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DEPRESSION AND DELIRIUM IN CARDIAC SURGERY PATIENTS

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Depression and delirium in cardiac surgery patients

Thesis for Doctoral Degree (Ph.D.)

By

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Till min bror Anders

Popular science summary of the thesis

Waking up after heart surgery, a relief, or a nightmare?

"I was terrified! If I could, I would have jumped out of the window. I didn´t care about being on the seventh floor, I just had to escape".

Imagine waking up after heart surgery, most certainly a frightening experience. Also, imagine that you are not in the hospital as expected, instead, you have been kidnapped by witches who want to kill you and if you fall asleep, they will probably succeed. This sounds like a horror movie but is a story told by a patient suffering from delirium after heart surgery. Delirium is often described as an acute state of confusion and implies a severe disturbance in mental abilities that results in disorganized thinking and reduced awareness of the surroundings. Delirium after heart surgery is common, almost every other patient suffers from delirium at some point. Although the hallucinations are not always as dramatic as in this scene, they are often traumatic for the patient. In addition to hallucinating, a delirious state sets the patient at risk of receiving other complications, like injuring themselves falling, developing pressure ulcers, or catching an infection like pneumonia. There is no medical cure for delirium, it will wear off, hopefully without too many traumas or complications even though some patients experience impaired memory and affected cognition even after coming home from the hospital.

During my years working as a nurse in the intensive care unit I have met plenty of patients with delirium. It is a challenging condition for the patient as well as for the healthcare staff. My experiences caring for patients with delirium led to my research project. This thesis is based on a project regarding depression and delirium in patients suffering from severe heart disease that will need treatment with heart surgery. Depression and cardiovascular disease are common conditions all over the world and depression is more common among persons with cardiovascular disease than others. Previous studies have shown associations between preoperative depression and complications after heart surgery.

In this thesis, we have shown that persons with symptoms of depression before heart surgery are at greater risk of developing postoperative delirium compared to persons without preoperative depressive symptoms. This information is important as preventive measures are recommended for patients at risk for delirium. In two of our studies, symptoms of depression were self-evaluated before surgery. The patients filled out a questionnaire about symptoms of depression before they underwent heart surgery. Afterward, we evaluated if the patients had suffered from delirium by reading their medical journals from the hospital stay. We detected that the patients with self-evaluated high depression scores before surgery to a larger extent developed delirium than the patients not reporting preoperative symptoms of depression.

Depression is not just associated with the development of delirium. Depression increases the risk of dying after heart surgery. In one study in this thesis, we discovered that patients with self-evaluated high depressive symptoms scores before heart surgery, had lower survival rates at one, five, and eight years after heart surgery. Patients without symptoms of depression had similar observed survival as the expected survival of persons of the same age and sex in the general Swedish population.

To prevent or treat delirium, we need to detect the symptoms, which can be challenging. Some patients, like the one being afraid of the witches, can be easily identified. A person in that situation will probably try to get out of bed and might be fighting for his or her life. However, some patients are suffering in silence. They might have heavy hallucinations but are too tired and drowsy to move. Nurses and doctors easily miss delirium in these patients, which increases the risk of consequences for the patient. We need to use delirium assessment tools to detect this quiet form of delirium. In one of the studies in this thesis, I interviewed 12 patients who had a quiet form of delirium. They described existing in parallel worlds, having intense emotions of shame and fear. The patients described their delirium as more extensive and long-lasting than documented in the medical journals which indicates that healthcare staff only observe a small part of a very complex and disturbing condition.

Summary

This thesis concludes that preoperative depression is associated with an increased risk of delirium, as well as worse long-term survival after heart surgery. Screening for depression before heart surgery is one way to identify patients at risk for delirium and a worse prognosis after surgery. Postoperative delirium can be difficult to detect, therefore the use of assessment tools for delirium is important.

Populärvetenskaplig sammanfattning av avhandlingen

Att vakna upp efter hjärtoperation, en dröm eller mardröm?

"Jag var livrädd! Om jag kunnat hade jag hoppat ut genom fönstret. Jag brydde mig inte om att jag var på sjunde våningen, jag var bara tvungen att fly"

Föreställ dig att vakna upp efter en hjärtoperation, säkert en skrämmande upplevelse. Tänk dig också att du inte befinner dig på sjukhuset som förväntat, utan har blivit kidnappad av häxor som vill döda dig, och om du somnar så kommer de förmodligen att lyckas. Det här låter som en skräckfilm men är en historia som berättats av en patient som drabbats av postoperativt delirium efter en hjärtoperation. Delirium beskrivs ofta som ett akut förvirringstillstånd och innebär oorganiserat tänkande och minskad medvetenhet om omgivningen. Delirium efter hjärtoperation är vanligt, nästan varannan patient drabbas. Även om hallucinationerna inte alltid är lika dramatiska som i det här fallet, är de ofta traumatiska för patienten. Förutom att hallucinera riskerar patienten med delirium andra komplikationer, som att ramla och skada sig själv, utveckla trycksår eller drabbas av en infektion som lunginflammation. Det finns inget medicinskt botemedel mot delirium, det kommer att försvinna, förhoppningsvis utan alltför många trauman och komplikationer även om vissa patienter upplever försämrat minne och påverkad medvetenhet under en längre tid efter hjärtoperationen.

Under mina år som sjuksköterska på intensivvårdsavdelning har jag träffat många patienter med postoperativt delirium. Det är ett utmanande tillstånd för patienten såväl som för vårdpersonalen. Mina erfarenheter av att vårda patienter med delirium ledde mig till mitt forskningsprojekt där jag har studerat depression och delirium hos hjärtopererade patienter. Depression och hjärt-kärlsjukdom är vanliga tillstånd över hela världen, och många personer med hjärt-kärlsjukdom lider även av depression. Tidigare studier har visat att det finns ett samband mellan preoperativ depression och komplikationer efter hjärtoperation.

I den här avhandlingen visar vi att personer med symtom på depression före hjärtoperation löper större risk att drabbas av delirium efteråt. Informationen är viktig eftersom det är angeläget att före hjärtoperationen identifiera personer med ökad risk för delirium så att förebyggande åtgärder kan vidtas. I två av våra studier fick patienterna själva, via ett frågeformulär, utvärdera depression före operationen. Efteråt bedömde vi om de fått delirium genom att läsa deras journaler från vistelsen på sjukhuset. Vi upptäckte att de patienter som självutvärderade höga depressionspoäng före operationen i större utsträckning utvecklade delirium än de patienter som inte rapporterade symtom på depression.

Depression är inte bara förknippat med utvecklingen av delirium. Depression försämrar även prognosen efter hjärtoperation. En studie i denna avhandling visade att patienter med depressionssymtom före hjärtoperation hade sämre överlevnad ett, fem och åtta år efter hjärtoperation jämfört med den förväntade överlevnaden i en den allmänna befolkningen (matchad för ålder och kön). Hos personer som genomgått hjärtoperation utan symtom på depression var det ingen större skillnad i den förväntade överlevnaden.

För att identifiera delirium hos patienter som genomgått hjärtoperation behöver vi upptäcka symtomen, vilket kan vara utmanande. Vissa patienter, som hen som var rädd för häxorna, har tydliga symtom och är lätt att upptäcka. En patient med sådana symtom försöker förmodligen ta sig ur sängen och kämpar tydligt för sitt liv. Men vissa patienter lider i det tysta. De kan ha kraftiga hallucinationer men är för trötta och dåsiga för att röra sig. Sjuksköterskor och läkare missar lätt delirium hos dessa patienter, vilket ökar risken för allvarliga konsekvenser för patienten. För att upptäcka denna tysta form av delirium måste vi använda bedömningsinstrument. I en av studierna i avhandlingen intervjuade jag 12 patienter som hade en tyst form av delirium. De beskrev hur de uppfattade att de existerade i parallella världar, och upplevde intensiva känslor av skam och rädsla. Patienterna beskrev sitt delirium som mer omfattande och långvarigt än vad som dokumenterats i deras journaler vilket indikerar att vårdpersonal endast observerar en liten del av ett mycket komplext och allvarligt tillstånd.

Sammanfattning

I den här avhandlingen drar vi slutsatsen att preoperativ depression är förknippad med ökad risk för postoperativt delirium, samt försämrar prognosen efter hjärtoperation. Att depressionsscreena alla patienter före hjärtoperation är ett sätt att upptäcka patienter med högre risk för delirium och sämre prognos. Patienter med tyst delirium beskrev intensiva hallucinationer och starka känslor. Omfattningen av deras upplevelser uppmärksammades inte av vårdpersonalen, vilket visar vikten av att använda bedömningsinstrument för postoperativt delirium för att upptäcka alla typer av delirium.

Abstract

Depression is common in persons with cardiac disease, and there is a well-known association between depression and increased cardiovascular morbidity and mortality. Preoperative depression has been associated with postoperative delirium (POD) after general surgery but the association between depression and POD in persons undergoing cardiac surgery is sparsely studied. Postoperative delirium affects a large proportion of patients undergoing cardiac surgery. Delirium phenotypes are commonly divided into hyper- and hypoactive, where hypoactive symptoms (reduced motor activity and withdrawal) often are overlooked due to their discreet character. To our knowledge, there are no studies describing patients' experiences of hypoactive delirium after cardiac surgery. Although the association between depression and mortality after coronary artery bypass grafting has been confirmed, the association between preoperative depression and long-term survival after cardiac surgery is sparsely studied.

The overall aim of this thesis was to contribute to the understanding of the association between depression and delirium, as well as depression and mortality in patients undergoing cardiac surgery.

Study I was a systematic literature review and meta-analysis including cohort studies reporting odds ratios (ORs) and 95% confidence intervals (CIs) for POD after cardiac surgery in patients with preoperative depression compared to patients without depression. ORs and 95% CIs for POD were calculated using random-effects models. Seven studies were included with a combined study population of 2066 patients. The pooled prevalence of POD was 26% and preoperative depression was present in 9% of the total study population. All studies showed a positive association between preoperative depression and POD. Patients with depression had a pooled OR of 2.31 (95% CI 1.37–3.90) for POD.

Study II was a population-based cohort study including 1120 persons undergoing cardiac surgery from 2013–2016. Preoperative depression was defined by the Patient Health Questionnaire-9, and baseline characteristics were contained in the Swedish Cardiac Surgery Registry. POD was evaluated by assessing medical records. The association between preoperative depression and POD was determined through multivariable logistic regression analysis. A total of 162 patients (14,5%) reported depressive symptoms preoperatively. The incidence of POD was 26%. The overall adjusted odds of delirium were 2.19 times higher in patients with depressive symptoms compared to controls (95% CI 1.43–3.34).

Study III was a qualitative descriptive semi-structured interview study aiming to describe cardiac surgery patients' experiences of hypoactive delirium. Twelve cardiac surgery patients with hypoactive symptoms of delirium were purposefully selected. The data were analyzed by qualitative content analysis with an inductive, latent approach. Two themes based on eight sub-themes emerged: *"Dream or reality in parallel worlds"* included disturbing experiences of existing in parallel realities with cognitive effects, residual nightmares, and illusions that occasionally persisted after hospital discharge. *"Managing the state of hypoactive delirium"* included experiences of intellectually dealing with hypoactive delirium with assumptions of causes and cures, and through interactions like communicating with others. The delirium experienced by the participants was

considerably more extensive than what had been documented in their medical journals, an indication that hypoactive delirium is overlooked.

