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**DISPARITIES IN CARE AND
OUTCOMES AMONG PATIENTS
ADMITTED WITH DEPRESSION**

**BY
LINE RYBERG RASMUSSEN**

DISSERTATION SUBMITTED 2023



AALBORG UNIVERSITY
DENMARK

DISPARITIES IN CARE AND OUTCOMES AMONG PATIENTS ADMITTED WITH DEPRESSION

by

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AALBORG UNIVERSITY
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ENGLISH SUMMARY

Depression is common and the prevalence seems to be increasing. With symptoms such as feeling sad, irritable, or empty, poor concentration, low self-worth and feelings of guilt, depression is a serious disease associated with poor physical health and functioning, occupational impairment, and significant comorbidities. People with depression are vulnerable and have an increased risk of early death and suicide. Multiple factors may determine outcomes among patients with depression, and the organization and delivery of health care is likely to play an important role for patients. Within the area of somatic diseases there is substantial evidence for disparities in treatment and the course of illness, e.g., in relation to gender, socio-economic conditions, ethnicity or geography, but there is still sparse knowledge about these conditions within psychiatry.

This thesis aims to examine disparities in the quality of inpatient care, as well as in the clinical outcomes based on age, sex, inpatient volume, and geographical residence for patients admitted with a depression.

Three register-based, nationwide studies were conducted including all patients with depression and a first-time admission to a psychiatric hospital in Denmark between 2011-2016. Disparities were investigated as differences in the quality of care defined as fulfilment of guideline-concordant process performances measures of care and differences in clinical outcomes at 1-year follow-up, i.e., readmission, suicidal behaviour and all-cause mortality.

For all three studies, disparities were observed. Study I found that, regardless of sex, patients aged 66 years or older were more likely to receive overall high-quality care as well as most of the individual process performance measures when compared to patients aged 18-39. Study II showed that patients admitted to a high-volume psychiatric hospital had a higher all-cause mortality within a year from admission compared to patients admitted to a low-volume hospital. Lastly, study III found variation of all-cause mortality and suicidal behaviour for incident patients between the five administrative regions in Denmark, with the highest risk seen in Northern Denmark.

In conclusion, the results of this thesis demonstrate that disparities are present among inpatients with depression in terms of receiving guideline-recommend care and in clinical outcomes. This emphasizes the importance of systematically monitoring and improving the quality of care in order to locate disparities, evaluate initiatives and improve patient outcomes, including all-cause mortality and suicidal behaviour for this vulnerable group. Further studies are warranted in order to investigate whether the identified associations reflect causal mechanisms.

DANSK RESUME

Depression er almindelig, og forekomsten ser ud til at være stigende. Med symptomer som at føle sig trist, irriteret eller tom, dårlig koncentration, lavt selvværd og skyldfølelse, er depression en alvorlig sygdom forbundet med dårligt fysisk helbred og funktionsevne, erhvervsmæssig funktionsnedsættelse og betydelige komorbiditeter. Mennesker med depression er sårbare og har en øget risiko for tidlig død og selvmord. Flere faktorer kan være med til at bestemme udfaldet blandt patienter med depression, og organiseringen og leveringen af sundhedsydelser vil sandsynligvis spille en vigtig rolle for patienterne. Inden for somatiske sygdomme er der betydelig evidens for forskelle i behandling og sygdomsforløb, fx i forhold til køn, socioøkonomiske forhold, etnicitet eller geografi, men der er stadig sparsom viden om disse forhold inden for psykiatrien.

Denne afhandling har til formål at undersøge uligheder i kvaliteten af behandling, såvel som i de kliniske udfald baseret på alder, køn, indlæggelsesvolumen og geografisk bopæl for patienter indlagt med en depression.

Der er gennemført tre registerbaserede, landsdækkende studier der inkluderede alle patienter med depression og en førstegangsindlæggelse på psykiatrisk hospital i Danmark mellem 2011-2016. Ulighed blev undersøgt som forskelle i kvaliteten af pleje defineret som opfyldelse af procesindikatorer for pleje og forskelle i kliniske udfald efter 1 år, dvs. genindlæggelse, selvmordsadfærd og 1-års mortalitet.

For alle tre studier blev der observeret forskelle. Studie I fandt, at uanset køn havde patienter i alderen 66 år eller ældre større sandsynlighed for at modtage pleje af høj kvalitet samt de fleste af de individuelle procesindikatorer, sammenlignet med patienter i alderen 18-39. Studie II viste, at patienter indlagt på et psykiatrisk hospital med høj volumen havde en højere 1-års mortalitet efter deres indlæggelse sammenlignet med patienter indlagt på et hospital med lavt volumen. Studie III fandt variation af 1-års mortalitet og selvmordsadfærd for patienter mellem de fem administrative regioner i Danmark, med den højeste risiko i Region Nordjylland.

Afslutningsvis viser resultaterne af denne afhandling, at der er ulighed blandt indlagte patienter med depression med hensyn til modtagelse af guideline-anbefalet pleje og i kliniske udfald. Dette understreger vigtigheden af systematisk at monitorere og forbedre kvaliteten af plejen for at lokalisere uligheder, evaluere initiativer og forbedre patientresultater, herunder mortalitet og selvmordsadfærd for denne sårbare gruppe. Yderligere studier er berettigede for at undersøge, om de identificerede associationer afspejler kausale mekanismer.

LIST OF PAPERS

This thesis is based on the following three papers:

PAPER I

Rasmussen LR, Videbech P, Mainz J, Johnsen SP. Gender- and age-related differences in the quality of mental health care among inpatients with unipolar depression: a nationwide study. *Nord J Psychiatry*. 2020 Nov;74(8):569-576. doi: 10.1080/08039488.2020.1764619. Epub 2020 May 13. PMID: 32401125.

PAPER II

Rasmussen LR, Mainz J, Valentin JB, Videbech P, Johnsen SP. Hospital inpatient volume and clinical outcomes among patients with incident depression: a nationwide study. Manuscript in review.

PAPER III

Rasmussen LR, Mainz J, Valentin JB, Videbech P, Johnsen SP. Geographical variation in clinical outcomes among patients with depression: a nationwide study. Manuscript under preparation.

LIST OF ABBREVIATIONS

| | |
|----------------|--|
| aOR | Adjusted odds ratio |
| aRR | Adjusted relative risk |
| CCI | Charlson Comorbidity Index |
| CI | Confidence interval |
| CPR | Central Person Register number |
| GP | General practitioner |
| HAM-D17 | Hamilton Depression Scale |
| HR | Hazard ratio |
| ICD-10 | International Statistical Classification of Diseases and Related Health Problems 10th Revision |
| OECD | Organisation for Economic Co-operation and Development |
| OR | Odds ratio |
| RKKP | The National Clinical Registries |
| RR | Relative risk |
| SE | standard error |
| WHO | World Health Organization |

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*Line Ryberg Rasmussen
Copenhagen, 2023*

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CHAPTER 1. INTRODUCTION

Depression is among the most costly diseases to society (1) and has major negative impact on public health due to loss of quality of life and shorter life expectancy for those affected. Recent studies have showed that individuals with major depression, on average, die about 10 years earlier than those who are not depressed, even when excluding deaths by suicide (2-4) The first scientific publication on excess morbidity among patients with mental illness was published in 1932 (5), however, a significant mortality gap still persists today with the average life expectancy reduced by 15-20 years for patients with severe mental illness (6). Furthermore, studies indicate that the gap may even have widened in recent years (2,7).

Since depression is a major public health and clinical challenge for the health care system, it is particularly important that the health care system is organized in the most appropriate way, so that patients are ensured the best possible treatment and outcomes and that resources are used in the most efficient way.

