untreated' if none of these) - 1 year all-cause mortality	- 759 (18.7%) patients with depression; 231 (30.4%) were treated - 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) - 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] - *Health Psychol* - 2015	- Meta-analysis - BDI - 1975–2011	- MI patients (n=6,775 in 9 studies) - Depression during admission - All-cause mortality	- aHR = 1.14 (95% CI 1.04–1.25) - Left ventricular ejection fraction available only for 4,744 patients; missing depression data (imputated); study heterogeneity, publication bias
Meijer *et al*.[49] - *Br J Psychiatry* - 2013	- Meta-analysis - SRQ or standardized structured diagnostic interviews	- MI patients (n=2225 in 3 studies) - Depression within 3 months after MI - All-cause mortality	- Pooled aHR = 1.23 (95% CI 1.15–1.31) - Study heterogeneity; publication bias
Smolderen *et al.*[50] - *Circ Cardiovasc Qual Outcomes* - 2009	- Cohort study - MR; MI databases; SRQ - US, 19 hospitals (2003–2004)	- MI patients (n=2347) - Depression, depressive symptoms (somatic/cognitive) during admission - 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) - Medical record review and questionnaire as data sources
Carney *et al.*[51] - *Psychosom Med* - 2009	- Post-hoc analyses of RCT - ENRICHD trial data, diagnostic interview, SRQ - US, 8 hospitals (1996–1999)	- MI patients and depression (n=920) - Patients with MI but no depression - 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) - Study population composed of participants enrolled in a clinical trial; no information on duration of depression
Parakh *et al.*[52] - *Am J Cardiol* - 2008	- Cohort study - SRQ (incl. BDI) - US (Jul 1995 – Dec 1996)	- MI patients (n=284) - Depression evaluated within 5 days of MI admission - 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) - Single-center study; small sample size
Drago *et al.*[53]	- Cohort study	- MI patients (n=100)	- OR 12 (95% CI 2.6–56)

- *Int J Cardiol* - 2006	- Diagnostic interview; SRQ (BDI) - Italy (Jan 1999 – Dec 1999)	- Major Depressive Disorder between the 7th and 14th day from admission - 5-year all-cause mortality	- Single-center study; small sample size with following imprecise estimates
Nicholson *et al.*[54] - *Eur Heart J* - 2006	- Meta-analysis - SRQ, diagnostic interview, physician diagnosis, antidepressants	- MI patients (n= 17,842 in 34 studies) - Depression at baseline - All-cause mortality	- Pooled RR 1.80 (95% CI 1.50–2.15) - Study heterogeneity
Parashar *et al.*[55] - *Arch Intern Med* - 2006	- Cohort study - SRQ - US, 19 medical centers (Jan 2003 – Jun 2004)	- MI patients (n=1873) - Depressive symptoms (transient [only during hospitalization], new [only at 1 month after discharge], or persistent [at both times]) - 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 - 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] - *Acta Psychiatr Scand* - 2006	- Cohort study - SRQ (MDI) - Denmark (17 hospitals) (Mar 1999 – Dec 2000)	- MI patients (n=763) - Depression at discharge - 1-year all-cause mortality	- aHR = 1.1 (95% CI 0.1–9.0) - 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] - *Arch Intern Med* - 2005	- Cohort study (patients from the ENRICHED trial) - BDI and DSM-IV - USA (4 hospitals) (1997–2000)	- MI patients (n=678) - Depression at discharge - 30-month all-cause mortality	- aHR = 2.8 (95% CI 1.4–5.4) - Small sample size; excluded patients who did not meet the inclusion criteria for the ENRICHED trial
Rumsfeld *et al.*[58] - *Am Heart J* - 2005	- Post hoc analysis of RCT - SRQ (MOS-D) - Multicenter international setting (Dec 1999 – Dec 2001)	- MI patients with heart failure (n=634) from the EPHESUS trial - Depression at baseline - 2-year all-cause mortality	- aHR = 1.75 (95% CI 1.15–2.68) - 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] - *Psychosom Med* - 2004	- Meta-analysis - SRQ and clinical interviews	- MI patients (n= 3082 in 9 studies) - Depressive symptoms at baseline - All-cause mortality	- OR = 2.38 (95% CI 1.76–3.22) - Study heterogeneity; publication bias; modest sample size
Carney *et al.*[60] - *Am J Cardiol* - 2003	- Post-hoc analysis of RCT - Data from the ENRICHD trial, diagnostic interview for depression, SRQ - US (Oct 1997– Jan 2000)	- MI patients (n=766) - Depression at baseline - 30-month all-cause mortality	- aHR = 2.4 (95% CI 1.2–4.7) - 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] - *CMAJ* - 2003	- Cohort study - SRQ (BDI) - Canada (10 hospitals in Quebec) (1996–1998)	- MI patients (n=587) - Depression at baseline - 1-year all-cause mortality	- aHR 1.3 (95% CI 0.59–3.05) - 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] - *Int J Epidemiol* - 2002	- Cohort study - SRQ (BDI) - UK (1997 – 1998)	- MI patients (n=288) - Depression at baseline - 3-year all-cause mortality	- OR = 1.04 (95% CI 0.50–2.16) - Small sample size, unadjusted estimates
Bush *et al.*[46] - *Am J Cardiol* - 2001	- Cohort study - Clinical interview; SRQ (BDI) - US, Single-center study (1995–1996)	- MI patients (n=285) - Depression at baseline - 4-month all-cause mortality	- Depressive symptoms: RR = 2.6 (p=0.06); depression disorder: RR = 2.0 (p=0.18) - Small sample size; only unadjusted estimates; all-cause mortality based on phone call to a surviving contact
Lane *et al.*[63] - *Psychosom Med* - 2001	- Cohort study - SRQ (BDI) - UK (1997–1998)	- MI patients (n=288) - Depression at baseline - 1-year all-cause mortality	- OR = 1.15 (95% CI 0.49–2.67) - 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), out-come, exposure (if applicable)**	**Results, limitations**
Outcome: Ischemic stroke			
- Ulvenstam *et al.* [64] - *Stroke* - 2014	- Population-based cohort study - Sweden - Nationwide registries - 1998–2008	- MI patients (n=173,233) - 1-year ischemic stroke	- 7185 of 173,233 patients with acute MI had an ischemic stroke within 1 year (4.1%) - 20% relative risk reduction during the study period (1998–2000 *vs*. 2007–2008); relative risk = 0.80 (0.75–0.86) - Short-term (1 year) follow-up; no comparison cohort
- Kajermo *et al.* [65] - *Stroke* - 2014	- Population-based cohort study - Sweden - Nationwide registries - 1998–2008	- MI patients (n=173,233) - 30-day ischemic stroke	- 3571 of 173,233 patients with acute MI had an ischemic stroke within 30 days (2.1%) - Incidence of ischemic stroke was lower during 2007 to 2008 compared to 1998 to 2000 (2.0% *vs*. 2.2%, p=0.02) - Short-term (30 days) follow-up; no comparison cohort
- Koton *et al.* [66] - *Int J Cardiol* - 2012	- Community-based cohort study - Israel - 8 hospitals in central Israel - 1992–1993	- MI patients aged ≤ 65 years (n=1261) - 11-year ischemic stroke - Exposure: Unfavora-ble 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 - Patients > 65 years old were not included; unfavorable socioeconomic factors were self-reported; findings may not be generalizable
- Ikram *et al.* [67] - *Neurology* - 2006	- Community-based cohort study - Rotterdam, the Neth-erlands - MI: ECG/interview - 1990–1993	- Recognized MI (n=442), unrecog-nized MI (n=361), and no MI (reference, n=5636) - 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 - MI was ascertained by interview and computer interpretation of ECG; find-ings may not be generalizable
- Witt *et al.* [68] - *Am J Med* - 2005	- Meta-analysis - Population-based studies (restricted to 1978-2004, >100 sub-jects), reporting the number or percent of ischemic strokes in MI survivors	- MI patients - Ischemic stroke during first year after MI	- 22 articles included - 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 - <1 year follow-up; no comparators to MI patients
- Mooe *et al.* [69] - *Stroke* - 1999	- Population-based case-control study - The two northernmost counties in Sweden - 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%) - <1 year follow-up
Outcome: Hemorrhagic stroke			
- Binsell-Gerdin *et al.* [70] - *Int J Cardiol* - 2014	- Population-based cohort study - Sweden - Nationwide registries - 1998–2008	- MI patients (n=173,233) - 30-day hemorrhagic stroke	- 375 patients (0.22%) had hemorrhagic stroke within 30 days of MI - Incidence decreased from 0.2% (n = 94) in 1998–2000 to 0.1% (n = 41) in 2007–2008 - No differentiation between intracerebral hemorrhage and subarachnoid hemorrhage; no comparison cohort
Outcome: Both ischemic and hemorrhagic stroke			
- Hachet *et al.* [71] - *Stroke* - 2014	- Community-based cohort study - French region: data from the RICO survey - 2001–2010	- MI patients (n=8485) - 1-year stroke or transient ischemic attack (n=168, 1.98%)	- 123 MI patients (1.4%) had an in-hospital stroke (86% ischemic, 11% hemor-rhagic, 3% undetermined) - During 1-year follow-up, only 45 (0.6% of survivors) had a post-discharge stroke (96% ischemic, 4% hemorrhagic) - 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] - *Circulation* - 2005	- Multinational cohort study - 94 hospitals in 14 countries - 1999–2003	- Patients admitted with ACS (n=35,233, 37% with STEMI, 30% with NSTEMI, and 33% with unstable angina) - 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 - <1 year follow-up; no comparators to MI patients
Outcome: Unspecified stroke			