Study IV was a population-based cohort study investigating the same study cohort as in Study II. The vital status at end of the study was collected from the Swedish Cardiac Surgery Registry on December 15, 2022. During a mean follow-up of 7.2 years (maximum 9.2 years), there were 36 deaths in 1129 person-years (PYs) in the depressed group, compared to 160 deaths in 6889 PYs in the non-depressed group. In the adjusted analysis, self-reported depressive symptoms were associated with worse long-term survival (HR=1.66; 95% CI, 1.09-2.54) compared with no reported depressive symptoms. The absolute survival differences (% and 95% CI) between the non-depressed and the depressed patients were -1.9 (-3.9–0.19), -5.7 (-11– -0.01), and -9.7 (-19– -0.4) after one, five, and eight years, respectively.

In conclusion, depression is a significant, independent risk factor for POD and worse long-term survival after cardiac surgery. Depression screening is important to identify patients at risk, and delirium assessment tools should be used to detect all kinds of POD.

Keywords

Depression, Postoperative delirium, Hypoactive delirium, Screening, Patient Health Questionnaire, Cardiac surgery, Cardiopulmonary bypass, Mortality, Meta-analysis, Cohort study, Qualitative content analysis, Qualitative study

List of scientific papers

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals as indicated below.

I. **Anna Falk**, Jessica Kåhlin, Carolin Nymark, Rebecka Hultgren, Malin Stenman. Depression as a predictor of postoperative delirium after cardiac surgery: a systematic review and meta-analysis.
Interactive CardioVascular and Thoracic Surgery 32 (2021) 371–379.

II. **Anna Falk**, Jessica Kåhlin, Carolin Nymark, Rebecka Hultgren, Malin Stenman. Depression is associated with delirium after cardiac surgery—a population-based cohort study.
Interactive CardioVascular and Thoracic Surgery 35 (2) (2022).

III. **Anna Falk**, Malin Stenman, Jessica Kåhlin, Rebecka Hultgren, Carolin Nymark. Suffering in silence – cardiac surgery patients recalling hypoactive delirium. A qualitative descriptive study.
Manuscript submitted.

IV. **Anna Falk**, Ulrik Sartipy, Malin Stenman.
Self-reported preoperative depressive symptoms and survival after cardiac surgery.
Manuscript submitted.

Papers not included in the thesis

V. **Anna Falk**, Mats Eriksson, Malin Stenman.
Depression and/or anxiety scoring instruments used as screening tools for predicting postoperative delirium after cardiac surgery: a pilot study.
Intensive and Critical Care Nursing. Vol 59, August (2020).

VI. **Anna Falk**, Malin Stenman.
Editorial: Delirium assessment – Often ignored, always important
Intensive and Critical Care Nursing. Vol 62, February (2021).

Contents

List of abbreviations

AHA	American Heart Association
AF	Atrial fibrillation
BCE	Before the common/current era
BIS	Bispectral Index
BMI	Body Mass Index
CRP	C-reactive protein
CPB	Cardiopulmonary Bypass
CVD	Cardiovascular disease
CI	Confidence Interval
CAM	Confusion Assessment Method
CABG	Coronary Artery Bypass Grafting
CAD	Coronary artery disease
COPD	Chronic obstructive pulmonary disease
DM	Diabetes mellitus
DSM-V	Diagnostic and Statistical Manual of Mental Disorders fifth edition
EEG	Electroencephalogram
eGFR	Estimated glomerular filtration rate
GCS	Glasgow Coma Scale
HR	Hazard ratios
ICU	Intensive Care Unit
IL-6	Interleukin-6
ICD	International Classification of Diseases
LVEF	Left ventricular ejection fraction
LOS	Length of hospital stay
MDD	Major depressive disorder
Nu-DESC	Nursing Delirium Screening Scale
OR	Odds Ratios
PHQ	Patient Health Questionnaire
PVD	Peripheral vascular disease
PYs	Person-years
POCD	Postoperative cognitive dysfunction
POD	Postoperative delirium
RASS	Richmond Agitation-Sedation Scale
SD	Standard Deviation
ThICU	Thoracic Intensive Care Unit
ThPACU	Thoracic Post-anesthesia Care Unit

1 Introduction and background

Glenn N. Levine (2019) and the Mind-Heart-Body connection:

The time has come for us as clinicians to take heed of the interconnected, interdependent being of the heart and body with the mind, a relationship that can be termed the Mind-Heart-Body connection. (p. 1363) (1).

Figure 1. Coma by Zara Slattery. Publisher, Myriad Editions 2021

Depression and delirium have been observed since ancient times. Descriptions of depression were found in early Egyptian papyrus scrolls (2) and delirium was described by Hippocrates already 500 years BCE (3). Cardiovascular disease (CVD) is often considered a diagnosis for the modern world, but atherosclerosis in the aorta and in coronary arteries has been detected in 4000-year-old mummies from different regions of the world (4).

Today, depression and CVD are two of the most prevalent and costly diseases worldwide (5). It has been shown that depression is related to several cardiovascular comorbidities such as stroke and myocardial infarction (6). Furthermore, symptoms of depression are often seen in persons with CVD, and depression has been associated with adverse outcomes such as prolonged length of hospital stay (LOS) and mortality after coronary artery bypass grafting (CABG) (7, 8).

Many patients suffer from delirium after cardiac surgery. Delirium can be defined as an acute brain dysfunction and is often a challenging condition for the patient, as well as for healthcare professionals. Delirium is characterized by a sudden change in mental function with disturbed cognition and attention, and hallucinations and delusions are common (6). Today, there is no effective medical treatment for delirium, and preventive measures are recommended for patients at risk (9). Obtaining a further understanding of

risk factors and predictors of delirium in cardiac surgery patients is important to identify risk groups and offer preventive measures.

Even though depression, delirium, and CVD have affected humans for thousands of years, obscurities about the conditions still prevail. It has been stated that depression is a significant independent risk factor for worse prognosis in patients with CVD and that it is important to detect depression in patients undergoing CABG (10, 11). This conclusion, along with the clinical challenges of delirium in all cardiac surgery patients (not only CABG patients) generated considerations in our research group. The association between depression and POD in patients undergoing cardiac surgery is sparsely studied as well as the effect of depression on long-term mortality after cardiac surgery (12). Depression has been associated with increased postoperative mortality in patients undergoing CABG and increased perioperative mortality after cardiac surgery (8, 13). However, few studies have investigated the association between preoperative depression and long-term survival after cardiac surgery.

This thesis aims to contribute to the understanding of the association between depression and delirium, as well as depression and mortality, in patients undergoing cardiac surgery.

1.1 Depression

1.1.1 Definition, prevalence and treatment

Depression is a mental disorder defined by negatively affected emotions, sleep disturbances, affected appetite, feelings of guilt, and/or thoughts of death or dying. Major depressive disorder (MDD) can be diagnosed using the Diagnostic and Statistical Manual of Mental Disorders fifth edition criteria (DSM-V) (6) (Table 1).

Depression is common worldwide, with a 12-month prevalence of MDD of approximately 6% (14). The prevalence is similar in high-income (5%), low-income and middle-income countries (5-9%) (14). The lifetime risk of depression has been reported to be 6-21% (14, 15). Depression is more common in women, who are twice as likely to get depressed in life compared to men (16).

The purpose of depression treatment is to decrease symptoms and recover to the former functional level. Different kinds of measures are suggested depending on the severity of depression symptoms; advice on lifestyle changes, pharmacological antidepressant treatment, and non-pharmacological treatments such as electroconvulsive therapy and psychotherapy (17, 18).

1.1.2 Risk factors, pathogenesis, and lifestyle aspects

Depression can be caused by an interaction between external factors such as stress and grief, and a person's genetic vulnerability to depression (19). Some of the risk factors for MDD are low socioeconomic status, chronic disease, alcohol dependence, childhood trauma, female sex, older age, and a personal or family history of depression (19). Individuals suffering from depression show elevated levels of specific pro-inflammatory cytokines, and acute phase proteins in the peripheral blood, central nervous system, and cerebrospinal fluid (20, 21). However, the association between a pro-inflammatory state and the development of depression remains unelucidated.

1.1.3 Depression screening

To assess psychological health status depression screening is recommended for patients with, or at risk for CVD (22, 23). Depression screening implies a standard set of questions that the patient answers to help diagnose depression and assess its severity. Several well-known psychometric evaluated screening instruments are available to assess depression. To assess depression in persons with CVD, the American Heart Association (AHA) has recommended the Patient Health Questionnaire (PHQ) (23, 24). The PHQ is a psychometric evaluated depression diagnostic screening instrument based on the diagnostic criteria from the DSM-V (6).

Table 1. DSM-V Criteria for Major Depressive Disorder (MDD)

≥5 symptoms during a two-week period that is a change from previous functioning; the symptoms of depressed mood and/or loss of interest/pleasure must be present.

Depressed mood	Most of the day, nearly every day (subjective or observed by others)
Loss of interest/pleasure	Markedly reduced interest/pleasure in all/almost all activities most of the day, nearly every day (subjective or observed by others)
Weight loss or gain	Significant weight loss or gain, or decreased or increased appetite nearly every day
Insomnia or hypersomnia	Nearly every day
Psychomotor agitation or retardation	Nearly every day and observable by others
Fatigue	Or loss of energy, nearly every day
Feeling worthless or excessive/inappropriate guilt	Nearly every day; guilt may be delusional
Decreased concentration	Nearly every day; indecisiveness (subjective or observed by others)
Thoughts of death/suicide	Recurrent thoughts of death, recurrent suicidal ideation, suicide attempt, or a specific plan for suicide

Additional required criteria (Must have all 4, plus ≥5 depressive symptoms above)

1. Symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
2. The episode is not attributable to the physiological effects of a substance or another medical condition.
3. The episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.
4. No history of a manic or hypomanic episode.

The exclusion does not apply if all manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition.

1.1.4 Depression and cardiac disease

Psychological well-being has been found to affect cardiovascular health (22). Depression is more common in persons with CVD compared to the general population (25). The prevalence of depression in persons with CVD ranges between 15-45% (25-27). Depressed persons with CVD have a 2–2.5-fold increased risk of mortality, recurrent

cardiac events, rehospitalization, poorer self-reported quality of life, and deprived physical functioning (25, 28). Moreover, there is an established association between depression and coronary artery disease (CAD) (25, 29), and depression is a significant risk factor for increased mortality after CABG (8, 10).

Possible behavioral mechanisms associated with depression and CAD have been acknowledged, for example, lifestyle factors like eating and drinking habits, inactivity and smoking can affect both psychological and cardiovascular health (30, 31). Alterations in the autonomic nervous system and hypothalamic pituitary adrenal axis functioning, platelet activation, and inflammation with interleukin-6 (IL-6) and C-reactive protein (CRP) are important components of systematic inflammation that may contribute to CVD and that also covariate in depression (27, 32).

The importance of psychological well-being for patients with or at risk for CVD has been emphasized in scientific statements from the AHA (22, 23). The AHA recommends interventions to enhance psychological health as it may affect cardiovascular outcomes (22). Depression in persons with cardiac disease can easily be missed since several symptoms of depression are similar to symptoms of cardiac disease, such as loss of energy, poor appetite, and weight changes (28).

1.2 Cardiac surgery

Cardiac surgery defines surgical procedures involving the heart or the vessels transporting blood to and from the heart. The most frequent cardiac surgery procedure in Sweden is CABG, which is a common treatment for ischemic coronary heart disease, followed by aortic valve surgery to treat aortic stenosis or aortic insufficiency (33). Cardiac surgery is usually performed with cardiopulmonary bypass (CPB), a procedure where a heart-lung machine replaces functions of the heart and lungs during surgery. To provide a blood-free and motionless surgical area, a cross-clamp is placed across the ascending aorta preventing blood flow through the heart, and infusion of cardioplegia (a potassium-containing solution that is given into the coronary arteries of the heart when the aorta is clamped) stops the heart from beating (34). Cardiac surgery and CPB generate a systemic inflammatory response and cause disturbances of the inflammatory and fibrinolytic system, which can cause vasoplegia and coagulopathy (35).