For a number of years, there has been a focus on improving the quality of health care efforts in the psychiatric field in Denmark through the implementation of a number of national quality improvement initiatives provided by the tax-financed and public Danish health care system (8-10). The most consistent effort has been made using systematic monitoring and auditing of quality-of-care performance measures based on data reported to nationwide clinical quality databases (9-12). The majority of indicators in the psychiatric databases are process performance measures, i.e., they reflect the extent to which patients receive specific clinical services in accordance with national clinical guidelines. Outcome measures try to describe the health status that follow and may be affected by health care and can be expressed as death, disease, discomfort, disability, and dissatisfaction (13).

The universal health coverage and the organization of the health care system in Denmark is intended to ensure free and equal access to health care and a high level of uniform treatment for all residents regardless of their background, e.g., age, sex and residence (14). Further, the unique Danish patient identifier enables linkage between the national health databases which contains high-quality data and covers the whole population. This setting creates a unique opportunity to access potential disparities in hospital quality of care and clinical outcomes after incident admission, as well as investigate whether equal access also implies equal and sufficient medical care for patients admitted with depression.

1.1. DEPRESSION

Depression is a common mental illness that affects an estimated 3.8% of the global population, including 5.0% among adults and 5.7% among adults over the age of 60 years (15). According to the World Health Organization (WHO), depression is the fourth leading cause of loss of quality of life and life years worldwide (16). It is consequently an important cause of the disease burden worldwide, with more than 264 million people affected and it is expected to be the leading cause of the disease burden globally in 2030 (17). Many cases become chronic, leaving treatment results unsatisfactory, and an increasing number of patients with depression end up receiving disability pensions (18). As a consequence of the disease burden, the economic burden on society is also substantial due to the high indirect costs caused by loss of productivity and unemployment (19-23). The estimated yearly cost of lost production due to depression in Denmark alone is approximately 0.5 billion US dollars (24).

In Denmark, the point prevalence of major depression is 3.3% (25) and the lifetime risk of depression is 17-18% (16). Hospitalization is usually recommended for patients with more severe symptoms and functional impairment and based on the Danish National Patient Register (26), there is yearly 11,000 new cases of depression admitted to a psychiatric hospital and it is estimated that 59,000 women and 32,000 men are living with depression (24).

1.1.1. MENTAL / MEDICAL CONSEQUENCES

Depression is typically the result of a complex interaction of social, psychological, and biological factors. Stressful life events, such as unemployment, bereavement, traumatic events can trigger a depression (15). Depression can be characterized as mild, moderate or severe, depending on the level of functioning and symptoms such as feeling sad, irritable or empty together with several psychophysiological changes, such as disturbances in appetite, sleep and sexual desire, loss of pleasure or interest in activities and low energy (15,27). Other symptoms such as poor concentration, low self-worth, feelings of guilt, and thoughts about dying might also be present (15). These changes and symptoms must be present for at least two weeks and interfere significantly with work and family relations in order to qualify for a diagnosis of clinical depression (15,27). Thus, depression is a serious disease associated with poor physical health and functioning, occupational impairment, significant comorbidities and an increased risk of early death and suicide (2,28,29). Suicide is the fourth leading cause of death among 15-29-year-olds, accounting for more than 700.000 deaths every year (15). The lifetime risk of suicide attempts is 3.45 times higher for patients with depression (30). In addition, there is a link between somatic and mental illnesses, which can reinforce or lead to each other. For

example, patients with cardiovascular disease have more depression than the general population and patients with depression are more likely to eventually develop cardiovascular disease and also have a higher mortality rate than the general population (31). A systematic review and meta-analysis have found that patients with depression have a 1.71 times higher all-cause mortality rate, and a reduction in life expectancy with a median of 10 years compared to the general population or people without mental disorders (32).

1.2. PSYCHIATRY IN DENMARK

The Danish health care system is organized on three administrative levels (33). Legislation, national guidelines, and health care financing are all overseen by the state through the Ministry of Health. Primary care in general practice, outpatient specialist care, and in- and outpatient hospital care are all under the control of the five Danish regions. Finally, public health, prevention, rehabilitation, home nursing, child dental care, and school health are all responsibilities of 98 municipalities (33).

For the psychiatric field that means the regions are responsible for providing psychiatric services, which includes inpatient and outpatient treatment in psychiatric hospitals, centres, and departments. In addition, the responsibility includes outreach psychosis teams, other outgoing teams, and district psychiatry, which is for people who have a mental disorder and need psychiatric treatment, but who do not need to be hospitalized. Further, the regions must provide consultancy assistance to regional and municipal institutions (34). The municipalities are responsible for social psychiatry, which includes various types of social services for citizens with mental health issues. In social psychiatry, services such as residences, shelters and activity centres, support and contact person schemes and support for employment are offered. In a number of cases, the regions are suppliers of social psychiatric services (34).

However, the scope of this thesis only focuses on inpatients with incident depression.

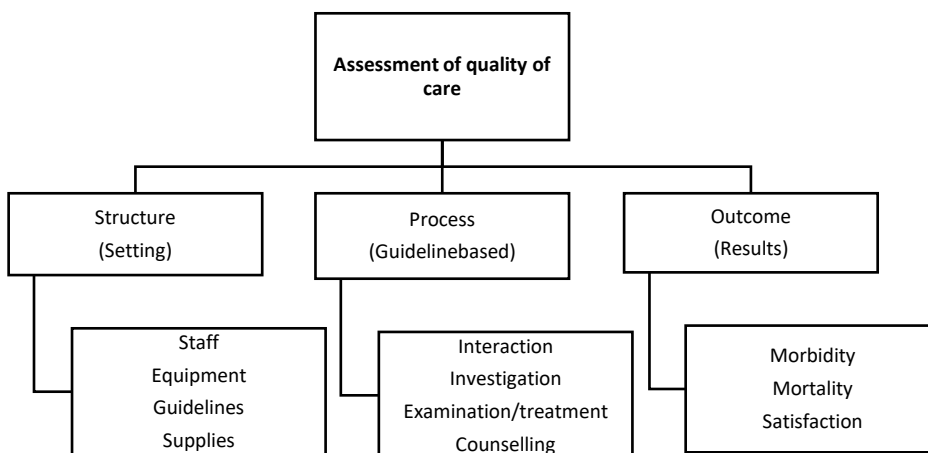
1.3. QUALITY OF CARE

Denmark has been a pioneer country in monitoring and policy development for quality of care among countries in the Organisation for Economic Co-operation and Development (OECD) (14). Quality of care has been defined as “the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge”

(13,35,36). Thus, health care quality is defined as the extent to which fundamental health services increase the likelihood of patients or patient groups attaining the expected treatment results based on current evidence (37). In order to evaluate and improve quality of care, the quality needs to be measured. This can be done using specific quality indicators (12,13). Quality indicators or performance measures are used to evaluate and monitor to which extent the patient care is consistent with the evidence-based standards of care and whether the health care system meets patients' needs (12,13).

Quality of health care can be assessed with Donabedian's three components model. The model assesses quality of care according to structure, process and outcome (Figure 1) (38,39). Structure performance measures describe the setting in which the care occurs, process performance measures describe what the practitioner have done for the patient, and outcomes measures describe the effect of care on the related health outcomes (13). The fundamental assumption is that having a good structure most likely will lead to good processes and, as a result, good patient pathways, all of which increase the likelihood that patients attain the best outcome (38,39). In this thesis, the analyses regarding the quality of care were based on process performance measures.

Figure 1 Modified Donabedian model for assessment of quality of care.



The quality of care delivered by the Danish healthcare system has been systematically monitored for more than a decade by a nationwide multidisciplinary initiative (8-10). However, there have only been very little focus on the equity aspect of quality of treatment, which was criticized in 2019 in a report made by the

Danish National Audit Office (Rigsrevisionen) (40). The report concludes that neither administrative nor political authorities have made progress in initiating systematic monitoring of disparities in the quality of care in the Danish hospitals (40).