- Saczynski *et al.* [73] - *Arch Intern Med* - 2008	- Community-based cohort study - US - 16 Worcester medical centers - 1986–2005	- MI patients (n=9220) - 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) - <1 year follow-up; no comparators to MI patients; findings may not be generalizable
- Witt *et al.* [74] - *Ann Intern Med* - 2005	- Community-based cohort study - Olmsted County, Minnesota, US - 1979–1998	- MI patients (n=2160) - Comparison: General population - 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. - HR (post-MI stroke mortality) = 2.89 (95% CI, 2.44–3.43) - Unadjusted SMRs; outcomes from medical records
- Tanne *et al.* [75] - *J Am Coll Cardiol* - 1997	- Nationwide cohort study - Israel - 1981–1983 and 1992–1994	- MI admissions (n=5839 in 1981–1983 and n=2012 in 1992–1994) - Cerebrovascular events	- Incidence = 0.74% (43 of 5839) in 1981–1983 (prethrombolysis era) *vs*. 0.75% (15 of 2012) in 1992–1994 (thrombolysis era) - 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, outcome**	**Results, limitations**
Outcome: All-cause dementia			
- Ikram et *al.* [76] - *Stroke* - 2008	- Cohort study and cross-sectional study - Rotterdam, the Netherlands - MI based on ECG/interview - Dementia based on MMSE, Cambridge examination, and neuropsychological testing - 1990–1993	- Recognized MI (n=424), unrecognized MI (n=345), and no MI (reference, n=5578) - 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 - Recognized MI was not associated with dementia in either sex - Men (but not women), with recognized MI more often had brain infarction, but not white matter lesions - Small sample size
- Bursi *et al.* [77] - *Am J Epidemiol* - 2006	- Case-control study - Minnesota, United States - Registry-based diagnoses - 1985–1994 (dementia patients)	- 916 cases of all-cause dementia and 916 age- and sex-matched controls - 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) - Small sample size, case-control design
Outcome: Cognitive impairment			
Haring *et al.* [78] - *J Am Heart Assoc* - 2013	- Cohort study - United States (Women's Health Initiative Memory Study (WHIMS)) - Questionnaire for CVD, MMSE for dementia - 1996–1999	- Cognitively intact, postmenopausal women (65–79 years, n=6455) - CVD, including MI - 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) - 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.

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.

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.

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]

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.

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.

METHODS

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]

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.