In 2021, 5452 cardiac surgery procedures were performed in Sweden and the majority of cardiac surgery patients in Sweden are male (about 75%) (33). Female cardiac surgery patients have worse outcomes than male patients, such as in-hospital mortality (36, 37) and long-term mortality (37, 38). Women often appear later in the disease having more comorbidities and getting less aggressive care (39, 40), all being possible explanations for the worse outcomes.

1.2.1 Peri- and postoperative care

The standard procedure for cardiac surgery is CPB and general anesthesia. During CPB the ventilator is usually switched off, therefore anesthetic drugs cannot be inhaled. Volatile anesthesia is possible if a gasifier is connected to the oxygenator in the heart-lung machine. Alternatively, total intravenous anesthesia is given during CPB (41). In the department where the studies in this thesis were conducted, general anesthesia was induced with Propofol and Fentanyl along with a muscle relaxant and maintained with volatile anesthesia (Sevoflurane), except during CPB, when Propofol was used. For postoperative sedation, Propofol was infused until appropriate for tracheal extubation. After surgery, the patients were transported intubated to the thoracic intensive care unit

(ThICU) and usually extubated within a couple of hours. After spending the first night at the ThICU most patients were transferred to the cardiac surgery ward, where they stayed for four to five additional days.

1.2.2 Cerebral complications

Cerebral complications after cardiac surgery can be classified as stroke and postoperative neurocognitive disorders including POD and postoperative cognitive dysfunction (POCD) (42, 43). The causes of cerebral complications are multifactorial and complex of which hypoperfusion, cerebral embolism, and inflammation associated with the use of CPB are important factors (43).

Stroke is a devastating complication of cardiac surgery, affecting roughly one percent of patients undergoing CABG (44). Stroke can occur intraoperatively, in the early postoperative phase, as well as later and can be caused by thromboembolic events such as atrial fibrillation or by embolism from the atherosclerotic aorta, air embolism, or by cerebral hypoperfusion (45).

POCD is a prolonged state of cognitive impairment that affects cognitive skills such as perception, information processing and memory after a surgical procedure (42, 46). It is usually transient but can occur for a few weeks to several months after surgery (47). POCD is common after cardiac surgery. Risk factors for POCD are high age, impaired preoperative cognitive function, depression, CPB, and use of anesthetics (46).

1.3 Delirium

Delirium is often called a state of acute confusion. It is a brain dysfunction characterized by a sudden change in mental function with disturbed cognition and attention, that cannot be explained by a severe reduction in the level of consciousness or a preceding neurocognitive disorder (6). Psychotic symptoms with hallucinations and delusions are common (48). Delirium can cause agitation and restlessness as well as drowsiness and inactivity, or a combination of both (49). The delirious patient is unable to focus and sustain or shift attention. Impaired memory, perceptual disturbance, and disorientation are examples of cognitive disturbances. Furthermore, the alterations in attention and cognition are sudden with symptoms fluctuating during the day which distinguishes delirium from dementia, having a more gradual onset (6, 50) (Table 2).

Table 2. DSM-V Criteria for Delirium

Diagnostic and statistical manual of mental disorders (DSM-5) criteria for delirium	
A	A disturbance in attention and awareness (reduced orientation to the environment).
B	The disturbance develops over a short period of time and is a change from baseline attention and awareness that tends to fluctuate in severity during the day.
C	An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception).
D	The disturbances in Criteria A and C are not explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma.
E	There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal, exposure to a toxin, or is due to multiple etiologies.

Based on the patient's psychomotor behavior, delirium phenotypes are often divided into hyper-, hypoactive, or mixed forms. Hyperactive delirium is characterized by increased motor activity, such as restlessness, vigilance, and agitation. The hypoactive, or quiet form of delirium manifests in more discreet symptoms such as reduced motor activity, drowsiness, and lethargy, symptoms that may be mistaken for depression (51). Mixed delirium refers to a disorder with features of both hyper- and hypoactive delirium with symptoms often fluctuating during the day (6). Hypoactive delirium is a common delirium phenotype among the elderly (50, 52) that often goes unrecognized due to healthcare professionals´ difficulty in identifying the syndrome (53). Subsyndromal delirium is a milder state of delirium with one or more diagnostic features of delirium (reduced ability to concentrate, agitation, irritability, drowsiness, hypersensitivity to stimuli or hallucinations) but not meeting all the DSM-V criteria for diagnostic threshold (6, 54, 55).

The time point at which delirium is diagnosed is of interest when classifying delirium. In emergency delirium, psychomotor agitation occurs as the patient emerges from a general anesthetic and lingers for only a short period. Patients that meet delirium diagnosis criteria after surgery are suffering from POD (50). If delirium occurs in the intensive care unit (ICU) it is called ICU delirium. Usually, symptoms of delirium disappear after a couple of days (56, 57), but delirium may persist for weeks or months, called prolonged or persistent delirium (58).

There are few studies on sex and gender aspects of delirium. Men have been reported to be particularly prone to developing delirium (57, 59). However, women with delirium might be underdiagnosed (60) since there are reports on differences in delirium phenotypes between women and men, describing men as having more symptoms of hyperactive delirium symptoms, such as agitation hallucinations, impulsiveness and combativeness compared to women (61, 62). Furthermore, men are more likely to be

prescribed antipsychotic medications to treat hyperactive symptoms of delirium than women (62).

The best way to diagnose delirium is through assessment by a psychiatrist using the DSM-V criteria (6, 63). However, assessment by a psychiatrist is not feasible in most hospital settings, therefor several delirium assessment tools have been developed for bedside diagnosis. Early detection of delirium may result in a better outcome in critically ill patients (64). Structured delirium screening (described in the materials and methods section) is recommended in guidelines to be initiated already in the recovery room (65) and critically ill patients should be regularly assessed for delirium using a valid tool (66). Furthermore, delirium screening should be performed several times a day due to the fluctuation of symptoms (65, 67, 68). Despite the importance of a structured evaluation of delirium and the plethora of delirium assessment instruments, compliance among healthcare professionals is often inadequate and delirium is frequently overlooked (69).

1.3.1 Pathogenesis, risk factors and triggers

The pathogenesis of delirium is still poorly understood but it has been hypothesized that perioperative neurocognitive disorders, including POD, correlate and begin with neuroinflammation triggered by a systemic inflammatory activation (70, 71). Delirium is a complex syndrome with several risk factors where high age is crucial (72). Other preceding risk factors are frailty (73), preoperative cognitive impairment (74, 75), a history of delirium (76), depression, substance abuse (12, 77), diabetes mellitus, pre-operative atrial fibrillation (AF), (75, 77) and a history of stroke (76). Trigger factors for delirium are surgery, hospitalization, acute illness, hemodynamic instability, bleeding and blood transfusion (78), infection, pain (79), and medications (benzodiazepines, steroids) (75, 78). Post-operative triggers include immobility, poor quality of sleep, electrolyte imbalance, prolonged ICU stay, and prolonged mechanical ventilation (43, 80-83).

1.3.2 Patients´ experiences

Patients have described delirium as something that affects their perception with disorientation, unreal experiences, and hallucinations (84). Delirium is furthermore described as generating strong emotions like fear, insecurity, and guilt. Emotions such as feeling secure and relieved have also been described by patients (85). Delirium affects interaction with others and interactions are often perceived as challenging (86). Many patients have described being misunderstood and feeling suspicious. Patients often try to hide their delirium due to a lack of trust or due to being afraid and ashamed of their behavior (87, 88).

Figure 2. Coma By Zara Slattery. Published by Myriad Editions 2021

1.3.3 Consequences of delirium

In addition to the suffering delirium can cause affected patients, the syndrome has severe short- and long-term consequences. Patients with delirium are prone to be mechanically ventilated for a longer period (89), which is a risk for further complications such as ventilator-associated pneumonia (90). Delirious patients are also more likely to remove tubes and catheters and are at risk of developing pressure ulcers, nosocomial infections, and malnutrition, and they have longer ICU and hospital stays as well as increased in-hospital mortality (56, 72, 91). Moreover, patients who develop delirium in the ICU are more likely to later on in life suffer from psychiatric symptoms such as depression or post-traumatic stress (92, 93), and have an increased risk of developing dementia (94).

1.3.4 Delirium in cardiac surgery patients

Delirium is common in cardiac surgery patients (72, 95). The prevalence of delirium after cardiac surgery depends on different factors, such as age and comorbidity status in the studied cohort (91, 96). Furthermore, to get a reasonable opinion about delirium prevalence, correct delirium assessment is important (50, 97). Delirium prevalence in cardiac surgery patients has been reported to be 11-55% (72, 95). An important factor distinguishing cardiac surgery from general surgery is CPB. The exposure and duration of CPB (75) as well as the aortic cross-clamp may increase the risk for POD in cardiac surgery patients (72, 89). Moreover, the use of CPB causes a systemic inflammatory response, leading to dysregulation of cytokines and interleukins (34). Besides the inflammatory and circulatory effects, CPB and aortic cross-clamping make the monitoring of anesthetic depth difficult since clinical signs, such as heart rate, blood pressure, and end-tidal anesthetic concentration often are absent or unreliable (34).

An association between preoperative depression and POD has been hypothesized both in general surgery- and cardiac surgery patients (12, 98). As previously mentioned, depression is common in patients with CVD (26). In addition, many cardiac surgery patients have severe comorbidity burdens, making them particularly exposed to the risk of delirium (51).

1.3.5 Prevention and management

About 30-40% of delirium cases are estimated to be able to prevent through multicomponent interventions (99). Examples of nursing activities to prevent and treat symptoms of POD are reorienting the patient, providing good prerequisites for sleeping, maintaining nutrition and hydration, removing catheters and chest tubes as early as possible, offering therapeutic activities and cognitive stimulation, encouraging family engagement and focusing on early mobilization after surgery, the last one being the most important delirium prevention action (65, 100-102). Delays in preventive caring activities can prolong POD, resulting in delayed functional and cognitive recovery and higher morbidity and mortality (102). The ABCDEF (Assessment and management of pain; Both daily, regular spontaneous awakening trials and spontaneous breathing trials to limit analgesia and sedation needs; Choice of analgesia and sedation; Delirium detection and management; Early mobility and exercise; Family engagement and empowerment) care bundle for delirium consists of multi-professional and evidence-based interventions for the prevention and management of delirium and is recommended in ICU settings (78). The bundles have expanded after the Covid-19 pandemic with three additional parts incorporating humanitarian care (Gaining insight into patient needs, habits, and lifestyle; Holistic and personalized care; and reconsidering the ICU architectural design to create an environment in which patients feel safe and

comfortable) (103). These interventions are in line with person-centered care, an individualized approach to enhance patient outcomes (104, 105).

There are studies suggesting that deep levels of anesthesia should be avoided in order to prevent POD (106). Burst suppression is a state of deep brain inactivation that presents a pattern with high voltage activity (burst) and flatline (suppression) on an electroencephalogram (EEG) (107). The Bispectral Index (BIS) monitor uses EEG recording and is used as a predictor of the level of anesthesia. A BIS value between zero and 100 is displayed based on the EEG signal, where zero represents the absence of brain activity and <20 indicates burst suppression. BIS values between 40 - 60 represent adequate general anesthesia for surgery (108). Anesthesia with BIS guidance has been suggested to result in less anesthetic exposure and may help to prevent POD (106, 107, 109-111).