The National Clinical Registries (RKKP) was established in 2010 and covers more than 85 national clinical quality registries which monitor the quality of care for specific diseases (10,33). The data provided to the national clinical quality registries is systematically collected in relation to patient pathways in terms of process and outcomes indicators. The performance measures are created by expert health professionals appointed by scientific societies and professional organizations and are often based on recommendations from national clinical guidelines (8,10,12,13,33). Even though no systematic collection of data on possible disparities in the quality of care have been made, data from the national clinical registries have been used in several scientific studies to explore potential disparities between population groups. Studies have found disparities in the quality of care among patients with chronic obstructive pulmonary disease (41), heart failure (42), and diabetes (43). Despite our knowledge of existing disparities in the quality of care for somatic illnesses, it is unclear how extensive our understanding of potential disparities in mental health care is, i.e., the potential disparities created in the interaction between the health care system and the mentally ill patient.

1.4. INPATIENT VOLUME

In many advanced health care systems high patient volume and centralized treatment have been prioritized for decades. This, however, have primarily been in relation to somatic diseases, whereas the research activity in the psychiatric field is sparse. In 1979 Luft et al., published their first study on the subject of surgical volume (44,45). Since then, numerous studies have examined the connection between patient volume and outcome for somatic diseases. There is growing evidence that a higher inpatient volume per ward is associated with improved clinical outcomes, including lower mortality rates and fewer complications for a variety of medical conditions and surgical procedures (46-49). A trend toward centralized care across medical specialties and health care systems has been sparked by these findings; However, centralization is a complicated process, and it cannot be assumed that the findings from specific medical conditions can be applied to all areas or that expanding centralized units to ever larger sizes will always lead to better outcomes for patients. Thus, some studies indicate the existence of potential patient volume thresholds above which the overall outcome for patients will be negative. For instance, a higher 30-day mortality rate following hip fracture surgery was reported in high-volume hospitals in a setting where care was already quite centralized (50). Therefore, it will

be of interest for patients, policymakers, and society to get an insight into the association between psychiatric inpatient volume and clinical outcomes.

1.5. GEOGRAPHICAL VARIATION

Small-area analyses or analyses of geographical variation focuses on specific areas or populations to find unwarranted variation among small areas within a larger statistical pattern. John Wennberg, a pioneer and leading researcher of unwarranted variation in health care, has investigated and documented unwarranted variation in treatment and clinical outcomes among patients in the United States for decades (51). It has previously been demonstrated that small-area variation analyses in use of effective therapies is a useful method for identifying and describing unwarranted variation in health care (52). Analysis of small-area variation can identify disparities in health and service delivery, which can uncover underserved areas, lack of access, and communities that experience a variety of adverse health, economic, and social problems more severely than others, and identifying and reducing such variation should be a priority for health providers (52).

1.6. CLINICAL OUTCOMES

When investigating depression, multiple outcomes would be relevant to examine such as attachment to the labour market, recurrence of depression, quality of life etc. For the purpose of this thesis, readmission, suicidal behaviour, and 1-year all-cause mortality was chosen due to the importance of these outcomes and availability of valid data.

1.6.1. READMISSION

The association between inpatient hospital volume and readmission among patients hospitalized with depression, and geographical variation of readmission on regional level is investigated in this thesis. Readmission can be defined as the event where a patient after discharge from hospitalization is admitted again, often with the same diagnosis, within a specific time frame, such as 30-day, 90-day or 1-year readmission.

Readmission rates have been widely used in psychiatry as a measure for complications after hospitalization or relapse of the condition (53) and in general it has been reported that a significant proportion of psychiatric inpatients are

readmitted following medical hospitalizations (54,55). A recent study from Canada found a 30-day readmission rate of 6.8% and a 5-year readmission rate of 34% for mood disorders following their first psychiatric hospitalization (56).

Some reason that predischarge factors such as the length of stay and the quality of inpatient care of the preceding hospitalization can condition readmission rates (53). This assumes that the readmission to the hospital would not have occurred if sufficient treatment had been provided to stabilize the patient's mental condition and planning for further treatment in primary care had been made (57), which emphasizes events following discharge and the need of continuity of treatment, with a focus on outpatient institutions' lack of coordination or follow-up (53). Younger patients may have a stronger network and more resources to adhere to treatment, rehabilitation, and secondary prevention, while older patients might be more vulnerable. Likewise, place of residence could be a proxy for socioeconomic variables and the resources to remain compliant. If factors such as sex, age, hospital inpatient volume and place of residence effects the quality of care received by individuals at hospitalization, these differences could result in variations in readmissions.

1.6.2. ALL-CAUSE MORTALITY AND SUICIDE

In this thesis, the association between hospital inpatient volume and all-cause mortality and suicidal behaviour and geographical variation in all-cause mortality and suicidal behaviour are investigated among inpatients with depression. Compared to the general population, patients with severe mental disorders have a life expectancy approximately 20 years shorter for men and 15 years shorter for women in Nordic countries (6). Further, higher mortality only related to depression specifically (32) as well as higher mortality among patient with depression and somatic diseases have been found (58-61). A study found that overall mortality is approximately two times higher among a Danish population with depression, which reduces life expectancy 10 years for women and 14 years for men (3). The mortality rate ratio was found to be highest for unnatural death causes such as suicide and accidents (3).

Worldwide suicide is the 17th leading cause of death, accounting for 1.4% of all deaths (62). According to a previous meta-analysis, approximately 80% of people committing suicide had a mental disorder at the time of death, and around 40% of all the suicides were committed by people with a depression (63). Another study found that among patients with depression about 15% died by suicide (64). Patients recently discharged from or admitted to psychiatric wards are particularly vulnerable. A Danish register study from 2020 found that, in comparison to those who were never hospitalized, the suicide rate among those admitted to or discharged

from psychiatric hospitals was >100 times higher (65). The increased risk for hospitalized and discharged patients is observed for both affective disorders in general (66,67) and patients with depression (65,68,69).

1.7. LITERATURE AND EXISTING KNOWLEDGE

To clarify what is already known about the topic covered in this thesis, a search for scientific publications was conducted. The search focused on identifying publications regarding, respectively, the association between sex, age and the quality of inpatient care, the association between inpatient volume and clinical outcomes (i.e., 1-year all-cause mortality, suicidal behaviour and readmission), and the association between geographic residence and clinical outcomes.

The literature search was done in PubMed, Embase and PsycINFO with a combination of MESH terms, Emtree and free-text such as *Health care disparities*, *Quality of health care*, *Outcome and process assessment*, *Inpatient volume*, *Geographical variation*, and *Small-area analysis*. The search had no limitations on publication year and literature in Scandinavian languages and English were included. Studies were excluded if they were considered non-relevant based on the title, abstract or full text. Additionally, the reference lists of the included papers were reviewed to identify relevant publications.

1.7.1. QUALITY OF CARE

The literature search identified six relevant publications examining the quality of care among patients with depression: five research studies and one national report (70-75). Table 1 provides an overview of the identified studies, listed by publication year. Among these is a study from USA by Bauer et al., which examined whether demographic characteristics, including sex and age, were associated with treatment quality of the depression (74). The quality was assessed as contact with a follow-up care manager within the first three weeks of treatment and medical treatment given according to the national guidelines. They found an age-related difference, with the odds of receiving appropriate pharmacotherapy increasing by 9.6% for each decade of age. Contrary to this finding, four other studies found that, compared to younger patients, older patients had less access to quality care regarding mental health (70,71,73,75). One of the U.S. studies found that depression treatment was provided less frequently to older patients compared to younger adults, regarding both receiving psychotherapy (odds ratio (OR) 0.28 (95% confidence interval (CI) 0.26-0.31)) and antidepressant drug treatment (OR 0.67 (95% CI: 0.63-0.72)) (75). Another study from USA by Fischer et al., found that younger patients were more likely to report that their physicians asked diagnostic-related questions (i.e.,

questions about affect, suicide risk, past treatment) (71). Patients aged 75 or older had an OR of 0.06 (95% CI: 0.02-0.15) and patients aged 35-44 had an OR 0.62 (95% CI: 0.39-0.99) when compared to patients aged 35 or younger, respectively (71). Furthermore, two studies analysed sex-related differences in mental health care and showed that, compared to men, women had a statistically significant higher chance of receiving treatment according to clinical guidelines (70,72). However, no significant sex-related differences in quality of care were observed in the study by Bauer et al. It is, however, worth mentioning that only 17% of the treated patients were men (74).