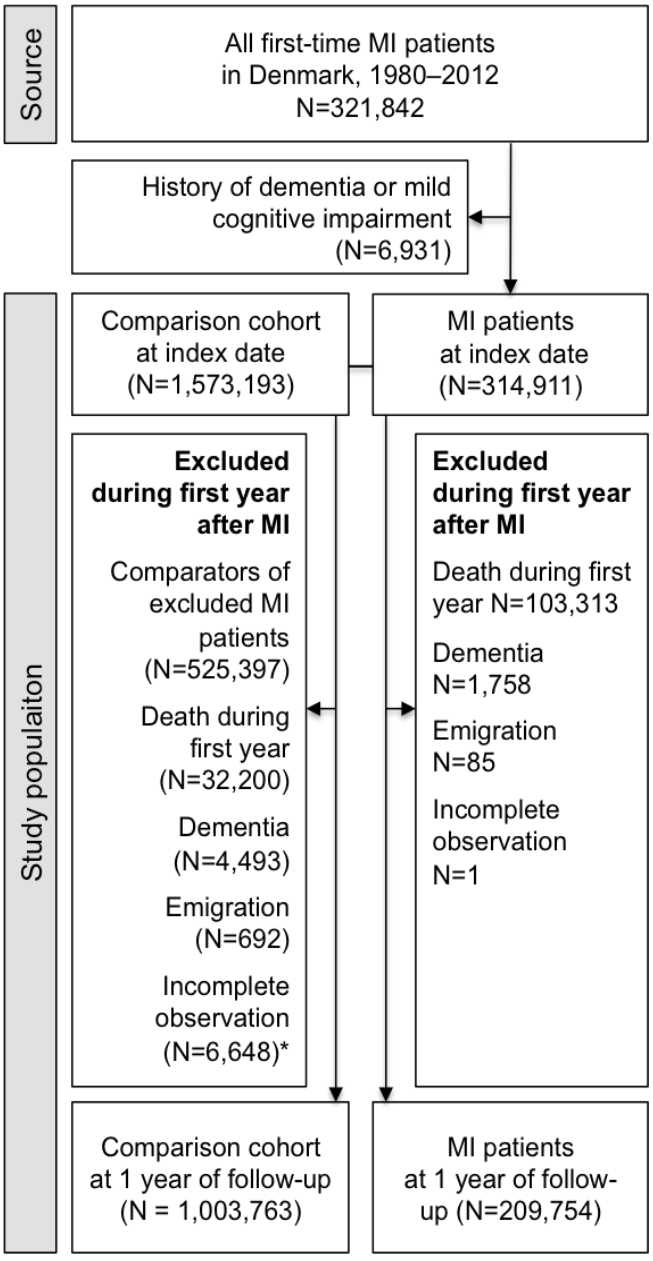
The Danish Psychiatric Central Research Register (studies II and IV)

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.

Figure 1. 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.



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]

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.

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.[118]

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.

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.

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[33,119] from inpatient and outpatient diagnoses,[111,114] as well as data on age, sex, vital status,[110] procedures,[120] comedication use,[115] and socioeconomic data.[113]

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[121] 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.[122] 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.[123] 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).[123]

Relative estimates were computed in time-to-event analyses[124] 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).[125]

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).

RESULTS

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).

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 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. *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. *"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.

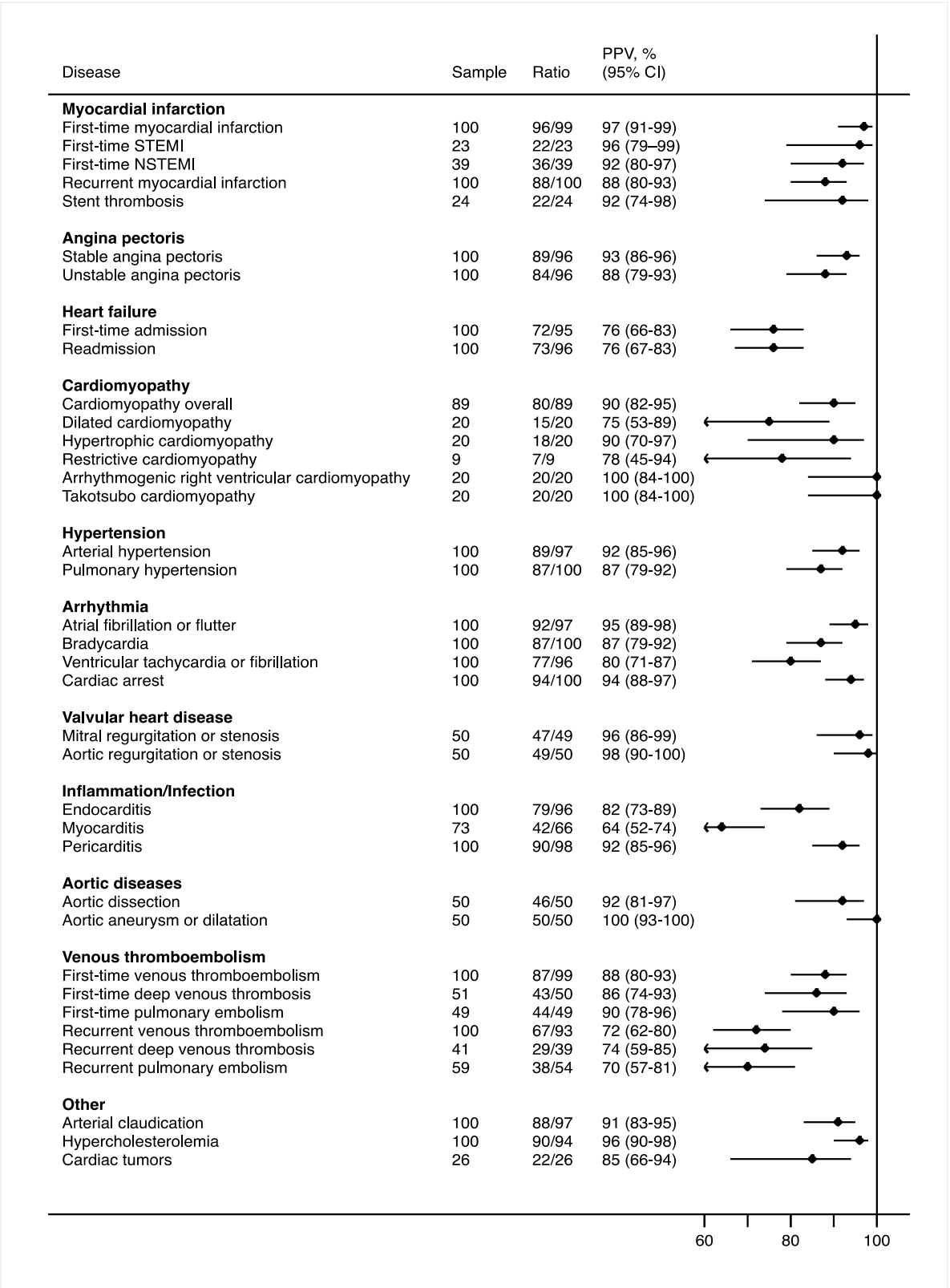


Figure 2. Positive predictive values of cardiovascular diagnoses in the Danish National Patient Registry. Abbreviations: Ratio, confirmed diagnoses/available records; PPV, positive predictive value; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-STEMI.

Table 7. 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. 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.

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).

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 9. 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.

Table 10. 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)**	**HR controlled for matching factors[a] (95% CI)**	**Adjusted HR (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; HR, hazard ratio

DISCUSSION

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.

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).