Although a recent meta-analysis concluded that dexmedetomidine may reduce the incidence of POD compared with propofol after cardiac surgery (112) and some medications can help reduce delirium symptoms like agitation (113), there is no convincing evidence displaying medication-based strategies (antipsychotics or sedatives) preventing or treating delirium (114). Therefore, the best way to treat delirium is so far by non-medical prevention strategies (66, 100) and multidisciplinary nonpharmacological interventions to prevent POD in high-risk patients are recommended (66, 67).

1.4 Rationale

The Mind-Heart-Body connection has been recognized during the recent decade (1, 22, 23) but clinical challenges and knowledge gaps remain. It is well known that depression is common in patients with CVD and that depression entails risks of worse outcomes such as perioperative complications and increased mortality after CABG (10, 23, 115). The effect of preoperative depression on long term-survival after cardiac surgery is however unelucidated.

Postoperative delirium is a common and challenging condition after cardiac surgery that often goes unrecognized, especially the hypoactive phenotype that can be mistaken for depression (60, 116). Little is known about cardiac surgery patients' experiences of hypoactive delirium. Preoperative depression has been associated with POD after general surgery (117, 118), the association between preoperative depression and POD after cardiac surgery is however sparsely studied. POD can often be prevented, and preventive measures are recommended for patients at risk (67). Increased knowledge of patients at risk for POD is therefore needed.

2 Aims of the thesis

The overall aim of this thesis was to contribute to the understanding of the association between depression and delirium, as well as depression and mortality in patients undergoing cardiac surgery.

The specific aims were:

- **I.** To analyze the association between depression and postoperative delirium in patients undergoing cardiac surgery through a systematic review and meta-analysis of cohort studies
- **II.** To study the association between preoperative depression and postoperative delirium in patients undergoing cardiac surgery
- **III.** To describe cardiac surgery patients' experiences of hypoactive delirium
- **IV.** To study the association between self-reported preoperative depressive symptoms and long-term survival in patients undergoing cardiac surgery

Overview of Conceptual framework and research questions

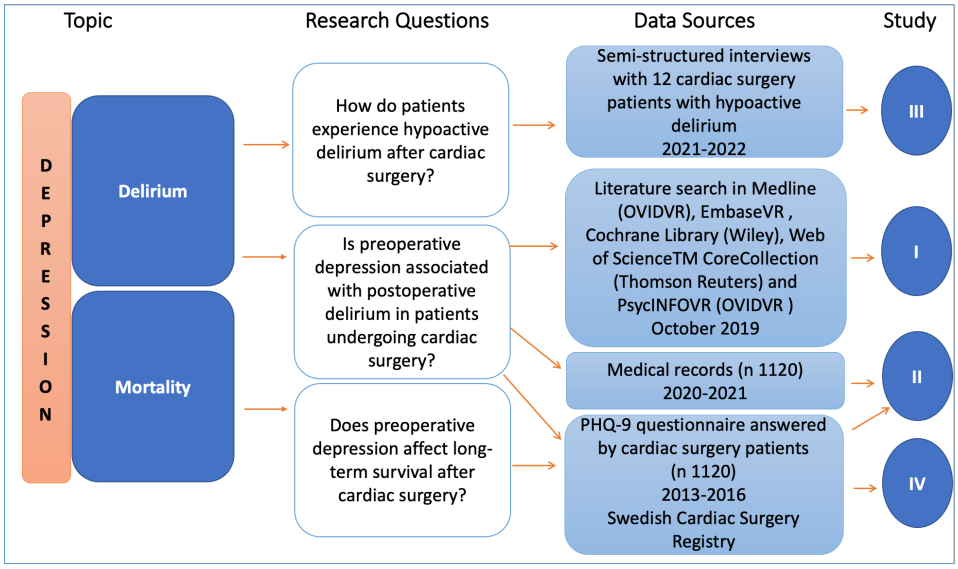

Figure 3. Overview of Conceptual framework and research questions

3 Materials and methods

3.1 Ethical considerations

Study I was a literature review and meta-analysis, and no ethical permit was applied for. The data was collected from peer-reviewed papers with data from clinical trials in which informed consent had been contained.

Study II-IV were approved by the Swedish Ethical Review Authority and performed by the principles outlined in the Declaration of Helsinki (119).

3.2 Definitions

3.2.1 Definition of cardiac surgery

In Study II, III and IV cardiac surgery was defined as thoracic aortic surgery, isolated valve surgery, isolated CABG, and combined procedures via median sternotomy, hemi-sternotomy (minimally invasive), or via thoracotomy.

3.2.2 Definition and assessment of depression

The PHQ-9 is a depression questionnaire consisting of nine questions, with answers presented on a four-point Likert scale from zero to three points (24). A PHQ-9 score ≥10 has been considered to have a sensitivity of 88% and a specificity of 88% for MDD (120) (Table 3).

In Study I depression was assessed through self-assessment or international classification of diseases (ICD) diagnoses (121). In Study II and Study IV preoperative depression was assessed through depression screening using the PHQ-9.

Table 3. Patient Health Questionnaire - 9 (PHQ-9)

Patient Health Questionnaire – 9 (PHQ-9)				
Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3
For coding				
0 + _____ + _____ + _____ =Total Score:				
If you have experienced any of these symptoms, how difficult were they?				
Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult	

3.2.3 Definition and assessment of delirium

The Confusion Assessment Method (CAM) (122) is an instrument for detecting delirium in clinical settings. It includes four features based on the DSM criteria (6) that characterize delirium: Acute onset and fluctuating course, inattention, disorganized thinking, and altered level of consciousness. When the onset is acute or has a fluctuating course and the feature inattention is present combined with either disorganized thinking or an altered level of consciousness, a diagnosis of delirium is suggested (122). The CAM-ICU is a development of the CAM for use in mechanically ventilated patients in the ICU. Both the CAM and the CAM-ICU are psychometric-evaluated instruments with high sensitivity, high specificity, and high interrater reliability (97, 122) (Table 4).

Table 4. Confusion Assessment Method for the ICU (CAM-ICU)

Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)			
Feature 1 **Acute onset or a fluctuating course**	**Feature 2** **Inattention**	**Feature 3** **Altered levels of consciousness**	**Feature 4** **Disorganized thinking**
Is the patient different than their baseline mental status? OR Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation scale (i.e., RASS, GCS) or previous delirium assessment?	Letters attention test: The patient is instructed to squeeze the caregiver's hand when they hear the letter A: S-A-V-E-A-H-A-A-R-T or C-A-S-A-B-L-A-N-C-A Errors are counted when the patient fails to squeeze on the letter "A" or when the patient squeezes on any letter other than "A."	Present if the patient is anything other than alert and calm (anything but RASS score zero)	Commands or Yes/No questions Example commands: "Hold up this many fingers" (Hold 2 fingers in front of patient) "Now do the same thing with the other hand." Example question: Will a stone float on water? Errors are counted if the patient is unable to complete the entire command or incorrectly answers a question.
Feature 1 is positive when the answer to either question is yes	Feature 2 is positive when number of errors are >2	Feature 3 is positive when RASS is anything other than zero	Feature 4 is positive when the combined number of errors is >1
CAM-ICU is positive if the patient expresses feature 1 and 2, plus either feature 3 or 4			

Abbreviations: RASS = Richmond Agitation Sedation Scale, GCS = Glasgow Coma Scale

The Nursing Delirium Screening Scale (Nu-DESC) is a delirium assessment instrument, commonly used in hospital wards and ICUs. The Nu-DESC helps bedside identification of delirium by evaluating the patient according to five features representative of delirium. The instrument has been psychometric evaluated and has shown high sensitivity and specificity (123) and is being used in several cardiothoracic departments in Sweden (Table 5).

Table 5. Nursing Delirium Screening Scale (Nu-DESC)

Nursing Delirium Screening Scale (Nu-DESC) **Features and descriptions**	**Symptoms rating** **0 = absent** **1 = mild** **2 = severe**		
Symptom	07-15	15-21	21-07
1. Disorientation			
2. Inappropriate behavior			
3. Inappropriate communication			
4. Illusions/hallucinations			
5. Psychomotor retardation			
Positive Nu-DESC is score ≥2, the maximum total score is 10 Total score:			

In this thesis, delirium is defined according to the DSM-V as inattention, disorganized thinking, and an altered level of consciousness with acute onset and fluctuating course (6). In Study I delirium was assessed in various ways in the included studies, i.e., using different delirium assessment instruments or through psychiatrists evaluating delirium using the DSM criteria. In Study II and Study III delirium was assessed by reading medical journals and searching for notes about delirium, ICD-codes, and CAM-ICU and Nu-DESC results.

3.2.4 Survival

In Study IV, the date of death was ascertained by using the continuously updated Swedish Cardiac Surgery Registry. Information about the expected survival rates in the general population matched by age, sex, and year of surgery was obtained from the Human Mortality Database (124).

3.2.5 Outcome measures

Postoperative delirium was the primary endpoint in Study I and Study II. In Study IV the primary outcome measure was all-cause mortality at one, five, and eight years after cardiac surgery.

3.3 Study designs and patient selection

Table 6. Overview of study design and methods in Studies I-IV

Study	I	II	III	IV
Design	Systematic literature review and meta-analysis	Population-based cohort study	Qualitative interview study	Population-based cohort study
Participants	Individuals undergoing cardiac and vascular surgery (n 2066)	Individuals undergoing cardiac surgery (n 1120)	Individuals with hypoactive or mixed delirium after cardiac surgery (n 12)	Individuals undergoing cardiac surgery (n 1120)
Data collection	October 2019 Systematic literature research: Medline (OVID®), Embase®, Cochrane Library (Wiley), Web of Science™ Core Collection (Thomson Reuters) and PsycINFO® (OVID®)	2013-2016 PHQ-9 scores 2020-2021 medical journals, notes about delirium symptoms, ICD-codes, CAM-ICU	October 2021-November 2022 Semi-structured interviews	2013-2016 PHQ-9 scores December 15, 2022, information about vital status (mortality) Swedish Cardiac Surgery Registry Human Mortality Database
Data analyses	Random effects meta-analysis	Student´s t-test Chi-square Logistic regression	Qualitative content analysis with inductive and latent approach	Weighted flexible parametric survival models

3.4 Data collection and study population

3.4.1 Study I

A systematic literature review and meta-analysis was performed following an established study protocol in October 2019 (12). The inclusion criteria was cohort studies investigating the association between preoperative depression and POD in cardiac surgery patients reporting ORs. Extracted data included the first author's name, year of publication, study period, country, surgical procedure, assessment of depression, assessment of delirium, the total number of patients, number of patients in the exposed (depressed) and non-exposed (non-depressed) groups, number of exposed patients with POD, number of unexposed patients with POD, unadjusted and multivariable-adjusted ORs and 95% CIs. Quality assessment of the included studies was performed using the quality assessment tool New Castle Ottawa Scale (125).

Seven articles published between 2004-2019 were included in the meta-analysis and comprised a total of 2.066 adult patients undergoing cardiac and cardiovascular surgery and interventions (CABG, cardiac valve replacement, combined procedures, endovascular aortic repair, and percutaneous TAVI) in the USA, Australia, Japan, Brazil, Belgium, and Poland. The number of patients in each study ranged from 131 to 563.

3.4.2 Study II and Study IV

Self-reported data about preoperative depression symptoms (PHQ-9) were collected as part of a depression screening project at the cardiac surgery department at Karolinska University Hospital between mid-September 2013 and the beginning of August 2016 (26) (Figure 4).