In general, the existing studies on age and sex related differences in depression care focused on the quality of treatment after the discharge and in primary care settings. Hence, there is a paucity of data on in-hospital care.

Table 1 Summary of identified literature on the association between sex, age and the quality of care among patients with depression

| Author, year, country | Study design (period) | Study size and setting | Quality of care measures | Main results | Limitations |
|--------------------------------|--|--|--|--|--|
| Young et al., 2001, USA (70) | Cross-sectional telephone survey 1997 to 1998 | 1322 respondents with major depression, dysthymia or both. | Appropriate psychotropic medication; at least two months of antidepressant medicine at an adequate dosage or a benzodiazepine. | Appropriate treatment was less likely for men and those younger than 30 or older the 59 years. | Use of a brief diagnostic screening instrument to identify patients with a probable disorder. The use of health care services during the prior 12 months were self-reported, which could lead to possible information bias. |
| Fischer et al., 2003, USA (71) | Survey, chart audits 1998 to 1999 | 1023 respondents with incident depression who had an appointment in one of nine primary care | Care processes (assessment, resources) and improvement in depression symptoms. | Younger patients (<35) were more likely to report that the physician asked diagnostic-related questions. Male sex was likewise associated positively with care | The study sample is drawn from a health maintenance organization (HMO) in the Midwest and is not representative for the US population. The younger patients had |

| | | | | | |
|---|---|---|--|---|--|
| Hinton et al., 2006, USA (72) | Cross-sectional | clinics in the Midwest. | | process variables. | a lower response rate, which could make for selection bias among the younger subsamples. The self-report survey could also make for information bias among the older patients. |
| | 1613 patients aged 60 or older with major depression or dysthymic disorder from 18 primary clinics. | Use of antidepressant medication, receiving psychotherapy and any depression care; all within the last three months. Any lifelong depression care. Potentially effective depression treatment - defined as at least two months of medical treatment or four sessions of psychotherapy within the last three months | Depressed men were less likely to have received prior treatment on four of the five measurements of depression care. | Limited to patients ≥ 60 years old. The specific study period and location in USA was unclear. | |
| Healthcare Commission, 2009, England (73) | National report February and | Six mental health trusts, representing approximately 10% of all mental | Access to out-of-hours and crisis services, psychological therapies, and alcohol services. | Studies from the mental health centres indicated that there was age discrimination in psychiatry in general, as | The report is based on visits and interviews with six different mental health trust, and examination of |

DISPARITIES IN CARE AND OUTCOMES AMONG PATIENTS ADMITTED WITH DEPRESSION

| | | | | | |
|---------------------------------|-----------------------------------|---|---|--|---|
| | March 2008 | health trust in England. | | older patients over the age of 65 received far from the full range of available treatment compared to younger patients | national datasets. |
| Bauer et al., 2012, USA (74) | Follow-up study 2006 to 2009 | 2821 patients with symptoms of depression from six community health organizations in Texas. | Receipt of high-quality care; receiving a follow-up contact within the first three weeks of treatment. Appropriate pharmacotherapy was received if the treatment plan included an antidepressant medication at a therapeutic dose based on public guidelines. | Older patients were more likely to receive appropriate pharmacotherapy and to be retained in treatment. Gender was unrelated to depression outcomes. | All data was collected during routine clinical care of patients; thus information on variables with a possible association to depression, such as income, education and concurrent medical illness, were unavailable. |
| Sanglier et al., 2015, USA (75) | Matched cohort study 2003 to 2006 | 31,580 patients (6316 \geq 65 and 25,264 aged 25-64) with a new episode of depression. | Psychotherapy dispensing; two or more occurrences of psychotherapy within 120 days of the diagnosis. Antidepressant | During the 120 days follow-up from the diagnosis, treatment was provided less frequently to the older patients than the younger adults: both regarding psychotherapy | Possible selection bias due to lesser detection of depression in the elderly compared with the younger adults. |

CHAPTER 1. INTRODUCTION

| | | | | | |
|--|--|--|---|------------------------------------|--|
| | | | dispensing; presence of any antidepressant drug treatment claim within 120 days of the diagnosis. | and antidepressant drug treatment. | |
|--|--|--|---|------------------------------------|--|

1.7.2. INPATIENT VOLUME

The literature search identified no publications investigating 1-year mortality or suicidal behaviour among patients with depression. One paper was identified on the association between inpatient volume and readmission among patients with mental disorders (76). This publication reported from a study including 77,106 consecutive psychiatric admissions to 128 hospitals in Taiwan during 2003. Volume was measured as the total number of psychiatric admissions at hospital-level and the primary outcome was 30-day readmission. The study found a 30-day readmission rate of 16.6% for major depressive disorder and reported higher odds of 30-day readmission for medium-volume hospitals (OR: 1.64 (95% CI: 1.27-2.12)) and for high-volume hospitals (OR: 4.75 (95% CI: 3.55-6.36)).

Readmission rates for psychiatric inpatients have also been examined by inpatient volumes per psychiatrist in two publications (77,78). These studies found that patients with major depression and mood disorders admitted to high-volume hospitals had a higher risk of readmission compared to patients at hospitals with low volume.

The literature search indicates that there could be an association between inpatient volume and readmission, however, the evidence is very limited.

1.7.3. GEOGRAPHICAL VARIATION IN DEPRESSION OUTCOMES

The literature search identified no publications on the geographical variation in 1-year mortality, suicidal behaviour, or readmission among patients with depression.

However, a study from the US has shown that the cumulative incidence of depression was higher in low-socioeconomic status neighbourhoods compared to high-socioeconomic status neighbourhoods (19.4 per 100 persons (95% CI: 13.5-25-3) vs. 10.5 (95% CI: 5.9-15.2)) (79).

Another US study examined trends in bipolar disorder and depression as a cause of death on death certificates by demographic subgroups including the four regions of the US (80). For depression, the age-standardized mortality rate was highest in the Midwest with a rate of 7.480 (standard error (SE) 0.114) that was statistically significantly higher than for the entire US. The lowest rate was found in the South (4.027 (SE 0.066)), with an age-standardized mortality rate that was statistically significantly lower than for the entire US (80).

Likewise, a Danish study from 1996 found geographical variations in first ever admission rates for manic-depressive psychosis (81). The study showed that over the

period of 1977 to 1993, a comparison of the individual counties discovered significant geographical variations in terms of incidence level and temporal trends.

The research on geographical/small area variation are sparse in the psychiatric field; however, the above studies on geographical variation show differences in cumulative incidence of depression depending on socioeconomic status neighbourhoods, in age-standardized mortality rate of depression as cause of death and in admission rates for incident manic-depressive psychosis, which indicate that more research is needed on the association between place of residence and clinical outcomes among patients with depression.

1.7.4. SUMMARY AND LIMITATIONS OF THE IDENTIFIED LITERATURE

In summary, the existing evidence on disparities in quality of care and the clinical outcomes 1-year mortality, suicidal behaviour, and readmission among inpatients with depression is sparse and lacking. Most of the identified literature studied the association between sex and age and quality of care, however, the measures of the quality of care differed from study to study. Furthermore, the few studies identified are more than ten years old. Two studies used data from the last century and most of the studies used a cross-sectional design.