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.

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.

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.

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.

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.[126] Systematic error encompasses selection bias, information bias, and confounding.[127] Selection and information biases are systematic errors inherent to the study design and cannot be corrected in the analysis phase.[127] 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.[127] Moreover, registry-based studies are dependent on the quality of the registry data, which can be evaluated only through cumbersome validation studies.[128,129]

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

Statistical precision

The width of the CIs reflected the precision in all studies.[126] CIs enable inference based on the strength of an association in combination with the level of precision.[130]

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.[126] 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.

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.[127] 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.[127]

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.

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.[127] 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).[127] 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.[131] 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.[132]

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%).[118] 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.[133] 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.[133] The sensitivity of overall stroke in the DNPR (inpatients with a primary diagnosis) has been reported to be roughly 60%.[134] 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.[135] 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.

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.[127] Thus, a confounder must be a cause (or marker) of the outcome and unbalanced between the exposure groups.[127] 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, smoking is associated with a decreased risk of death after MI,[136] 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.[137] 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[138] and dementia[139] 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.[105,140,141]

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.

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.

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.

REFERENCES

1. Hildebrand R. Robert Willis (1799-1878): the works of William Harvey, M. D., London 1847. A bibliographical note. 2007.
2. Fuller, R. G. What happens to mental patients after discharge from the hospital? Psychiatr Quart. 1935;9:95–104.
3. Malzberg, B. Mortality among patients with involution melancholia. Am J Psychiatry. 1937;93:1231–1238.
4. Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, Cammann VL, Sarcon A, Geyer V, Neumann CA, Seifert B, Hellermann J, Schwyzer M, Eisenhardt K, Jenewein J, Franke J, Katus HA, Burgdorf C, Schunkert H, Moeller C, Thiele H, Bauersachs J, Tschöpe C, Schultheiss H-P, Laney CA, Rajan L, Michels G, Pfister R, Ukena C, Böhm M, Erbel R, Cuneo A, Kuck K-H, Jacobshagen C, Hasenfuss G, Karakas M, Koenig W, Rottbauer W, Said SM, Braun-Dullaeus RC, Cuculi F, Banning A, Fischer TA, Vasankari T, Airaksinen KEJ, Fijalkowski M, Rynkiewicz A, Pawlak M, Opolski G, Dworakowski R, MacCarthy P, Kaiser C, Osswald S, Galiuto L, Crea F, Dichtl W, Franz WM, Empen K, Felix SB, Delmas C, Lairez O, Erne P, Bax JJ, Ford I, Ruschitzka F, Prasad A, Lüscher TF. Clinical Features and Outcomes of Takotsubo (Stress) Cardiomyopathy. *N Engl J Med*. 2015;373:929–938.
5. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. *Arch Intern Med*. 1987;147:1561–1564.
6. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991;22:983–988.
7. Wolf PA, Dawber TR, Thomas HE, Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. *Neurology*. 1978;28:973–977.
8. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, Lau CP, Fain E, Yang S, Bailleul C, Morillo CA, Carlson M, Themeles E, Kaufman ES, Hohnloser SH, ASSERT Investigators. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med*. 2012;366:120–129.
9. Koch MB, Davidsen M, Andersen LV, Juel K, Jensen GB. Increasing prevalence despite decreasing incidence of ischaemic heart disease and myocardial infarction. A national register based perspective in Denmark, 1980-2009. *Eur J Prev Cardiol*. 2015;22:189–195.
10. Schmidt M, Jacobsen JB, Lash TL, Bøtker HE, Sørensen HT. 25 year trends in first time hospitalisation for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study. *BMJ*. 2012;344:e356.
11. The top 10 causes of death worldwide [Internet]. [cited 2017 Feb 27]. Available from: http://www.who.int/mediacentre/factsheets/fs310/en/
12. Steinberg BA, Bhatt DL, Mehta S, Poole-Wilson PA, O'Hagan P, Montalescot G, Ballantyne CM, Cannon CP. Nine-year trends in achievement of risk factor goals in the US and European outpatients with cardiovascular disease. *Am Heart J*. 2008;156:719–727.
13. Mons U, Müezzinler A, Gellert C, Schöttker B, Abnet CC, Bobak M, de Groot L, Freedman ND, Jansen E, Kee F, Kromhout D, Kuulasmaa K, Laatikainen T, O'Doherty MG, Bueno-de-Mesquita B, Orfanos P, Peters A, van der Schouw YT, Wilsgaard T, Wolk A, Trichopoulou A, Boffetta P, Brenner H, CHANCES Consortium. Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: meta-analysis of individual participant data from prospective cohort studies of the CHANCES consortium. *BMJ*. 2015;350:h1551.
14. Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE, Giles WH, Capewell S. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. *N Engl J Med*. 2007;356:2388–2398.
15. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined—a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol 2000;36:959-969.
16. Fox KAA, Steg PG, Eagle KA, Goodman SG, Anderson FAJ, Granger CB, Flather MD, Budaj A, Quill A, Gore JM. Decline in rates of death and heart failure in acute coronary syndromes, 1999-2006. *JAMA*. 2007;297:1892–1900.
17. Wolff JL, Starfield B, Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. *Arch Intern Med*. 2002;162:2269–2276.
18. Beller GA. Are you ever too old to be risk stratified? *J Am Coll Cardiol*. 1992;19:1399–1401.
19. Nagurney JT, Huang C, Heredia O, Sane S, Lewis SC, Chang Y, Jang I-K. The new and old definitions of acute myocardial infarction: a data-based comparison. *Am J Emerg Med*. 2008;26:523–531.
20. Thygesen K, Alpert JS, White HD, Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *Eur Heart J*. 2007;28:2525–2538.
21. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Writing Group on the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction, Thygesen K, Alpert JS, White HD, Jaffe AS, Katus HA, Apple FS, Lindahl B, Morrow DA, Chaitman BA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand J-P, Menasché P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon J-L, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S, ESC Committee for Practice Guidelines (CPG). Third universal definition of myocardial infarction. 2012. p. 2551–2567.
22. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes

of acute myocardial infarction. *N Engl J Med*. 2010;362:2155–2165.
23. Warburg E. Om Coronarkredsløbet og om Thrombosen af en Coronararterie med en historisk Oversigt. Bibliotek for læger. 1930;122:1–102.
24. Nabel EG, Braunwald E. A Tale of Coronary Artery Disease and Myocardial Infarction. *N Engl J Med*. 2012;366:54–63.
25. Falk E. Unstable angina with fatal outcome: dynamic coronary thrombosis leading to infarction and/or sudden death. Autopsy evidence of recurrent mural thrombosis with peripheral embolization culminating in total vascular occlusion. *Circulation* 1985;71:699–708.
26. Meier P, Hemingway H, Lansky AJ, Knapp G, Pitt B, Seiler C. The impact of the coronary collateral circulation on mortality: a meta-analysis. *Eur Heart J*. 2012;33:614–621.
27. Mahmood SS, Levy D, Vasan RS, Wang TJ. The Framingham Heart Study and the epidemiology of cardiovascular disease: a historical perspective. *The Lancet*. 2014;383:999–1008.
28. Anand SS, Islam S, Rosengren A, Franzosi MG, Steyn K, Yusufali AH, Keltai M, Diaz R, Rangarajan S, Yusuf S, INTERHEART Investigators. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. *Eur Heart J*. 2008;29:932–940.
29. Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, Goodman SG, Granger CB, Steg PG, Gore JM, Budaj A, Avezum A, Flather MD, Fox KAA, GRACE Investigators. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA*. 2004;291:2727–2733.
30. Tang EW, Wong C-K, Herbison P. Global Registry of Acute Coronary Events (GRACE) hospital discharge risk score accurately predicts long-term mortality post acute coronary syndrome. *Am Heart J*. 2007;153:29–35.
31. Schardt C, Adams MB, Owens T, Keitz S, Fontelo P. Utilization of the PICO framework to improve searching PubMed for clinical questions. *BMC Med Inform Decis Mak*. 2007;7:16.
32. Coloma PM, Valkhoff VE, Mazzaglia G, Nielsson MS, Pedersen L, Molokhia M, Mosseveld M, Morabito P, Schuemie MJ, van der Lei J, Sturkenboom M, Trifirò G, EU-ADR Consortium. Identification of acute myocardial infarction from electronic healthcare records using different disease coding systems: a validation study in three European countries. *BMJ Open*. 2013;3:e002862.
33. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sørensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol*. 2011;11:83.
34. Joensen AM, Jensen MK, Overvad K, Dethlefsen C, Schmidt E, Rasmussen L, Tjønneland A, Johnsen S. Predictive values of acute coronary syndrome discharge diagnoses differed in the Danish National Patient Registry. *J Clin Epidemiol*. 2009;62:188–194.
35. Madsen M, Davidsen M, Rasmussen S, Abildstrom SZ, Osler M. The validity of the diagnosis of acute myocardial infarction in routine statistics: a comparison of mortality and hospital discharge data with the Danish MONICA registry. *J Clin Epidemiol*. 2003;56:124–130.
36. Mard S, Nielsen FE. Positive predictive value and impact of misdiagnosis of a heart failure diagnosis in administrative registers among patients admitted to a University Hospital cardiac care unit. *Clin Epidemiol*. 2010;2:235–239.
37. Schmidt M, Johannesdottir SA, Lemeshow S, Lash TL, Ulrichsen SP, Bøtker HE, Sørensen HT. Obesity in young men, and individual and combined risks of type 2 diabetes, cardiovascular morbidity and death before 55 years of age: a Danish 33-year follow-up study. *BMJ Open*. 2013;3:e002698.
38. Nielsen HW, Tuchsen F, Jensen MV. Validiteten af diagnosen essentiel hypertension i Landspatientregistret. *Ugeskr Laeger*. 1996;158:163–167.
39. Rix TA, Riahi S, Overvad K, Lundbye-Christensen S, Schmidt EB, Joensen AM. Validity of the diagnoses atrial fibrillation and atrial flutter in a Danish patient registry. *Scand Cardiovasc J*. 2012;46:149–153.
40. Frost L, Andersen LV, Vestergaard P, Husted S, Mortensen LS. Trend in mortality after stroke with atrial fibrillation. *Am J Med*. 2007;120:47–53.
41. Frost L, Vestergaard P. Alcohol and risk of atrial fibrillation or flutter: a cohort study. *Arch Intern Med*. 2004;164:1993–1998.
42. Schmidt M, Cannegieter SC, Johannesdottir SA, Dekkers OM, Horváth-Puhó E, Sørensen HT. Statin use and venous thromboembolism recurrence: a combined nationwide cohort and nested case-control study. *J Thromb Haemost*. 2014;12:1207–1215.
43. Severinsen MT, Kristensen SR, Overvad K, Dethlefsen C, Tjønneland A, Johnsen SP. Venous thromboembolism discharge diagnoses in the Danish National Patient Registry should be used with caution. *J Clin Epidemiol*. 2010;63:223–228.
44. Abrams TE, Vaughan-Sarrazin M, Rosenthal GE. Psychiatric comorbidity and mortality after acute myocardial infarction. *Circ Cardiovasc Qual Outcomes*. 2009;2:213–220.
45. Dickens C, McGowan L, Percival C, Tomenson B, Cotter L, Heagerty A, Creed F. Depression Is a Risk Factor for Mortality After Myocardial Infarction. *J Am Coll Cardiol*. 2007;49:1834–1840.
46. Bush DE, Ziegelstein RC, Tayback M, Richter D, Stevens S, Zahalsky H, Fauerbach JA. Even minimal symptoms of depression increase mortality risk after acute myocardial infarction. *Am J Cardiol*. 2001;88:337–341.
47. Smolderen KG, Buchanan DM, Gosch K, Whooley M, Chan PS, Vaccarino V, Parashar S, Shah AJ, Ho PM, Spertus JA. Depression Treatment and 1-Year Mortality After Acute Myocardial Infarction: Insights From the TRIUMPH Registry (Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients' Health Status). *Circulation*. 2017;135:1681–1689.
48. de Miranda Azevedo R, Roest AM, Carney RM, Denollet J, Freedland KE, Grace SL, Hosseini SH, Lane DA, Parakh K, Pilote L, de Jonge P. A bifactor model of the Beck Depression Inventory and its association with medical prognosis after myocardial infarction. *Health*