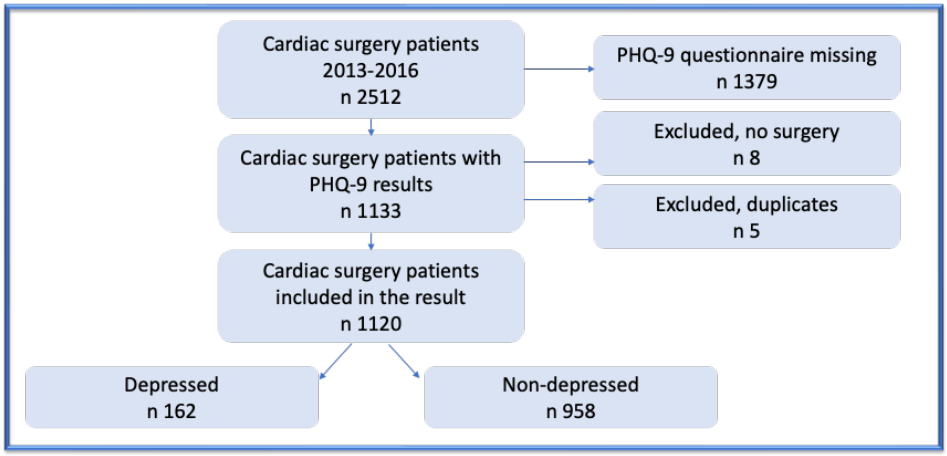

Figure 4. Flowchart depression screening project

All adult patients scheduled for elective or urgent cardiac surgery at Karolinska University Hospital were eligible for inclusion in the study. Patients scheduled for elective surgery received the PHQ-9 by mail two weeks before surgery. Urgent patients (patients not electively admitted for operation, who for medical reasons required surgery on the

current admission) were asked to fill out the PHQ-9 before surgery on the ward as part of the clinical routine.

The PHQ-9 results were gathered in a study database and linked to the continuously updated Swedish Cardiac Surgery Registry which is a part of the SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) registry to obtain information about additional baseline characteristics by using the Swedish personal identity number (126-128).

In Study II information and data about POD were collected through medical records assessment from January 2020 until February 2021. POD was assessed through CAM-ICU, ICD code, or documented symptoms of POD at the ThICU and postoperative cardiac surgery ward.

In Study IV information about vital status was collected from the continuously updated Swedish Cardiac Surgery Registry on December 15, 2022, by using the Swedish personal identity number. Information about the expected survival in the general population in Sweden matched by age, sex, and year of surgery was obtained from the Human Mortality Database (124).

3.4.3 Study III

Data collection was based on purposive sampling. Patients with hypoactive or mixed delirium during their in-hospital stays after cardiac surgery were eligible for participation. Twelve patients (three women and nine men) with ages ranging from 53-82 years participated. Data was collected from October 2021 to November 2022. Because of the Covid-19 pandemic, all interviews were conducted by telephone (129). Participants were interviewed three to 14 weeks after cardiac surgery and the interviews lasted for 25-72 minutes. A topic-based interview guide with semi-structured open-ended questions about patients' experiences of hypoactive delirium was used. After the first pilot interview, questions were added to the interview guide.

3.5 Statistical analysis

3.5.1 Study I

Unadjusted and adjusted ORs and 95% CIs were extracted from the selected articles. In the studies that lacked ORs, the number was manually calculated. Because of the clinical diversity and methodological variation among the included studies, the random effects model was used to calculate the summary statistics and their 95% CIs. To determine the impact of individual studies on the pooled estimate, a series of new meta-analyses were performed in which pooled estimates were calculated excluding one study at a time using a random-effects model. Publication bias was assessed through the visual examination of a funnel plot.

3.5.2 Study II

Baseline characteristics were described with frequencies and percentages for categorical variables and median values for continuous variables. Student's t-test was used for continuous variables, and the chi-square test was used for categorical variables. Logistic regression was used to estimate ORs and 95% CIs for the association between depression

and POD using non-depression as the reference category. The multivariable model included all baseline variables presented in Table 8. The statistical analyses were performed with Stata version 16.1 software (StataCorp LP, College Station, TX).

3.5.3 Study III

The interviews were conducted within three to 14 weeks after cardiac surgery, and each interview lasted for an average of 40 minutes (25–72 minutes). The interviews were analyzed using qualitative content analysis with an inductive and latent approach (130). The interviews were recorded digitally and transcribed verbatim. The text was divided into meaning units according to the aim, and the meaning units were condensed preserving the core meaning and labeled with codes (130). The codes were grouped into eight sub-themes that generated two themes on an abstract, interpretative level. Themes can be described as the expression of the latent content of the text (130).

3.5.4 Study IV

The relative survival was defined as the ratio between the observed survival rates and the expected survival rates in the general population (131). The expected survival from the general population in Sweden matched by age, sex, and year of surgery was obtained from the Human Mortality Database (124). The standardized mortality was calculated as the ratio of the observed to the expected number of deaths. We used weights (132) to balance the differences in baseline characteristics. All variables reported in Table 8 were used to derive the weights. Standardized mean differences were used to assess the balance between groups before and after weighting (133). A flexible parametric survival model was used to calculate hazard ratios (HR) and the absolute survival differences in the weighted study population. Data management and statistical analyses were performed with the use of R programming language and Stata and included the use of the strs (131) and stpm2 (134) programs and the R package WeightIt (WeightIt. Accessed January 27, 2023https://cran.rproject.org/package=WeightIt).

4 Results

4.1 Study I

Is preoperative depression associated with postoperative delirium in patients undergoing cardiac surgery?

Characteristics of the studies included in the meta-analysis are presented in Table 7. Depression prior to surgery was present in 198 patients. The number of patients ranged between 131 and 679 in each study.

All studies included in the meta-analysis showed a positive association between preoperative depression and POD; and in five of the studies, the association was statistically significant. The overall pooled OR for preoperative depression and POD was 2.31 (95% CI 1.37–3.90) according to a random-effects model (Figure 5).

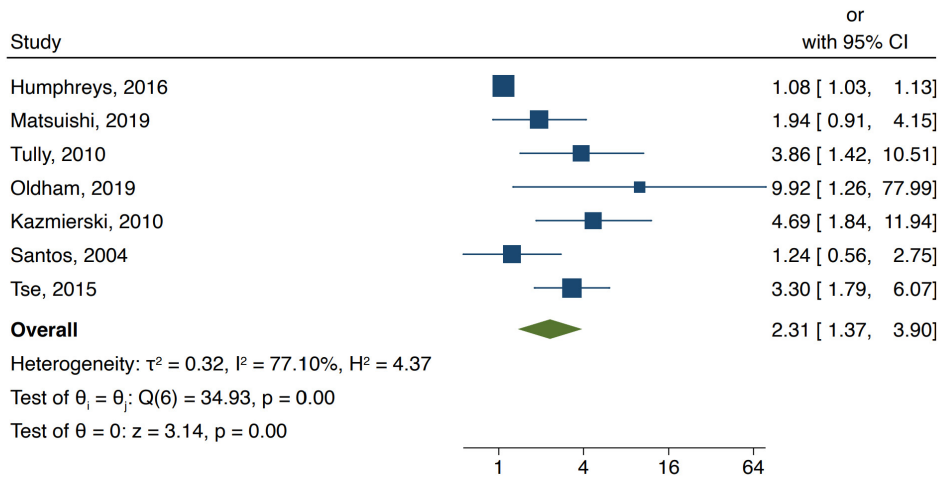

Figure 5. Forest plot of preoperative depression and postoperative delirium following cardiovascular surgery

To determine the impact of individual studies on the pooled estimate in the meta-analysis, several meta-analyses were performed in which pooled estimates were calculated excluding one study at a time using a random-effects model. The results were robust with an OR between 2.06 (95% CI 1.20–3.51) and 2.78 (95% CI 1.76–4.40). Due to the different types of surgeries in the different studies in the meta-analysis, a separate meta-analysis only including studies of patients undergoing CABG was performed. The pooled OR in this analysis was 2.36 (95% CI 1.10–5.05).

Table 7. Characteristics of included studies in the meta-analysis

First author, year	Study period	Country	Procedure	Assessment of depression	Assessment of delirium	No. of patients (depressed / non-depressed)	Crude OR	Multivariable adjusted	Adjusted OR (95% CI)	NOS
Humphreys, 2016	2003- 2011	Australia	CABG	DASS	DSI, SPMSQ	173 (-/-)	Not reported	Male gender, hyper-cholesterolemia, diabetes, urgent surgery	1.08 (1.03-1.13)	5
Kazmierski, 2009	2004-2007	Poland	CABG, CABG + valve surgery, valve surgery	MINI	DSM-IV	563 (35/528)	3.85 (1.87-7.88)	Age, MMSE <25, MD, Anemia, AF, Intubation >24 h, pO2 <60 mmHg	4.69 (1.84-11.93)	7
Oldham, 2018	2012-2016	USA	CABG	DISH, HDRS, PHQ-9, GDS	CAM, MMSE, DSI	131 (13/118)	3.98 (1.16-13.71)	Age, sex, MCI, Preoperative depression, MCA stenosis >50%, CCI, Lawton score	9.92 (1.26-77.88)	6
Tully, 2010	2007- 2009	Australia	CABG, concomitant valve surgery	MINI	DSI	158 (27/131)	3.49 (1.48-8.26)	Sex, age, cross-clamp time, Hb, psychotropic drug use	3.86 (1.42-10.52)	7
Santos, 2004	1996-1999	Brazil	CABG	GDS	DSM-IV	220 (29/191)	1.24 (0.56-2.75)	Not reported	Not reported	6
Matsuishi, 2019	2015-2016	Japan	Cardio-vascular, thoracic and abdominal artery surgery	HADS	RASS, CAM-ICU	142 (37/105)	1.94 (0.91-4.16)	Not reported	Not reported	6
Tse, 2015	2008	Canada	CABG, CABG + other, TAVI	DSM IV	CAM, DSM-IV	679 (57/622)	Not reported	Age, history of delirium, stroke/TIA, Cognitive impairment, Depression, Preop beta-blocker use	3.3 (1.8-6.1)	6

NOS = New Castle Ottawa Scale, CABG = Coronary Artery Bypass Grafting, CI = Confidence Interval, TAVI = Transcatheter Aortic Valve Implantation DSI = Delirium Symptom Interview, SPMSQ = Short Portable Mental Status Questionnaire, CAM = Confusion Assessment Method, RASS = Richmond Agitation Scale, CAM-ICU = Confusion Assessment Method for the Intensive Care Unit, DASS = Depression Anxiety and Stress Scales, MINI = Mini International Neuropsychiatric Interview, DISH = Depression Interview and Structured Hamilton, HDRS = The Hamilton Depression Rating Scale, PHQ-9 = Patient Health Questionnaire-9, GDS = Geriatric Depression Scale, HADS = Hospital Anxiety and Depression Scale, DSM = Diagnostic and Statistical Manual of Mental Disorders, AF = Atrial fibrillation, Hb = Haemoglobin, MD = Major depression, MCI = Mild Cognitive Impairment, MCA = Middle Cerebral Artery, TIA = Trans Ischemic Attack

4.2 Study II

Is preoperative depression associated with postoperative delirium in patients undergoing cardiac surgery?

4.2.1.1 Baseline characteristics

During the study period 2013-2016, 2,512 patients underwent cardiac surgery in our institution. Of these patients, 1,120 (45%) completed PHQ-9, 824 (74%) were men, and 296 (26%) were women. The response rate in patients scheduled for elective surgery was 64%, and 15% in urgent patients. A total of 162 patients (14,5 %) had a PHQ-9 score ≥10 suggestive of depression prior to cardiac surgery. The mean age was 65.6 years in the non-depressed group, and 61.6 years in the depressed group. A PHQ-9 score ≥10 was twice as common in women as in men (22% vs 11%). Furthermore, the depressed group had higher consumption of alcohol, smoked, and had chronic obstructive pulmonary disease (COPD) to a larger extent than the non-depressed (Table 8).