Hence, the identified literature strongly suggests a need for population-based studies to fill in the gaps and provide new knowledge to clarify the disparities in quality of care and the clinical outcomes including mortality, suicidal behaviour, and readmission among inpatients with depression.

CHAPTER 2. AIMS AND HYPOTHESES

This thesis aims to examine the association between disparities in the quality of inpatient care for inpatients with depression, as well as in the clinical outcomes based on inpatient volume and geographical variation. This is investigated in three nationwide population-based cohort studies with the following objectives:

2.1. STUDY I

To examine the association between sex and the quality of inpatient care, and between age and the quality of inpatient care for depression as reflected by the fulfilment of specific clinical guideline-based process performance measures of care among Danish patients admitted with depression.

We hypothesized that male patients and younger patients were more likely to fulfil guideline recommend process performance measures compared to older patients.

2.2. STUDY II

To examine whether patient volume in depression wards is associated with 1-year all-cause mortality, suicidal behaviour, and readmission among patients with depression.

We hypothesized that patients admitted to a high-volume hospital would be less likely to be readmitted, to have less suicidal behaviour and have a lower 1-year mortality.

2.3. STUDY III

To examine the geographical variation in clinical outcomes such as 1-year all-cause mortality, suicidal behaviour, and readmission among patients with depression in Denmark.

We hypothesized that there is no geographical variation between the five Danish Regions in terms of 1-year mortality, suicidal behaviour, and readmission among patients with depression.

CHAPTER 3. METHODS

All three studies were designed as cohort studies based on The Danish Depression Database and nationwide registers. Table 2 gives a brief overview of the studies.

Table 2 Overview of materials and methods

| | Study I | Study II | Study III |
|-------------------------|---|--|--|
| Objectives | To investigate sex- and age-related differences in the quality of mental health care reflected as the fulfilment of process performance measures of care among inpatients with depression (82). | To examine the association between hospital inpatient volume and 1-year all-cause mortality, suicidal behaviour, and readmission among patients with depression. | To investigate the geographical variation in 1-year all-cause mortality, suicidal behaviour and readmission among patients admitted with depression. |
| Setting | Denmark 2011-2016 | Denmark 2011-2017 | Denmark 2011-2017 |
| Data sources | The Danish Depression Database | The Danish Depression Database, Registry of Causes of Death, the Danish Civil Registration System, The Danish National Patient Registry, Statistics Denmark. | The Danish Depression Database, Registry of Causes of Death, the Danish Civil Registration System, The Danish National Patient Registry, Statistics Denmark. |
| Study population | Patients admitted with a depressive disorder at a psychiatric hospital between 2001-2017 and identified in the Danish Depression Database. | | |
| Exposures | Age and sex | Inpatient volume defined as the annual number of inpatients with a depressive disorder treated at a psychiatric hospital per year. | Places of residence at the time of hospital admission defined as the five regions in Denmark. |
| Outcomes | Quality of mental of mental health care as reflected by the fulfilment of specific | 1-year all-cause mortality, suicidal behaviour up to 1 year after admission | 1-year all-cause mortality, suicidal behaviour up to 1 year after admission |

| | | | |
|-----------------------------|--|---|--|
| | clinical guideline-based process performance measures. | and readmission due to depression and all-cause readmission within 1 year. | and readmission due to depression and all-cause readmission within 1 year. |
| Covariates | Inpatient volume | Age, sex, ethnicity, Hamilton Depression Rating Scale, Charlson Comorbidity Index (CCI), substance misuse, place of residence, income, educational level. | Age, sex, ethnicity, income, educational level, CCI, substance misuse, inpatient volume, and Hamilton Depression Rating Scale. |
| Statistical analyses | Binomial regression adjusted for inpatient volume. The analysis was stratified by sex and age. High overall quality of care was defined as a patient fulfilling 80% or more of all relevant recommend process performance measures (82). | Separately for 1-year all-cause mortality, suicidal behaviour and readmission, we computed and plotted: - Cox proportional hazards regressions were calculated in three models. - Adjusted effect measures using Inverse probability of treatment weights. - Implemented restricted cubic splines to examine the non-linear association of inpatient volume and the clinical outcomes. | Multilevel mixed-effects regression with two levels: patient and region of residence random effect variable). A median relative risk was computed with the Poisson distribution in order to estimate the size of variation and absolute risks. |

3.1. SETTINGS

In Denmark the health care system is mainly tax-financed and covers approximately 85% of all health care expenses (33). This secures equal and free access to primary care in terms of general care, hospital care and outpatient specialist care, while co-payments are only required for pharmaceuticals and specialized services like psychology, dentistry, and physiotherapy (33). The health care system consists of primary and secondary sector, where the general practitioner in the primary sector treats general health problems and the public hospitals in the second sector treat patients requiring specialized treatment. The public hospitals consist of both emergency room contacts and in- and outpatients (83).

All residents in Denmark are assigned a CPR number, which is an abbreviation of 'Central Person Register'. The unique ten-digit personal identification number is used in all public, national registries, which ensures linkage of information on the individual level between the registries (33). In relation to the care provided, the collected variables include e.g., diagnostic and procedure codes, date of contact and the quality of care defined as receiving guideline-concordant performance measures of care (10,26). With the availability of comprehensive health care data, this setting creates a unique opportunity to examine potential disparities in hospital quality of care and clinical outcomes after incident admission, as well as investigate whether equal access also implies equal and sufficient medical care for patients admitted with depression.

3.2. DATA SOURCES

The data sources applied is described in the following, including the Danish Clinical Registries (the Danish Depression Database), the Danish National Patient Register, the Danish Civil Registration System, the Danish Register of Causes of Death and Statistics Denmark. It is mandatory for all public hospitals in Denmark to report to these registries.

3.2.1. THE DANISH DEPRESSION DATABASE

The Danish Depression Database is a nationwide clinical quality database, and a part of RKKP, that monitor the quality of treatment and care for all patients admitted to a psychiatric hospital or associated with an outpatient clinic in Denmark. The database was launched in 2011 and since then approximately 5.500 inpatients and 7.500 outpatients have been registered in the database each year. The database collects

data corresponding to performance measures for hospitalized and outpatients with depression (84).

All Danish psychiatric hospitals treating patients with depression are required to report data to the registry. The database comprises of data on process performance measures based on care recommendations from The Danish Health Authority's national clinical guidelines (16). An expert group comprised of psychiatrists, psychologists, nurses, occupational therapists, and social workers chose the performance measures (9). Of the 17 process performance measures of care monitored in the database, nine are relevant to inpatients, and eight are relevant to outpatients (83). Patients with permanent residency in Denmark over the age of 18 are included in the database. The database includes information on the quality of care along with admission and discharge dates for all patients discharged from Danish psychiatric hospitals with a primary diagnosis of unipolar depression (19). Denmark has no private psychiatric hospitals, thus, the registration of hospitalized patients with depression in the database is considered complete.

3.2.2. THE DANISH NATIONAL PATIENT REGISTER

The Danish National Patient Registry was established in 1977 and contains information on all patients discharged from Danish non-psychiatric hospitals. From 1995 all psychiatric inpatients, emergency department and outpatient contacts have been included (26). Every patient contact will be recorded according to the International Classification of Diseases with one primary diagnosis and an optional secondary diagnosis supplementing the primary diagnosis. The Danish National Patient Registry provides administrative data, data on diagnoses, certain medical treatments and surgical procedures, and examinations (26).