Psychol. 2016;35:614–624.
49. Meijer A, Conradi HJ, Bos EH, Anselmino M, Carney RM, Denollet J, Doyle F, Freedland KE, Grace SL, Hosseini SH, Lane DA, Pilote L, Parakh K, Rafanelli C, Sato H, Steeds RP, Welin C, de Jonge P. Adjusted prognostic association of depression following myocardial infarction with mortality and cardiovascular events: individual patient data meta-analysis. *Br J Psychiatry*. 2013;203:90–102.
50. Smolderen KG, Spertus JA, Reid KJ, Buchanan DM, Krumholz HM, Denollet J, Vaccarino V, Chan PS. The association of cognitive and somatic depressive symptoms with depression recognition and outcomes after myocardial infarction. *Circ Cardiovasc Qual Outcomes*. 2009;2:328–337.
51. Carney RM, Freedland KE, Steinmeyer B, Blumenthal JA, de Jonge P, Davidson KW, Czajkowski SM, Jaffe AS. History of depression and survival after acute myocardial infarction. *Psychosom Med*. 2009;71:253–259.
52. Parakh K, Thombs BD, Fauerbach JA, Bush DE, Ziegelstein RC. Effect of Depression on Late (8 years) Mortality After Myocardial Infarction. *Am J Cardiol*. 2008;101:602–606.
53. Drago S, Bergerone S, Anselmino M, Varalda PG, Cascio B, Palumbo L, Angelini G, Trevi PG. Depression in patients with acute myocardial infarction: influence on autonomic nervous system and prognostic role. Results of a five-year follow-up study. *Int J Cardiol*. 2007;115:46–51.
54. Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *Eur Heart J*. 2006;27:2763–2774.
55. Parashar S, Rumsfeld JS, Spertus JA, Reid KJ, Wenger NK, Krumholz HM, Amin A, Weintraub WS, Lichtman J, Dawood N, Vaccarino V. Time course of depression and outcome of myocardial infarction. *Arch Intern Med*. 2006;166:2035–2043.
56. Sørensen C, Brandes A, Hendricks O, Thrane J, Friis-Hasche E, Haghfelt T, Bech P. Depression assessed over 1-year survival in patients with myocardial infarction. *Acta Psychiatr Scand*. 2006;113:290–297.
57. Carney RM, Blumenthal JA, Freedland KE, Stein PK, Howells WB, Berkman LF, Watkins LL, Czajkowski SM, Hayano J, Domitrovich PP, Jaffe AS. Low heart rate variability and the effect of depression on post-myocardial infarction mortality. *Arch Intern Med*. 2005;165:1486–1491.
58. Rumsfeld JS, Jones PG, Whooley MA, Sullivan MD, Pitt B, Weintraub WS, Spertus JA. Depression predicts mortality and hospitalization in patients with myocardial infarction complicated by heart failure. *Am Heart J*. 2005;150:961–967.
59. van Melle JP, de Jonge P, Spijkerman TA, Tijssen JGP, Ormel J, van Veldhuisen DJ, van den Brink RHS, van den Berg MP. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. *Psychosom Med*. 2004;66:814–822.
60. Carney RM, Blumenthal JA, Catellier D, Freedland KE, Berkman LF, Watkins LL, Czajkowski SM, Hayano J, Jaffe AS. Depression as a risk factor for mortality after acute myocardial infarction. *Am J Cardiol*. 2003;92:1277–1281.
61. Lauzon C, Beck CA, Huynh T, Dion D, Racine N, Carignan S, Diodati JG, Charbonneau F, Dupuis R, Pilote L. Depression and prognosis following hospital admission because of acute myocardial infarction. *CMAJ*. 2003;168:547–552.
62. Lane D, Carroll D, Ring C, Beevers DG, Lip GYH. In-hospital symptoms of depression do not predict mortality 3 years after myocardial infarction. *Int J Epidemiol*. 2002;31:1179–1182.
63. Lane D, Carroll D, Ring C, Beevers DG, Lip GY. Mortality and quality of life 12 months after myocardial infarction: effects of depression and anxiety. *Psychosom Med*. 2001;63:221–230.
64. Ulvenstam A, Kajermo U, Modica A, Jernberg T, Söderström L, Mooe T. Incidence, trends, and predictors of ischemic stroke 1 year after an acute myocardial infarction. *Stroke*. 2014;45:3263–3268.
65. Kajermo U, Ulvenstam A, Modica A, Jernberg T, Mooe T. Incidence, trends, and predictors of ischemic stroke 30 days after an acute myocardial infarction. *Stroke*. 2014;45:1324–1330.
66. Koton S, Gerber Y, Goldbourt U, Drory Y. Socioeconomic risk factor aggregation and long-term incidence of ischemic stroke in patients after first acute myocardial infarction. *Int J Cardiol*. 2012;157:324–329.
67. Ikram MA, Hollander M, Bos MJ, Kors JA, Koudstaal PJ, Hofman A, Witteman JCM, Breteler MMB. Unrecognized myocardial infarction and the risk of stroke: the Rotterdam Study. *Neurology*. 2006;67:1635–1639.
68. Witt BJ, Ballman KV, Brown RD, Meverden RA, Jacobsen SJ, Roger VL. The incidence of stroke after myocardial infarction: a meta-analysis. *Am J Med*. 2006;119:354.e1–9.
69. Mooe T, Olofsson BO, Stegmayr B, Eriksson P. Ischemic stroke. Impact of a recent myocardial infarction. *Stroke*. 1999;30:997–1001.
70. Binsell-Gerdin E, Graipe A, Ögren J, Jernberg T, Mooe T. Hemorrhagic stroke the first 30 days after an acute myocardial infarction: incidence, time trends and predictors of risk. *Int J Cardiol*. 2014;176:133–138.
71. Hachet O, Guenancia C, Stamboul K, Daubail B, Richard C, Béjot Y, Yameogo V, Gudjoncik A, Cottin Y, Giroud M, Lorgis L. Frequency and predictors of stroke after acute myocardial infarction: specific aspects of in-hospital and postdischarge events. *Stroke*. 2014;45:3514–3520.
72. Budaj A, Flasinska K, Gore JM, Anderson FAJ, Dabbous OH, Spencer FA, Goldberg RJ, Fox KAA. Magnitude of and risk factors for in-hospital and postdischarge stroke in patients with acute coronary syndromes: findings from a Global Registry of Acute Coronary Events. *Circulation*. 2005;111:3242–3247.
73. Saczynski JS, Spencer FA, Gore JM, Gurwitz JH, Yarzebski J, Lessard D, Goldberg RJ. Twenty-year trends in the incidence of stroke complicating acute myocardial infarction: Worcester Heart Attack Study. *Arch Intern Med*. 2008;168:2104–2110.
74. Witt BJ, Brown RD, Jacobsen SJ, Weston SA, Yawn BP, Roger VL. A community-based study of stroke inci-