Table 8. Baseline characteristics in the total study population and stratified by preoperative depression

Variable	Total population	No depression	Depression	p-value	Missing data (%)
Number of patients	1120	958	162		
Age (years), mean (SD)	65.0 (11.7)	65.6 (11.4)	61.6 (12.5)	<0.001	0.0
Female sex	296 (26.4)	230 (24.0)	66 (40.7)	<0.001	0.0
Living alone	296 (27.7)	254 (27.6)	42 (27.8)	1.000	4.5
Body Mass Index (kg/m^2)				0.028	0.0
<18.5	10 (0.9)	7 (0.7)	3 (1.9)		
18.5-24.9	395 (35.3)	347 (36.2)	48 (29.6)		
25-29.9	487 (43.5)	421 (43.9)	66 (40.7)		
>30	228 (20.4)	183 (19.1)	45 (27.8)		
Smoking				<0.001	0.0
Non-smoker	514 (45.9)	456 (47.6)	58 (35.8)		
Prior smoker	347 (31.0)	290 (30.3)	57 (35.2)		
Current smoker	110 (9.8)	78 (8.1)	32 (19.8)		
Unknown	149 (13.3)	134 (14.0)	15 (9.3)		
Preoperative AF				0.288	0.0
No	812 (72.5)	687 (71.7)	125 (77.2)		
Yes	183 (16.3)	163 (17.0)	20 (12.3)		
Unknown	125 (11.2)	108 (11.3)	17 (10.5)		
Preoperative COPD	105 (9.4)	77 (8.0)	28 (17.3)	<0.001	0.0
Preoperative PVD	76 (6.8)	62 (6.5)	14 (8.6)	0.397	0.0
Preoperative PCI	80 (7.1)	66 (6.9)	14 (8.6)	0.525	0.0
Prior cardiac surgery	57 (5.1)	46 (4.8)	11 (6.8)	0.383	0.0
LVEF				0.051	0.0
>50%	752 (67.1)	656 (68.5)	96 (59.3)		

30-50%	317 (28.3)	262 (27.3)	55 (34.0)		
<30%	51 (4.6)	40 (4.2)	11 (6.8)		
Preoperative diabetes	184 (16.4)	149 (15.6)	35 (21.6)	0.071	0.0
eGFR (mL/min/1.73 m^2)				0.594	0.0
>60	923 (82.4)	785 (81.9)	138 (85.2)		
45-60	136 (12.1)	119 (12.4)	17 (10.5)		
<45	61 (5.4)	54 (5.6)	7 (4.3)		
Preoperative stroke	81 (7.2)	65 (6.8)	16 (9.9)	0.215	0.0
Alcohol				<0.001	0.0
Never	100 (8.9)	68 (7.1)	32 (19.8)		
Moderate consumption	931 (83.1)	826 (86.2)	105 (64.8)		
High consumption	42 (3.8)	28 (2.9)	14 (8.6)		
Unknown	47 (4.2)	36 (3.8)	11 (6.8)		
Type of surgery				0.016	0.0
Isolated CABG	300 (26.8)	251 (26.2)	49 (30.2)		
Isolated valve	515 (46.0)	431 (45.0)	84 (51.9)		
Other	305 (27.2)	276 (28.8)	29 (17.9)		
Urgent surgery	139 (12.4)	116 (12.1)	23 (14.2)	0.537	0.0
EuroSCORE 2, mean (SD)	3.0 (3.9)	3.0 (3.9)	3.3 (4.3)	0.376	0.2

Numbers are n (%) unless otherwise noted. SD = standard deviation, AF: atrial fibrillation; BMI: body mass index; CABG: coronary artery bypass grafting; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention; PVD: peripheral vascular disease

4.2.1.2 Primary outcome measure

POD was detected in 287 of 1120 patients (26%). In the group of patients with depression, 34% developed POD compared to the group of non-depressed patients where 24% developed POD. In the total study population, there was a crude association between preoperative depression and POD: OR 1.61 (95% CI 1.13–2.30). After

multivariable adjustment for baseline characteristics, the association between preoperative depression and POD remained: OR 2.19 (95% CI 1.43–3.34) (Table 9).

Table 9. Association between depression and delirium in the total study population and according to sex and age

	Odds ratio (95% CI)		
	Crude	Age- and sex-adjusted	Multivariable adjusted
Total population	1.61 (1.13-2.30)	2.28 (1.54-3.36)	2.19 (1.43-3.34)
Sex			
Men	1.50 (0.95-2.37)	2.21 (1.35-3.63)	2.11 (1.23-3.61)
Women	1.93 (1.06-3.49)	2.38 (1.27-4.47)	2.43 (1.13-5.21)
Age group			
<62 years	2.95 (1.56-5.58)	3.03 (1.60-5.84)	3.76 (1.70-8.32)
62-72 years	1.74 (0.88-3.45)	1.87 (0.93-3.75)	2.06 (0.91-4.63)
>72 years	1.49 (0.80-2.76)	1.56 (0.83-2.92)	1.67 (0.80-3.49)

CI = confidence interval

4.2.1.3 Age, sex and delirium

The prevalence of POD was similar between the sexes. However, women with depression had a higher risk of developing POD compared to non-depressed women The prevalence of POD was highest among the oldest patients (>72 years), where 37% developed POD. However, the association between depression and POD was strongest among the youngest patients (<62 years) multivariable-adjusted OR 3.76 (95% CI 1.70–8.32) (Table 10).

A depressed 60-year-old patient has the same risk of developing POD after cardiac surgery as a non-depressed 75-year-old patient. The effect of depression on POD decreases after 65 years of age (Figure 6).

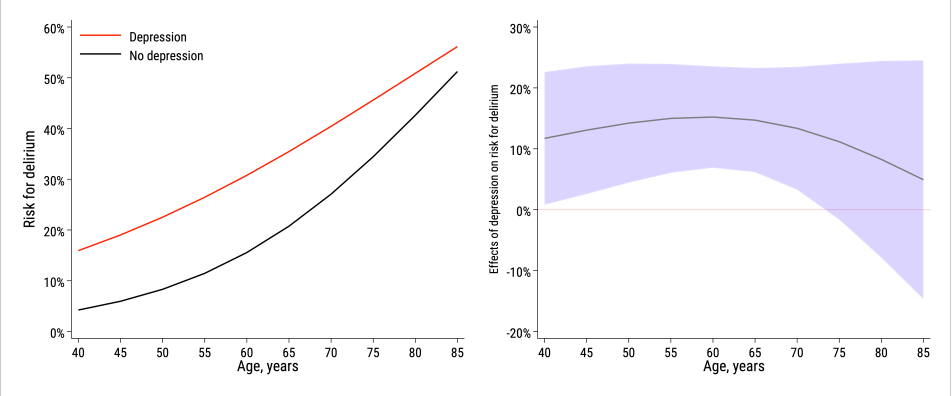

Figure 6. Effects of depression on risk for delirium

4.3 Study III

How do patients experience hypoactive delirium after cardiac surgery?

4.3.1.1 Participant characteristics

Twelve patients (nine men and three women) with ages ranging from 53-82 (mean age 73.5 years) participated in the interview study. All participants had undergone various types of cardiac surgery with CPB and showed symptoms of hypoactive delirium during the first days after surgery. Hypoactive symptoms of delirium were detected by ICD codes together with Nu-DESC and CAM-ICU results, or through descriptions of symptoms in medical journals (Table 10).

Table 10. Participant characteristics (n 12)

Aggregated participant characteristics								
Variable								
Age, median years (min-max)						73.5 (53-82)		
Sex, n (%)								
Female						3 (25)		
Male						9 (75)		
ICD code n (%)						8 (67)		
Nu-DESC positive n (%)						9 (75)		
CAM positive n (%)						1 (0.8)		
ThICU/ThPACU days mean (min-max)						4 (1-12)		
Length of hospital stay days mean (min-max)						11 (5-17)		
Interview number of weeks after surgery mean (min-max)						7.5 (3-14)		
Individual participant characteristics								
Participant number	Age	Sex	ICD code	Nu-DESC positive	CAM positive	ThICU/ ThPACU days	LOS days	Interview weeks after surgery
1	67	Male	-	Yes	-	1	11	4
2	53	Male	F059	No	No	12	17	7
3	74	Male	R443	Yes	-	2	7	7
4	73	Male	R410	Yes	-	6	15	14
5	74	Male	R443	Yes	-	5	8	6
6	72	Male	F059	Yes	-	1	7	6
7	64	Male	F059	Yes	-	2	16	7
8	77	Female	F059	Yes	Yes	9	16	12
9	82	Male	R410	Yes	-	1	6	4
10	80	Female	-	No	No	5	13	12
11	64	Male	-	No	No	8	12	3
12	78	Female	-	Yes	-	1	5	8

Abbreviations: International Statistical Classification of Diseases (ICD) code, Nursing Delirium Screening Scale (Nu-DESC), Confusion Assessment Method (CAM), Thoracic Intensive Care Unit (ThICU), Thoracic Post-Anesthesia Care Unit (ThPACU), Length of hospital stay (LOS)

4.3.1.2 Main findings

In Study III, the participants shared experiences of hypoactive delirium as considerable and long-lasting. Eight sub-themes resulted in two main themes (Table 11).

Table 11. Example codes, sub-themes and themes

Code	Sub-theme	Theme
My reality Malfunction Dream or reality Amnesia	Existing in a parallel reality	***Dream or reality in parallel worlds***
Seeing the dead Being ignored Responsible for deaths Feeling safe	Emotionally affecting hallucinations	
Being confused Being oblivious Horrible nightmares	Residual nightmares and cognitive impact	
Remember fragments No circadian rhythm Being somewhere else	Lacking a sense of time and space	
Dejected and stupefied Fear took over Touched Guilt	Intense emotions	
Medicine cause and cure Interactions Mobilization Returning home	Perceptions of cause and cure	***Managing the state of hypoactive delirium***
Unable to speak Too ashamed Telling spouse The staffs' perceptions Interactions with staff Spouse understood	Interaction with others	
The view of oneself Was dead Nobody Was someone else	The concept of self	

4.3.1.3 Dream or reality in parallel worlds

The theme *"Dream or reality in parallel worlds"* included disturbing experiences of existing in parallel realities with cognitive effects, residual nightmares, and illusions that occasionally persisted after hospital discharge. Sorted under the sub-theme existing in a parallel reality are descriptions of participants sensing malfunction with difficulties distinguishing reality from illusions. Some participants had several days of amnesia, not being able to remember having interacted with others (healthcare professionals or

relatives) which was difficult to grasp afterward. Hallucinations were often described as emotionally affecting, mostly disturbing experiences often involving dying and death. The emotions were described as intense, and these emotions could return even after recovering. Some participants had residual nightmares and experienced cognitive impact several weeks after discharge from the hospital. The cognitive impact was described as difficulties orienting themselves, forgetting words, misplacing things and not being able to read. Nights were often described as problematic due to fear of nightmares or fear of dying in their sleep.

4.3.1.4 Managing the state of hypoactive delirium

The theme of "*Managing the state of hypoactive delirium"* included experiences of intellectually dealing with hypoactive delirium with assumptions of causes and cures, and through interactions like communicating with others. Interacting with others was described as both calming and distressing during the delirious state. Nurses who prioritized getting to know the patient would build trust and be perceived as comforting; if the nurse prioritized activities such as providing medicine before building trust, interactions were perceived as inadequate and frightening. Different perspectives on communication were expressed. Some participants were not capable of communication, due to having trouble talking, or due to existing in a parallel reality. Some chose not to talk about their condition because of fear of being perceived as insane by healthcare professionals, being ashamed of having hallucinations too awkward to talk about or wanting to protect their next of kin. The perception of self was altered during delirium and many participants felt they lost their identity. Feelings of being disconnected, nobody, helpless, and entirely alone were described as generating passivity.