3.2.3. THE DANISH CIVIL REGISTRATION SYSTEM

The Danish Civil Registration System was established in 1968 as an administrative register and it contains individual-level information on all Danish residents. Information on migration and vital status are updated daily, which allows nationwide cohort studies with nearly complete long-term follow-up on emigration and mortality (85). The data in the Danish Civil Registration System are nearly complete and is considered highly accurate with unknown status of around 0.3% persons (12,85,86). Assigning a unique ten-digit Civil Personal Register number to all individuals in the Danish Civil Registration System enables accurate individual-level and cost-effective record linkage between Danish registers (85).

3.2.4. THE DANISH REGISTER OF CAUSES OF DEATH

Since 1970, The Danish Register of Causes of Death has been fully computerized and contains individual-based data of all deaths among Danish residents dying in Denmark. The register includes data on the immediate and underlying causes of death as well as contributory causes (87).

3.2.5. OTHER REGISTERS

Statistics Denmark is a state institution, containing individual-level data from administrative registers and governmental agencies. Data were retrieved from the following registries:

The Population Education Register (88) includes information about individuals' highest completed education and the eight-digit education code transforms easily into the code from the International Standard Classification of Education (ISCED) (88,89).

The Employment Registry is an annual labour market status based on labour-force participation in the population at the end of November (90). The Danish population are divided into three socioeconomic main groups depending on their connection to the labour market: those who are employed, those who are unemployed and people outside the labour market (90).

The Income Statistics Register include the total population living in Denmark who is economically active and pays taxes (91). The statistics are based on daily deliveries from the Central Population Register and are produced for individuals, households, and families. These units are described based on variables associated to households and families such as size of family and type of family or household. The statistics are based on CPR data on age, sex, marital status, information on address and references to partners and parents. The information on address data serves as the foundation for categorizing into households, municipalities, and regions.

3.3. STUDY POPULATION

The study population of all three studies were identified from the Danish Depression Database.

3.3.1. STUDY I

Study I (82) included all inpatients above the age of 18 who were treated at a psychiatric hospital and registered in the Danish Depression Database between 1 January 2011 and 31 December 2016. The Danish Depression Database includes patients with a primary diagnosis of depression as defined by the International Classification of Diseases version 10 (ICD-10, codes F32.0 to F32.99, F33.0 to F33.99, F34.1 and F06.32) (92). Since readmissions are not assumed to be comparable with one-time admissions, only the first recorded admission per patient at each psychiatric hospital in each calendar year were included. Hospital wards with only sporadic admissions of patients with depression were more likely to have insufficient routines for reporting data to the Danish Depression Database; therefore, hospital wards with fewer than 20 recorded admissions during the entire study period were excluded.

3.3.2. STUDY II + III

Study II (93) and study III (94) comprised all inpatients (≥ 18 years old) from the Danish Depression Database with an admission between 1 January 2011 and 31 December 2017. To ensure that only patients with incident depression were included, patients with a registration of a depressive diagnosis in the Danish National Patient Registry up to ten years before their first registration in the Danish Depression Database and all non-incident admissions were excluded. If admissions were shorter than 24 hours, they were excluded to ensure that the depression required treatment. Multiple admissions within four days were considered one and combined. The combined admission was excluded if all the admissions were shorter than 24 hours. Patients were excluded if they had immigrated to Denmark within ten years before admission or had left the country before admission. Lastly, due to the follow-up period, patients with admission in 2017 were excluded.

In study III, patients with missing information on residence were excluded.

3.4. OUTCOMES AND EXPOSURES

3.4.1. STUDY I

The first study investigated sex and age on the quality of care among inpatients with depression. Age was divided into age groups: 18-39, 40-65, 66-79 and ≥ 80 years. Quality of care was defined as fulfilment of the process performance measures found in the Danish Depression Database. For the outcome of quality of inpatient care, nine process performance measures were used; these are summarized in Table 3.

Table 3 Process performance measures for quality of inpatient care in the Danish Depression Database (82)

| Process performance measures | Definition |
|-------------------------------------|--|
| Examination by psychiatrist | Indication of whether the patient's psychopathological assessment was performed by a specialist in psychiatry within seven days after admittance to the hospital ward. |
| Somatic examination | Indication of whether somatic examinations were initiated within two days. |
| Assessment by a social worker | Indication of whether the patient was assessed for need of acute or longer-term support, such as help with changing housing, financial help to purchase medicine, rehabilitation, educational guidance, and application for disability benefits. |
| HAM-D17 ^a assessment (I) | Indication of whether the patient was assessed using HAM-D17 within seven days. |
| HAM-D17 assessment (II) | Indication of whether the patient was assessed using HAM-D17 at discharge from a hospital. |
| Suicide risk assessment (I) | Indication of whether the patient was assessed for suicide risk using structured interview at admittance. |
| Suicide risk assessment (II) | Indication of whether the patient was assessed for suicide risk when discharge from hospital is planned. |
| Contact with relatives | Indication of whether the staff had contact with the patient's relatives during hospitalization. |
| Psychiatric aftercare | Indication of whether the patient was referred to psychiatric aftercare. |

^a Hamilton Depression Scale (HAM-D17)

3.4.2. STUDY II + STUDY III

In the second study inpatient volume was defined as the average annual number of patients with a depressive disorder treated at a psychiatric hospital from January 1, 2011, and December 31, 2016. Inpatient volume was divided into tertiles and defined as low volume (< 267 patients per year), medium volume (268-477 patients per year) and high volume (> 478 patients per year) (93).

In the third study the exposure used was geographic residence on regional level: The North Denmark Region, Central Denmark Region, The Region of Southern Denmark, Region Zealand and The Capital Region of Denmark (94).

The same outcomes were used in study II and study III: All-cause mortality was determined from the Danish Civil Registration System and was defined as 1-year mortality, and follow-up started on the day of hospital admission. Suicidal behaviour was defined as death by suicide or poisoning or hospitalisation following a suicide attempt or poisoning up to 365 days after the day of hospital admission (ICD-10 codes DT36-DT39, T40-T49, T50.0-T50.9, DX50-X59, X60-X69, X70-X79, X80-X84 and DY87) (92). Readmission was divided into two groups: readmission with a depressive disorder as the primary diagnosis and all-cause readmission with any readmission within 365 days after discharge.

3.5. COVARIATES

The studies in this thesis used many common covariates (Table 4), which were extracted at the time of hospital admission. Family income was extracted the five calendar years before hospital admission.

Table 4 Covariates included in the studies

| Covariate | Details | Data source |
|--------------------|---|---------------------------------------|
| Sex | Dichotomous: Male or female | Danish Civil Registration System (86) |
| Age | Divided into four groups | |
| Migrant status | Divided into three groups: Not immigrant or descendent, Western country and other countries | |
| Cohabiting status | Dichotomous: cohabitating or living alone | |
| Place of residence | Grouped into the five regions of Denmark | |
| Comorbidity | Grouped in three: 0, 1 or ≥ 2 comorbidities defined using Charlson Comorbidity Index | |
| Substance misuse | Defined as a registration with a diagnosis of mental and behavioural disorder due to psychoactive substance use (ICD-10 codes DF10-DF19). | |
| Family income | Defined as the average yearly family income in the five years before admission and was divided into tertiles | The Income Statistics Register (91) |
| Employment status | Grouped in three: employed, unemployed | |

| | | |
|---|--|--|
| | and public pension | |
| Education | Defined by The International Standard Classification of Education (ISCED) as low (primary and lower secondary level), middle (upper secondary level) and high (short-cycle tertiary, bachelor, master and doctoral or equivalent level) (89) | The Population Education Register (88) |
| Hospital inpatient volume | Divided into tertiles and defined as low volume (≤ 267 patients per year), medium volume (268-477 patients per year) and high volume (≥ 478 patients per year) | The Danish Depression Database (84) |
| Hamilton Depression Rating Scale (17-items scale) | Grouped as no depression = ≤ 7 , subthreshold = 8-13, mild depression = 14-18, moderate depression = 19-22, severe depression = ≥ 23 (95) | |
| Calendar year | | The Danish Depression Database (58) |

3.6. STATISTICAL ANALYSES

Baseline characteristics were presented as numbers and percentages of the covariates inpatient hospital volume and place of residence, respectively. All analyses were carried out using STATA SE version 15.1 and 16 at Statistics Denmark remote server (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.).