dence after myocardial infarction. *Ann Intern Med*. 2005;143:785–792.
75. Tanne D, Gottlieb S, Hod H, Reicher-Reiss H, Boyko V, Behar S. Incidence and Mortality From Early Stroke Associated With Acute Myocardial Infarction in the Prethrombolytic and Thrombolytic Eras. *J Am Coll Cardiol*. 1996;30:1484–1490.
76. Ikram MA, van Oijen M, de Jong FJ, Kors JA, Koudstaal PJ, Hofman A, Witteman JCM, Breteler MMB. Unrecognized myocardial infarction in relation to risk of dementia and cerebral small vessel disease. *Stroke*. 2008;39:1421–1426.
77. Bursi F, Rocca WA, Killian JM, Weston SA, Knopman DS, Jacobsen SJ, Roger VL. Heart disease and dementia: a population-based study. *Am J Epidemiol*. 2006;163:135–141.
78. Haring B, Leng X, Robinson J, Johnson KC, Jackson RD, Beyth R, Wactawski-Wende J, Ballmoos von MW, Goveas JS, Kuller LH, Wassertheil-Smoller S. Cardiovascular disease and cognitive decline in postmenopausal women: results from the Women's Health Initiative Memory Study. *J Am Heart Assoc*. 2013;2:e000369.
79. Sander M, Oxlund B, Jespersen A, Krasnik A, Mortensen EL, Westendorp RGJ, Rasmussen LJ. The challenges of human population ageing. 2015. p. 185–187.
80. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med*. 2006;3:e442.
81. Belmaker RH, Agam G. Major depressive disorder. *N Engl J Med*. 2008;358:55–68.
82. Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *Lancet*. 2007;370:851–858.
83. King M, Weich S, Torres-González F, Svab I, Maaroos H-I, Neeleman J, Xavier M, Morris R, Walker C, Bellón-Saameño JA, Moreno-Küstner B, Rotar D, Rifel J, Aluoja A, Kalda R, Geerlings MI, Carraça I, de Almeida MC, Vicente B, Saldivia S, Rioseco P, Nazareth I. Prediction of depression in European general practice attendees: the PREDICT study. *BMC Public Health*. 2006;6:6.
84. Carney RM, Freedland KE. Depression and coronary heart disease. *Nat Rev Cardiol*. 2017;14:145–155.
85. Kleiger RE, Miller JP, Bigger JT, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol*. 1987;59:256–262.
86. Vreeburg SA, Hoogendijk WJG, van Pelt J, Derijk RH, Verhagen JCM, van Dyck R, Smit JH, Zitman FG, Penninx BWJH. Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: results from a large cohort study. *Arch Gen Psychiatry*. 2009;66:617–626.
87. Whitworth JA, Williamson PM, Mangos G, Kelly JJ. Cardiovascular consequences of cortisol excess. *Vasc Health Risk Manag*. 2005;1:291–299.
88. Ziegelstein RC, Fauerbach JA, Stevens SS, Romanelli J, Richter DP, Bush DE. Patients with depression are less likely to follow recommendations to reduce cardiac risk during recovery from a myocardial infarction. *Arch Intern Med*. 2000;160:1818–1823.
89. Deuschle M. Effects of antidepressants on glucose metabolism and diabetes mellitus type 2 in adults. *Curr Opin Psychiatry*. 2013;26:60–65.
90. Berkman LF, Blumenthal J, Burg M, Carney RM, Catellier D, Cowan MJ, Czajkowski SM, DeBusk R, Hosking J, Jaffe A, Kaufmann PG, Mitchell P, Norman J, Powell LH, Raczynski JM, Schneiderman N, Enhancing Recovery in Coronary Heart Disease Patients Investigators (ENRICHD). Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial. *JAMA*. 2003;289:3106–3116.
91. Carney RM, Blumenthal JA, Freedland KE, Youngblood M, Veith RC, Burg MM, Cornell C, Saab PG, Kaufmann PG, Czajkowski SM, Jaffe AS, ENRICHD Investigators. Depression and late mortality after myocardial infarction in the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study. *Psychosom Med*. 2004;66:466–474.
92. Banankhah SK, Friedmann E, Thomas S. Effective treatment of depression improves post-myocardial infarction survival. *World J Cardiol*. 2015;7:215–223.
93. Writing Group Members, Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Després J-P, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jiménez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB, American Heart Association Statistics Committee, Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation*. 2016;133:e38–360.
94. Ferro JM. Cardioembolic stroke: an update. *Lancet Neurol*. 2003;2:177–188.
95. Howard R, Trend P, Russell RW. Clinical features of ischemia in cerebral arterial border zones after periods of reduced cerebral blood flow. *Arch Neurol*. 1987;44:934–940.
96. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van 't Hof A, Widimsky P, Zahger D. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012;33:2569–2619.
97. Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S, Baumgartner H, Gaemperli O, Achenbach S, Agewall S, Badimon L, Baigent C, Bueno H, Bugiardini R, Carerj S, Casselman F, Cuisset T, Erol C, Fitzsimons D, Halle M, Hamm C, Hildick-Smith D, Huber K, Iliodromitis E, James S, Lewis BS, Lip GYH, Piepoli MF,

Richter D, Rosemann T, Sechtem U, Steg PG, Vrints C, Luis Zamorano J, Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016;37:267–315.

98. Sørensen R, Hansen ML, Abildstrom SZ, Hvelplund A, Andersson C, Jorgensen C, Madsen JK, Hansen PR, Kober L, Torp-Pedersen C, Gislason GH. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. *Lancet*. 2009;374:1967–1974.

99. Wimo A, Prince M. World Alzheimer report 2010. The global economic impact of dementia. http://www.alz.co.uk/research/files/ WorldAlzheimerReport2010.pdf (accessed March 8, 2017).

100. Matthews FE, Arthur A, Barnes LE, Bond J, Jagger C, Robinson L, Brayne C, Medical Research Council Cognitive Function and Ageing Collaboration. A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II. *Lancet*. 2013;382:1405–1412.

101. Brunnström H, Gustafson L, Passant U, Englund E. Prevalence of dementia subtypes: a 30-year retrospective survey of neuropathological reports. *Arch Gerontol Geriatr*. 2009;49:146–149.

102. O'Brien JT, Thomas A. Vascular dementia. *Lancet*. 2015;386:1698–1706.

103. Jorm AF, Jolley D. The incidence of dementia: a meta-analysis. *Neurology*. 1998;51:728–733.

104. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology*. 2005;64:277–281.

105. Seshadri S, Beiser A, Selhub J, Jacques PF, Rosenberg IH, D'Agostino RB, Wilson PWF, Wolf PA. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. *N Engl J Med*. 2002;346:476–483.

106. Scheltens P, Blennow K, Breteler MMB, de Strooper B, Frisoni GB, Salloway S, Van der Flier WM. Alzheimer's disease. *Lancet*. 2016;388:505–517.