4.4 Study IV

Is preoperative depression associated with worse prognosis after cardiac surgery?

Baseline characteristics are shown in Table 8 (same as in Study II).

4.4.1.1 Primary outcome measure

During a follow-up of 7.2 years (maximum, 9.2 years) there were 36 deaths in 1129 person-years (PYs) among patients with depression compared to 160 deaths in 6889 PYs in the group without depression. A PHQ-9 score of ≥10 was significantly associated with worse long-term survival in the weighted analysis (HR= 1.66; 95% CI, 1.09-2.54*)* (Table 12).

Table 12. Number of events, person-years of follow-up, and associations between depression and all-cause mortality.

			Hazard ratio (95% CI)	
	Events/PY	Incidence rate (95% CI) per 100 PY	Unadjusted	Weighted
No depression	160/6889	2.3 (2.0–2.7)	1	1
Depression	36/1129	3.2 (2.3–4.4)	1.37 (0.95–1.97)	1.66 (1.09–2.54)

CI = confidence interval, PY = person-years. Hazard ratios were estimated from an unadjusted and weighted flexible parametric survival model, respectively.

The absolute difference in survival (% and 95% CI) between the non-depressed and the depressed patients were -1.9 (-3.9–0.19), -5.7 (-11– -0.01), and -9.7 (-19– -0.4) after one, five, and eight years, respectively (Table 13).

Table 13. Survival according to depression status, and the absolute survival difference after 1-, 5-, and 8-years following surgery.

Follow-up time	No depression	Depression	Difference in survival
1 year	97 (96–98)	95 (92–97)	-1.9 (-3.9–0.19)
5 years	91 (89–92)	85 (78–90)	-5.7 (-11– -0.01)
8 years	83 (80–85)	73 (63–81)	-9.7 (-19– -0.4)

Numbers are % and (95 CIs) estimated from a flexible parametric survival model after weighting.

After five years of follow-up, the non-depressed patients´ observed survival was close to the expected survival of an age, sex-, and calendar-year-matched Swedish population. In contrary, patients with depression had significantly lower observed survival compared to the expected survival in the general population (Figure 7).

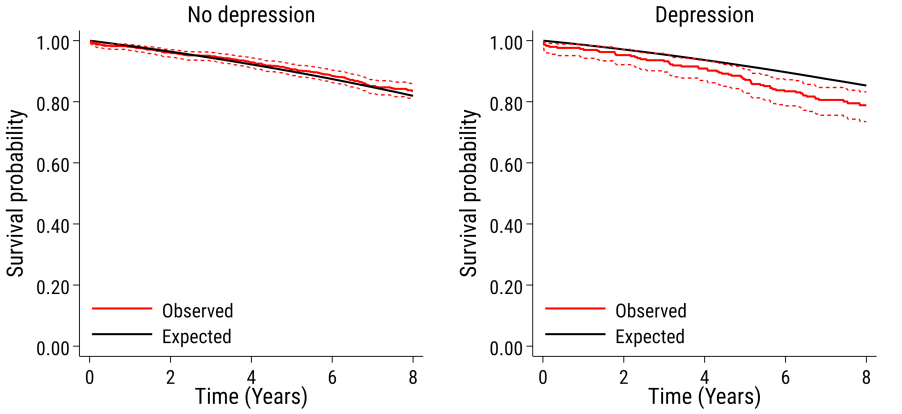

Figure 7. The observed survival (95% CI) in patients after cardiac surgery (red solid line and red dashed lines) compared to the expected survival of an age-, sex-, and calendar-year matched Swedish population (black line).

The association between depression and all-cause mortality was only significant in men (HR= 1.99; 95% CI, 1.09 - 3.63) (Figure 8).

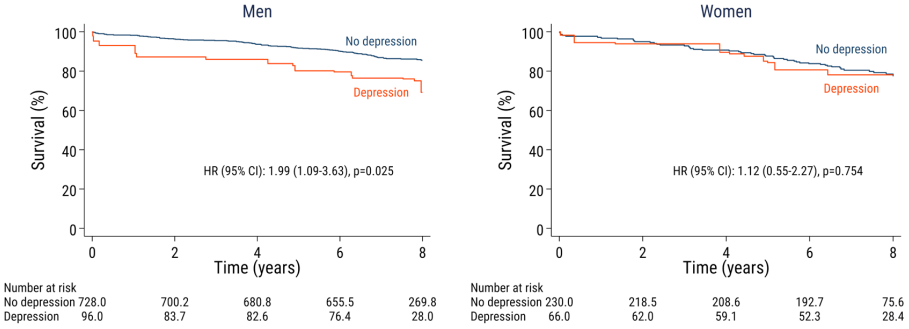

Figure 8. Kaplan–Meier estimated survival according to sex after weighting. Note that the number of patients in the groups are not necessarily integers because of weighting.: HR = Hazard ratio, CI = Confidence interval.

5 Discussion

5.1 Discussion of findings

In this thesis, the results confirm that preoperative depression is a significant risk factor for POD and an important risk marker for worse prognosis following cardiac surgery. The results emphasize the Mind-Heart-Body connection and strongly indicate that depression requires to be taken seriously in this group of patients. Another condition to be taken seriously is delirium. Even though the results demonstrate that delirium is common among cardiac surgery patients, our findings also imply that hypoactive delirium often goes unnoticed and that patients are suffering in silence which indicates knowledge gaps and insufficient use of delirium assessment instruments among health care professionals.

5.1.1 Preoperative depression and postoperative delirium

Study I and Study II in this thesis confirm the association between depression and POD in cardiac surgery patients. In both studies, patients with symptoms of depression before cardiac surgery developed POD to twice the extent compared to the non-depressed.

In study II we detected that the effect of depression on POD was strongest in the younger group of patients. This is an important finding since delirium often is perceived as a geriatric problem (135, 136). In our study, the depressed patients (< 62 years) had a similar risk of developing POD after cardiac surgery as the non-depressed 75-year-old patients. The elevated risk for POD in younger cardiac patients with depressive symptoms is a striking new finding. In contrast, the association between depression and delirium is weaker with increasing age. Resilience means the capacity to endure or to recover quickly from difficulties. In a study by Toukshati et al., resilience was evaluated in patients with cardiac disease. Their results showed that low psychological resilience is related to depression and that low resilience furthermore is more common in younger cardiac patients than in the elderly (137). This is an interesting finding and a possible explanation for elevated risk for POD in younger cardiac surgery patients with depression to be investigated in future studies.

There is no medical cure for delirium, although selected pharmacological support can alleviate symptoms (113, 138). The target for minimizing delirium should be prevention for risk patients such as reorienting the patient, minimally invasive surgery, and enhanced recovery after surgery (67). These findings support that future studies should focus on the effects of detailed monitoring of the depth of anesthesia by BIS during cardiac surgery, to prevent POD in cardiac surgery patients. In a small study by Soehle et al., delirious cardiac surgery patients remained significantly longer in a burst suppression state intraoperatively than the non-delirious (139).

5.1.1.1 Clinical implications

The reported association between depression and POD in cardiac surgery patients strengthens the indication to implement depression screening before cardiac surgery as recommended by international guidelines (23).

5.1.2 Preoperative depression and long-term survival

Study IV in this thesis demonstrates that preoperative depression, self-evaluated with the depression questionnaire, PHQ-9, has an adverse effect on survival at one, five, and eight years after cardiac surgery. Patients undergoing cardiac surgery with elevated PHQ-9 scores (≥10) had notably worse survival compared to the expected survival of an age and sex-matched general population. This worse prognosis could not be detected among non-depressed patients undergoing cardiac surgery since the survival in this group was close to the expected survival in the general Swedish population. A possible explanation is that patients undergoing cardiac surgery are considered healthy enough to manage cardiac surgery.

Understanding the consequences of depression for prognosis after cardiac surgery gives additional weight to the Mind-Heart-Body connection (1) and ought to encourage depression screening as a clinical routine at all cardiac surgery departments as suggested by the AHA (22, 23). Depression screening has also shown to be valuable in other areas, in a recent study by Gohari et al (140) patients with severe pain after cardiac surgery had significantly higher preoperative depression scores than patients with no pain or moderate pain (140). Depression screening with the PHQ-9 is feasible and non-resource-intensive before cardiac surgery (11).

This new knowledge about the severe consequences of depression demands action. With that in mind, the timing for depression screening should be considered. Screening patients only weeks before cardiac surgery gives no time for interventions. McCarron et al. (2021) recommend depression screening (preferably with PHQ) in primary care as a systematic evaluation of mood disorders in all adults, together with considering risk factors for MDD (19). Some studies have investigated prehabilitation and included the parameter depression before cardiac surgery. Furze et al. (2009) (141)tested adding interventions such as information about cardiac misconceptions, risk factors for secondary prevention, what to expect during the hospital stay, a relaxation program, and a diary for recording activity and risk factor reduction goals to routine nurse counseling for persons waiting for CABG and concluded that these interventions could reduce depression and cardiac misconceptions and improve physical functioning before CABG (141). Subramanian et al. (160, 161) investigated prehabilitation in cardiac surgery patients in two recent reviews. The first part focused on anemia, diabetes, obesity, sleep apnea, and cardiac rehabilitation (142). The second part focused on frailty, malnutrition, respiratory disease, alcohol/smoking cessation, and depression (143). The authors suggested that patients who test positive for depression should be offered preoperative counseling and education which could help diminish the effects of depression on the postoperative journey (143). Another intervention option is cognitive behavioral therapy (CBT). Preoperative CBT has been shown to be feasible for patients undergoing elective CABG and suggests reducing LOS as well as improving depressive and anxiety symptoms, and quality of life four weeks after discharge (144).

5.1.2.1 Sex differences

Vast sex differences are continuously reported in cardiac surgery cohorts, with men being younger and in the majority. In the study cohort used in Study II and Study IV, there were sex differences regarding depression status. Female patients reported an elevated PHQ-9 score (≥10) to a larger extent compared to men (22% vs 11%) which is in line with previously reported data, that depression is more often diagnosed in women, who are twice as likely to develop depression during their lifetime compared to men (16). Even though depression was more frequent in women, the effect of depression on all-cause

mortality was only significant in men (HR= 1.99; 95% CI, 1.09 - 3.63). This mirrors the known population-based patterns with women more often being diagnosed with depression than men but consequences of depression being more severe for men e.g., higher incidence of death by suicide (145).

However, in Study IV women, regardless of depression screening results, had significantly lower survival after cardiac surgery compared to the expected survival in the age- and sex-matched general population. The results in our study regarding women are in line with previous studies showing worse outcomes, such as in-hospital and long-term mortality after cardiac surgery in female patients (37). A possible explanation for this could be that the prognosis for women undergoing cardiac surgery is affected by other factors, studies have suggested that women appear later in the disease and get less aggressive care (39, 146). Altogether, the analysis could also just confirm the highly selected cohort of women subjected to cardiac surgery.

5.1.2.2 Clinical implications

Considering the prognosis for adverse outcomes in persons with depression undergoing cardiac surgery, depression screening is essential. Although the association between depression and all-cause mortality is stronger in men, depression is more common in women and the prognosis for women regardless of depression status is worse after cardiac surgery. Screening for depression in both men and women should be implemented already in primary care to detect depression as well as an unknown cardiac disease with symptoms resembling depression.