3.6.1. STUDY I

In study I, the number of fulfilled process performance measures divided by the number of relevant process performance measures for the individual patient was used to calculate the overall quality of inpatient care. Binomial regressions were used to obtain relative risks (RR) as effect measures for the association. The results were presented with 95% confidence intervals (CI), which were corrected for patient clustering using robust estimates of variance. Analyses were adjusted for the calendar year of admission and inpatient volume (82).

In the primary analysis, high overall quality of care was defined by setting a pragmatic cut off point of 80%, i.e., high overall quality of care was a patient fulfilling 80% or more of all relevant recommended process performance measures. The analysis was repeated using different cut off points of 60%, 70%, and 90% (82).

Sensitivity analyses were carried out to assess the robustness of the primary analysis. On the unstratified data, a binomial regression analysis was performed with sex and age as covariates, adjusting for calendar year and inpatient volume. An ordered logistic regression was used to examine the association between age, gender, and the quality of depression care, where quality of care was defined as 0-39%, 40-59%, 60-79%, and 80%, respectively. A beta regression was used to investigate the associations between sex and age and the proportion of fulfilled process performance measures (82,96).

3.6.2. STUDY II

For the association between hospital inpatient volume and all-cause mortality, suicidal behaviour and readmission, Cox proportional hazards regression analysis with cluster robust variance was used to compute hazard ratios (HR) and cause-specific HRs (95% CI) with death as competing risk (93). Inverse probability of treatment weights (IPTW) was used to adjust the effect measures and balance diagnostics were conducted according to Zhang et al. (97). To handle missing

patient-related characteristics multiple imputations used all available information to construct ten sets of imputation (93).

Several sensitivity analyses were conducted. First, an alternative distribution of hospital inpatient volume, restricted cubic spline, with four knots located at the 5th, 35th, 65th and 95th percentile of the distribution, was used. Second, the associations were examined with inpatient volume measured from ward perspective instead of hospital perspective. Lastly, the severity of depression defined by the Hamilton score was included as a covariate in the adjustment (93).

Restricted cubic splines

As an alternative distribution of inpatient volume restricted cubic splines was used. Restricted cubic splines are a transformation of an independent variable and a way to test if the relationship between an outcome and the explanatory variable is too non-linear to be used summarized by a linear relationship (98).

The range of values of the independent variable is divided, with a set of knots. The knots are defining the end of one segment and the start of the next, with separate curves or regression lines between the knots. Thus, the splines are defined to make the resulting fitted curve continuous and smooth (98).

3.6.3. STUDY III

In study III (94), a multilevel mixed-effects regression with two levels; patient and region of residence (random effect variable), were used to examine the association between region and the clinical outcomes all-cause mortality, suicidal behaviour and readmission. The Poisson distribution was used to obtain a median relative risk in order to estimate the size of the variation and subsequently to obtain absolute risks. Effect measures were adjusted using inverse probability of treatment weights (94).

Disparities in health care capacity may impact the outcomes; thus, stabilised weights and trimming were used to adjust for investigate the role of patients pr. general practitioner in each municipality as a potential confounding factor (94,99).

As a sensitivity analysis only the population of patients with data regarding the Hamilton Depression Rating Scale were included. Further, an alternative grouping of municipalities based on the number of inhabitants in the largest city in the municipality and the accessibility to jobs (capital municipalities, metropolitan municipalities, provincial municipalities, commuter municipalities, rural municipalities) were used to conduct the primary analysis (94,100).

3.7. ETHICAL CONSIDERATIONS

The three studies included in this thesis were approved by the Danish Data Protection Agency (J.no. 2008-58-0028) based on information from national population-based registries. Danish nationwide register data involves a large amount of personal data. All personal data are anonymized prior to data analysis; thus, it is not possible to identify any individuals since no results are reported with fewer than five individuals in each category. According to Danish legislation, register-based research protocols do not require approval from the Ethics Committee.

CHAPTER 4. RESULTS

Results from the three studies included in the thesis will be summarized and presented in the following chapter.

4.1. STUDY I

Study I comprised 16,858 patients with 19,679 admissions. The majority were women (60.4%) and 43.4% of patients were 40-65 years old (82).

Stratifying on sex and age, the proportion of patients receiving more than 80% of the process performance measures varied between 12.1% for 18-39-years-old men and 18.0% for 66-79-years-old women.

Table 5 presents the association between sex, age, and the overall quality of inpatient care among patients with depression ($\geq 80\%$ of all relevant process performance measures of depression care received). Compared to men aged 18-39, men and women aged 66-79 were more likely to receive high overall quality of inpatient care with an adjusted relative risk (aRR) for men of 1.34 (95% CI: 1.07-1.67), and an aRR for women of 1.47 (95% CI: 1.14-1.90). No sex-related differences were found. When applying alternative cut off points of 60-90% to describe the high overall quality of inpatient care the association was supported with aRR ranging between 1.31 (95% CI: 1.09-1.56) and 1.49 (95% CI: 1.08-2.05) for men and women aged 66-79, respectively (82).

Table 5 The association between sex, age, and high quality of care ($\geq 80\%$ of relevant process performance measures) among inpatients with depression (82)

| Sex and age group | Total inpatients | Received high-quality care (%) ^a | RR ^b (95% CI) |
|-------------------|------------------|---|--------------------------|
| Men 18-39 | 2,129 | 12.1 | 1.00 |
| Women 18-39 | 3,759 | 13.0 | 1.07 (0.95-1.20) |
| Men 40-65 | 3,912 | 14.1 | 1.15 (1.00-1.33) |
| Women 40-65 | 4,630 | 13.3 | 1.07 (0.93-1.24) |
| Men 66-79 | 1,354 | 16.5 | 1.34 (1.07-1.67) |
| Women 66-79 | 2,314 | 18.0 | 1.47 (1.14-1.90) |
| Men ≥ 80 | 405 | 17.5 | 1.43 (0.98-2.10) |
| Women ≥ 80 | 1,176 | 16.0 | 1.30 (0.90-1.90) |

^a Received $\geq 80\%$ of relevant recommended process performance measures

^b Adjusted for inpatient volume and calendar year of admission

For the nine individual process performance measures the proportion of patients receiving them was generally low and ranged from 18.9% for assessment with the Hamilton Depression Scale at discharge and 60.5% for receiving a suicide risk assessment at admission (Table 4 in Appendix B) (82).

For both men and women, increasing age was associated with a higher chance of receiving 6 out of 9 recommended individual process performance measures, including examination by a psychiatrist (women ≥ 80 ; aRR 1.26, 95% CI: 1.04-1.54), somatic examination (women ≥ 80 ; aRR 1.23, 95% CI: 1.06-1.43), assessment by a social worker (men ≥ 80 ; aRR 1.44, 95% CI: 1.07-1.76), assessment with the Hamilton Depression Scale at discharge (men 66-79; aRR 1.43, 95% CI: 1.14-1.81), contact with relatives (men ≥ 80 ; aRR 1.46, 95% CI: 1.18-1.80) and planned psychiatric aftercare (men ≥ 80 ; aRR 1.42, 95% CI: 1.12-1.80). The remaining process performance measures showed no particular differences between the groups (82).