107. Iemolo F, Duro G, Rizzo C, Castiglia L, Hachinski V, Caruso C. Pathophysiology of vascular dementia. *Immun Ageing*. 2009;6:13.

108. Corraini P, Henderson VW, Ording AG, Pedersen L, Horváth-Puhó E, Sørensen HT. Long-Term Risk of Dementia Among Survivors of Ischemic or Hemorrhagic Stroke. *Stroke*. 2017;48:180–186.

109. Henriksen DP, Rasmussen L, Hansen MR, Hallas J, Pottegård A. Comparison of the Five Danish Regions Regarding Demographic Characteristics, Healthcare Utilization, and Medication Use--A Descriptive Cross-Sectional Study. *PLoS One*. 2015;10:e0140197.

110. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014;29:541–549.

111. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449–490.

112. Helweg-Larsen K. The Danish Register of Causes of Death. *Scand J Public Health*. 2011;39:26–29.

113. Petersson F, Baadsgaard M, Thygesen LC. Danish registers on personal labour market affiliation. *Scand J Public Health*. 2011;39:95–98.

114. Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. *Scand J Public Health*. 2011;39:54–57.

115. Gaist D, Sørensen HT, Hallas J. The Danish prescription registries. *Dan Med Bull*. 1997;44:445–448.

116. Rothman KJ, Greenland S, Lash TL. Types of epidemiological studies. Modern Epidemiology. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.

117. Sundbøll J, Adelborg K, Munch T, Frøslev T, Sørensen HT, Bøtker HE, Schmidt M. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open*. 2016;6:e012832.

118. Bock C, Bukh JD, Vinberg M, Gether U, Kessing LV. Validity of the diagnosis of a single depressive episode in a case register. *Clin Pract Epidemiol Ment Health*. 2009;5:4.

119. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–383.

120. Adelborg K, Sundbøll J, Munch T, Frøslev T, Sørensen HT, Bøtker HE, Schmidt M. Positive predictive value of cardiac examination, procedure and surgery codes in the Danish National Patient Registry: a population-based validation study. *BMJ Open*. 2016;6:e012817.

121. Wilson EB. Probable Inference, the Law of Succession, and Statistical Inference. *J Am Stat Assoc*. 1927;22:209–212.

122. Greenland S, Rothman KJ. Fundamentals of epidemiologic data analysis. Modern Epidemiology. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.

123. Wolbers M, Koller MT, Stel VS, Schaer B, Jager KJ, Leffondré K, Heinze G. Competing risks analyses: objectives and approaches. *Eur Heart J*. 2014;35:2936–2941.

124. Greenland S, Rothman KJ, Lash TL. Measures of effect and measures of association. Modern Epidemiology. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.

125. Greenland S, Rothman KJ. Introduction to stratified analysis. Modern epidemiology. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.

126. Rothman KJ, Greenland S, Lash TL. Precision and statistics in epidemiologic studies. Modern Epidemiology. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.

127. Rothman KJ, Greenland S, Lash TL. Validity in epidemiologic studies. Modern Epidemiology. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.

128. Sørensen HT. Regional administrative health registries as a resource in clinical epidemiologyA study of op-

tions, strengths, limitations and data quality provided with examples of use. *Int J Risk Saf Med*. 1997;10:1–22.
129. Ehrenstein V, Petersen I, Smeeth L, Jick SS, Benchimol EI, Ludvigsson JF, Sørensen HT. Helping everyone do better: a call for validation studies of routinely recorded health data. *Clin Epidemiol*. 2016;8:49–51.
130. Rothman KJ. Six persistent research misconceptions. *J Gen Intern Med*. 2014;29:1060–1064.
131. Thombs BD, Bass EB, Ford DE, Stewart KJ, Tsilidis KK, Patel U, Fauerbach JA, Bush DE, Ziegelstein RC. Prevalence of depression in survivors of acute myocardial infarction. *J Gen Intern Med*. 2006;21:30–38.
132. Abbing-Karahagopian V, Huerta C, Souverein PC, de Abajo F, Leufkens HGM, Slattery J, Alvarez Y, Miret M, Gil M, Oliva B, Hesse U, Requena G, de Vries F, Rottenkolber M, Schmiedl S, Reynolds R, Schlienger RG, de Groot MCH, Klungel OH, Van Staa TP, van Dijk L, Egberts ACG, Gardarsdottir H, De Bruin ML. Antidepressant prescribing in five European countries: application of common definitions to assess the prevalence, clinical observations, and methodological implications. *Eur J Clin Pharmacol*. 2014;70:849–857.
133. Krarup LH, Boysen G, Janjua H, Prescott E, Truelsen T. Validity of stroke diagnoses in a National Register of Patients. *Neuroepidemiology*. 2007;28:150–154.
134. Wildenschild C, Mehnert F, Thomsen RW, Iversen HK, Vestergaard K, Ingeman A, Johnsen SP. Registration of acute stroke: validity in the Danish Stroke Registry and the Danish National Registry of Patients. *Clin Epidemiol*. 2014;6:27–36.
135. Phung TKT, Andersen BB, Høgh P, Kessing LV, Mortensen PB, Waldemar G. Validity of dementia diagnoses in the Danish hospital registers. *Dement Geriatr Cogn Disord*. 2007;24:220–228.
136. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes DR, Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ, ACC/AHA Task Force Members. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130:e344–426.
137. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, Rangarajan S, Islam S, Pais P, McQueen MJ, Mondo C, Damasceno A, Lopez-Jaramillo P, Hankey GJ, Dans AL, Yusoff K, Truelsen T, Diener H-C, Sacco RL, Ryglewicz D, Czlonkowska A, Weimar C, Wang X, Yusuf S, investigators OBOTI. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *The Lancet*. 2010;376:112–123.
138. Prescott E, Hippe M, Schnohr P, Hein HO, Vestbo J. Smoking and risk of myocardial infarction in women and men: longitudinal population study. *BMJ*. 1998;316:1043–1047.
139. Ott A, Slooter AJ, Hofman A, van Harskamp F, Witteman JC, Van Broeckhoven C, van Duijn CM, Breteler MM. Smoking and risk of dementia and Alzheimer's disease in a population-based cohort study: the Rotterdam Study. *The Lancet*. 1998;351:1840–1843.
140. Liu C-C, Liu C-C, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. *Nature Publishing Group*. 2013;9:106–118.
141. Rovio S, Kåreholt I, Helkala E-L, Viitanen M, Winblad B, Tuomilehto J, Soininen H, Nissinen A, Kivipelto M. Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. *Lancet Neurol*. 2005;4:705–711.