5.1.3 Patients´ experiences of hypoactive delirium

In Study III the participants with hypoactive delirium described communicating with others as challenging. Some described not being able to speak due to being in another reality, or not finding the words. Some avoided speaking since they were ashamed of what they were experiencing, and some thought interactions with healthcare professionals were frightening. Having difficulties communicating in combination with an affected perception of oneself during delirium can be challenging. Several participants felt that they had lost their identity, being a package, being nobody, or becoming someone else, and some participants withdrew from the staff. A person-centered approach means that a person´s values and preferences shall guide all aspects of their care, supporting their health and life goals (104) and could possibly benefit patients with delirium. Person-centered care is achieved through relationships between the patient, others who are important to them, and healthcare professionals (147). Listening to a patient's own narrative gives healthcare professionals a chance to involve them in their own care (104). With the demanding clinical environment in many ICUs and hospital wards, person-centered care can be difficult to achieve. Some studies have investigated the ability of trained volunteers to provide person-centered in-hospital care for older patients with dementia and/or delirium (148, 149). The results were promising with a reduction of 28-day readmission to hospital, shorter LOS increased safety and quality of care for patients as well as a reduced burden for staff and families (148, 149).

5.1.3.1 Hypoactive delirium and delirium assessment

The delirium experienced by the participants in Study III was considerably more extensive than what had been documented in their medical journals, an indication that hypoactive delirium is unrecognized. Our findings indicate that increased use of screening tools is warranted and that there is still ignorance of delirium among

healthcare professionals. This has been previously described, Zamoscik et al. described ICU-nurses perceiving delirium as a low-priority matter and that they felt frustrated due to a lack of confidence in assessing delirium, as well as the deficiency in effective delirium therapies (150). Gabby Rowley-Convey concluded that several of the barriers to effective assessment and management of delirium are due to a lack of knowledge of delirium and assessment tools as well as a lack of medical prioritization of the results (151). Other barriers to not using delirium assessment instruments are lack of training, lack of time, difficulties in integrating the instrument into daily working routines, and nurses feeling uncomfortable assessing delirium (69, 152-155). Further education to improve delirium expertise in healthcare professionals is needed. Interprofessional delirium education has been proven to improve awareness of factors associated with delirium as well as increase the use of delirium assessment tools (from 8.5% to 43%) (156).

5.1.3.2 Clinical implications

Using a delirium assessment instrument is essential for early and continuous detection and awareness of all kinds of delirium.

5.2 Methodological considerations

This research project included one literature review with meta-analysis, two observational studies, and one qualitative interview study.

5.2.1 Study I

A meta-analysis is an objective evaluation and pooling of different study populations. Study I gave us a valuable overview of the knowledge in the field that turned out to be sparsely studied. Even though we performed a thorough literature search we found only seven studies that fulfilled the inclusion criteria. As with any meta-analysis, there is a possibility that eligible articles have been missed. Furthermore, all studies included in our meta-analysis showed a positive association between depression and POD, and since studies with positive results more often get published, the effect measure might be overestimated (publication bias). The quality of systematic reviews depends on the quality of the included studies. For quality assessment of the included studies, the Newcastle–Ottawa scale was used (157) (assessed quality of the included studies is demonstrated in Table 7). Due to the heterogeneity of the included studies (according to type o surgery, assessment of depression and delirium as well as the different sizes of the study cohorts), a random-effects meta-analysis was performed. The random-effects model accepts that different studies show diversity and that the true effect size can vary from study to study (158), contrary to the fixed effects model which assumes that all studies share a common effect size (159).

5.2.1.1 Strengths and limitations

The meta-analysis was performed including only seven studies, however, the pooled study population consisted of 2.066 patients. The relatively high number of patients and strict inclusion criteria represent a strength of this study. Another considerable strength is that this study presumably is the first systematic review and meta-analysis investigating preoperative depression and POD in cardiac surgery patients.

5.2.2 Study II and Study IV

Study II and Study IV were observational population-based cohort studies based on the same study cohort. With observational studies conclusions about the effect of an exposure (in this case preoperative depression) can be drawn. A cohort study is one type of observational study that can produce incidence rates as well as relative risks and is appropriate when an association between an exposure and an outcome is studied, the time for follow-up is relatively short and the outcome is not too rare (160). With that in mind, the study designs for Study II and Study IV were adequate. Study II and Study IV were population-based which in this case means that all patients undergoing elective or urgent cardiac surgery in Stockholm, Sweden from 2013-2016 were eligible for inclusion. In cohort studies, the participation rate needs to be considered when evaluating the validity of the results. Volunteers participating in studies tend to have better health profiles compared to those who decline participation. As a consequence, estimates of prevalence and exposure may be biased, which is called selection bias (161).

5.2.2.1 Strengths and limitations

A strength of Study II and IV is that data regarding depressive symptoms were self-reported with a psychometrically tested instrument (24) that has been recommended for depression screening in patients with cardiac disease (23) and prospectively collected. A

potential bias is that patients scheduled for elective surgery filled out the PHQ-9 two weeks before surgery, contrary to the patients undergoing urgent surgery who filled out PHQ-9 within 24 hours before surgery. However, urgent surgery was adjusted for in the statistical analysis.

The low participation rate of 45% (64% among elective patients and 15% among urgent patients) as well as the studies being single centers may threaten the validity of the results. However, the high number of participants and that the study cohort included all patients eligible adds to the external validity (the ability to generalize study results to a more general population) (160).

In Study II delirium was detected by reading medical records. Even though CAM-ICU was implemented at the ThICU at that time, compliance was low. At the cardiac surgery ward, no delirium assessment instrument was used. The prevalence of delirium was 26% which is in line with delirium prevalence in our meta-analysis (24-26%). The prevalence of POD in Study II is possibly underestimated, previous studies have reported larger proportions of POD after cardiac surgery (95). As mentioned earlier, delirium prevalence depends on the age and comorbidity of the studied cohort, and delirium assessment is essential to detect all cases. In Study II we included adult patients of all ages, not just the elderly. In addition to the sparsely practiced CAM-ICU and sparsely reported ICD-codes, POD was identified by assessment of clinical symptoms documented in medical records. Delirium assessment is challenging, Saczynski et al (162) compared using the CAM to reviews of medical records for detecting delirium. The two methods had different challenges and combining the two methods was beneficial (162). The medical records-based method missed delirium in patients without psychomotor agitation or inappropriate behavior. The CAM-based method missed chart-identified cases occurring during the night shift (162). To validate the assessment of delirium, I examined all 1120 medical charts and in addition, we consulted an experienced ICU nurse who verified 20% of the medical records with a concordance of 90%. Furthermore, in cases of ambiguity an experienced ICU physician assisted in determining POD, and any disparity rendered an absence of a diagnosis. Another possible limitation of Study II is not taking sedation into account.

In Study IV, a considerable strength is the completeness of data acquisition. Follow-up was complete, due to the unique personal identification number assigned to all Swedish citizens (163) and the high quality of the Swedish Cardiac Surgery Registry (127)

5.2.3 Study III

When conducting a qualitative study, there are many different methods to use. In Study III qualitative content analysis according to Graneheim and Lundman (130), was chosen. Qualitative content analysis focuses on the subject and context and emphasizes resemblances as well as differences in the text. It is an independent method that can be used in different levels of abstraction and interpretation. i.e., from manifest and descriptive content with a low interpretation degree to a high abstraction level with a high interpretative degree (164). Since the aim of Study III was to describe the experiences of cardiac surgery patients with hypoactive delirium, the chosen method for analysis was suitable as a need to interpret the data on a more abstract level was identified (165).

The challenge of qualitative studies using qualitative content analysis concerns trustworthiness (164). Trustworthiness refers to the entire study and can be addressed

by the concepts of dependability, credibility, authenticity, confirmability and transferability (164). To address dependability, I conducted all the interviews, transcribed the interviews, and decided which codes and quotes to be included in the analyses. However, several researchers participated in the processes of coding, categorizing, discussing themes, and reaching a consensus in achieving alternative interpretations. To achieve credibility, there was a clear sampling method (purposive sampling). A pilot interview was conducted, and further questions were added to the interview guide. Also, examples of representative quotes were used to clearly illustrate the voice of the patient. In addition, to evaluate the credibility and authenticity, examples of the interpretation process are shown to highlight the logic of the abstraction and interpretation of the sub-themes and themes with the correlation to the aim. Confirmability can be achieved by respondents reviewing the interpretation of findings. However, this was not performed in Study III. In qualitative studies, the goal is not to generalize the results, although it is important to evaluate if the results can be transferred to similar contexts. To achieve transferability, the participants' characteristics and context are described in-depth. After 10 interviews saturation was reached. Additional two interviews were thereafter conducted. A sample size of 12 provided the needed variability in described experiences of hypoactive delirium. These findings may be transferable to similar patients and settings by including men and women of different ages.

5.2.3.1 Strengths and limitations

The variety of participants, men and women of different ages talking freely about their experiences of hypoactive delirium added strength to the study. The interviews were conducted in near time to assure the participants´ memories of the event. Conducting interviews by telephone instead of face-to-face can be perceived as a limitation due to not being able to observe the facial expressions of the participants. However, by conducting the interviews by telephone the participants could stay safely in their homes and did not have to transport themselves to other locations.

A potential limitation is difficulty detecting hypoactive delirium in clinical care. Because of this difficulty, in addition to including participants with a pure form of hypoactive delirium, participants with mixed delirium were included. When interviewing participants, emphasis was placed on the hypoactive aspects of delirium. Some participants still shared experiences of hyperactive symptoms of delirium, such as vigilance and being restless. In Study III, experiences of hyperactive symptoms of delirium were not considered. Furthermore, conducting interviews with persons recovering from hypoactive delirium is challenging since these patients often experience memory loss which is a possible limitation.

6 Conclusions

Depression is a significant, independent risk factor for postoperative delirium and worse long-term survival after cardiac surgery. Depression screening is important to identify patients at risk. The challenges in the recognition of hypoactive delirium need to be emphasized because the syndrome is still overlooked. The use of screening tools in clinical practice is essential to detect all kinds of delirium. A person-centered approach supports relationships between delirious patients and healthcare professionals.

7 Future perspectives

In this thesis, preoperative depression and POD are emphasized as two conditions to take seriously in cardiac surgery care. Considering the negative effects of depression, depression screening should be implemented with consideration of possible treatment. The timing of depression screening needs to be reflected upon; screening two weeks before cardiac surgery gives no time for action. Future studies should investigate the effect of prehabilitation and treatment for depression in persons with depressive symptoms already in primary care.

Furthermore, better clinically relevant delirium-prediction models need to be evaluated. A few delirium-prediction models for cardiac surgery patients have been developed (166, 167). The two-step model has good validity and includes preoperative predictors as well as postoperative predictors for delirium but does not include preoperative depression (167). Since preoperative depression is significantly associated with POD in cardiac surgery patients, depression should be added as a variable.

The effect of sedation on POCD and POD in cardiac surgery needs further investigation. Preferably in a randomized controlled trial.

Future focus should include the perspectives of patients' overall quality of life and cost-effectiveness for the hospital stay using standardized screening of depression and delirium assessment postoperatively as routine. Due to economic restraints in the contemporary healthcare system, all adjuncts in the daily activities regarding evaluations required by healthcare providers should be supported by certified cost-efficiency data. Our findings show the need for an urgent cost-effectiveness evaluation of the gain with decreased delirium among patients, both for short- and long-term benefits.

The recommended person-centered approach supports a beneficial relationship between delirious patients and healthcare professionals. However, in contemporary care, this is not always prioritized due to the lack of nurses. A challenge for the future is multifaceted, to find and keep nurses as well as educate all healthcare professionals in person-centered care, POD as well as the Mind-Heart-Body connection.

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