For the supplementary analyses we found, when investigating the association with all patients included, independent of the number of relevant processes, that

increasing age was associated with receiving a high quality of care. Men were less likely to receive the performance measures contact with relatives and psychiatric aftercare, according to the adjusted association between sex and individual performance measures (82).

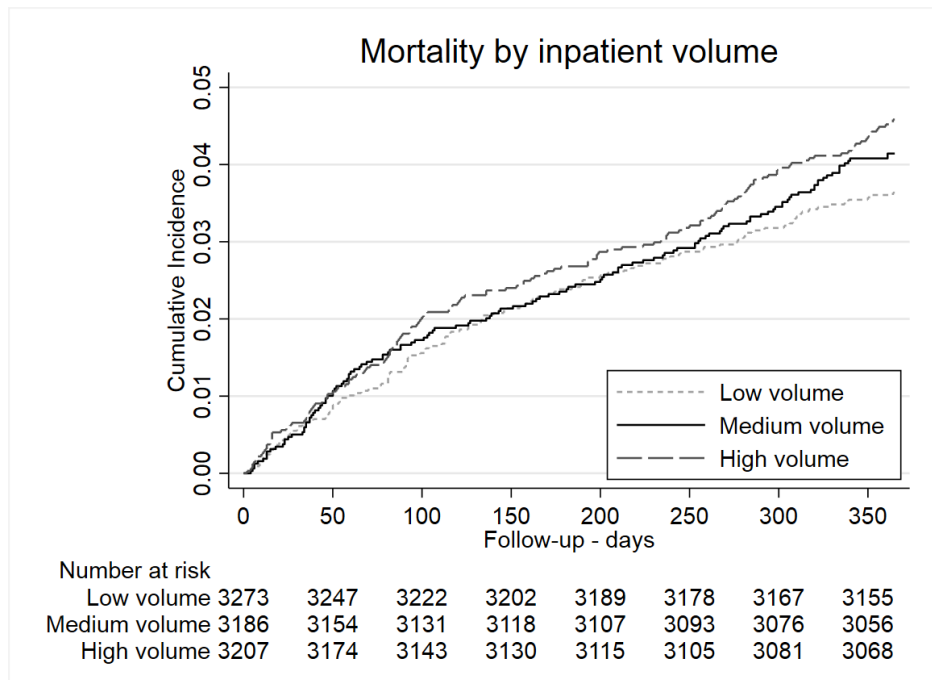
For age as a continuous variable in an unstratified binomial regression an aRR of 1.07 (95% CI: 1.06-1.13) per 10 years was found. Further, compared with women, male sex was not associated with the probability of receiving a high overall quality of care (aRR 0.99 (95% CI: 0.93-1.07)). The odds of receiving high quality of care increased with age when comparing to men aged 18-39 in an ordered logistic regression (men aged 66-79 had an adjusted odds ratio (aOR) of 1.51 (95% CI: 1.19-1.91)) and men ≥ 80 years had an aOR of 1.83 (95% CI: 1.19-2.81). For women aged 66-79 the aOR was 1.64 (95% CI: 1.26-2.12) and for women ≥ 80 years the aOR was 1.77 (95% CI: 1.23-2.56) (82).

For each year in age the quality of depression care received increased with 0.08% (95% CI: 0.02%-0.14%) while no difference according to sex was observed (82).

4.2. STUDY II

In study II 9,666 patients were considered eligible for inclusion in the analysis. Patients admitted to high-volume hospitals had a higher level of education, tended to be living alone and in larger cities compared to patients admitted to low-volume hospitals. No patients were lost to follow-up regarding survival or readmission (93).

The 1-year all-cause mortality for low-volume, medium-volume and high-volume hospitals was 3.6%, 4.1% and 4.6%, respectively. Figure 2 depicts the cumulative all-cause mortality by hospital inpatient volume (93).

Figure 2 Cumulative all-cause mortality by hospital inpatient volume (93)

The fully adjusted Cox proportional hazards regression showed that the mortality rate was higher in high-volume hospitals than in low-volume hospitals for all-cause mortality (adjusted HR 1.36 (95% CI: 1.01-1.83)), whereas no clear difference was seen for patients admitted to medium-volume hospitals (adjusted HR 1.15 (95% CI: (0.84-1.56))) (Table 6). When calculating inpatient volume as ward volume instead of hospital volume, the fully adjusted HR was 1.15 (95% CI: 0.75-1.75) for high-volume wards. Additionally, adjusting for the severity of depression gave an HR of 1.30 (95% CI: 0.93-1.81) for high-volume hospitals. The restricted cubic spline model showed signs of a threshold at around 500-600 patients per year with a steeper curve after this point for the association between inpatient volume and 1-year all-cause mortality (Figure 3) (93).

Suicidal behaviour was 4.9%, 4.1% and 5.3% for low-volume, medium-volume and high-volume hospitals. The rate for suicidal behaviour was higher in high-volume hospitals than in low-volume hospitals (adjusted cause-specific HR 1.22 (95% CI: (0.98-1.50))) although not reaching statistical significance. For patients admitted to medium-volume hospitals, we found an adjusted cause-specific HR of 0.98 (95% CI: 0.82-1.18). Calculating inpatient volume as ward volume resulted in an adjusted cause-specific HR of 1.05 (95% CI: 0.85-1.29) for medium-volume wards and 0.93

(95% CI: 0.74-1.17) for high-volume wards, respectively. The adjusted cause-specific HR for 1-year suicidal behaviour was 1.17 (95% CI: 0.88-1.56) for high-volume hospitals when we adjusted for the severity of depression. The restricted cubic spline for inpatient volume and suicidal behaviour showed signs of a threshold of around 500-600 patients a year with an increasing HR after this point (Figure 3) (93).

For low-volume, medium-volume, and high-volume hospitals, the proportions of patients requiring readmission due to depressive disorder were 43.8%, 48.6%, and 43.5%, respectively, whereas the proportions for all-cause readmission were 83.3%, 84.8%, and 83.1% (93). The fully adjusted cause-specific HR for high-volume was 1.01 (95% CI: 0.84-1.20) for readmission, due to depressive disorder, compared to low-volume hospitals, while patients at medium-volume hospitals had an adjusted cause-specific HR of 1.14 (95% CI: 0.94-1.38). When calculating inpatient volume as ward volume the adjusted cause-specific HR was 1.02 (95% CI: 0.84-1.24) for high-volume wards and 1.06 (95% CI: 0.92-1.22) for medium-volume wards. Adjusting for the severity of depression showed a cause-specific HR of 1.11 (95% CI: 0.89-1.39) for medium-volume hospitals. When admissions shorter than 24 hours were included, the adjusted cause-specific HR was 0.92 (95% CI: 0.76-1.11) for high-volume hospitals and 1.02 (95% CI: 0.84-1.24) for medium-volume hospitals (93).

The same pattern was observed for all-cause readmissions, with an adjusted cause-specific HR of 1.00 (95% CI: 0.89-1.12) for high-volume hospitals compared to low-volume hospitals, and an adjusted cause-specific HR of 1.08 (95% CI: 0.96-1.21) for medium-volume hospitals. When calculating inpatient volume as ward volume the adjusted cause-specific HR was 1.03 (95% CI: 0.91-1.17) for high-volume wards and 1.06 (95% CI: 0.97-1.16) for medium-volume wards, while adjusting for the severity of depression gave an adjusted cause-specific HR of 1.08 (95% CI: 0.96-1.21) for medium-volume hospitals. Including admissions shorter than 24 hours, showed an adjusted cause-specific HR of 1.01 (95% CI: 0.89-1.14) for high-volume hospitals and 1.06 (95% CI: 0.95-1.18) for medium-volume hospitals. Both for all-cause readmission and readmission due to depression, the restricted cubic splines showed a non-linear association (Figure 3). It indicated a threshold of around 300 patients a year; however, around 800 patients a year, the HR started to increase again (93).

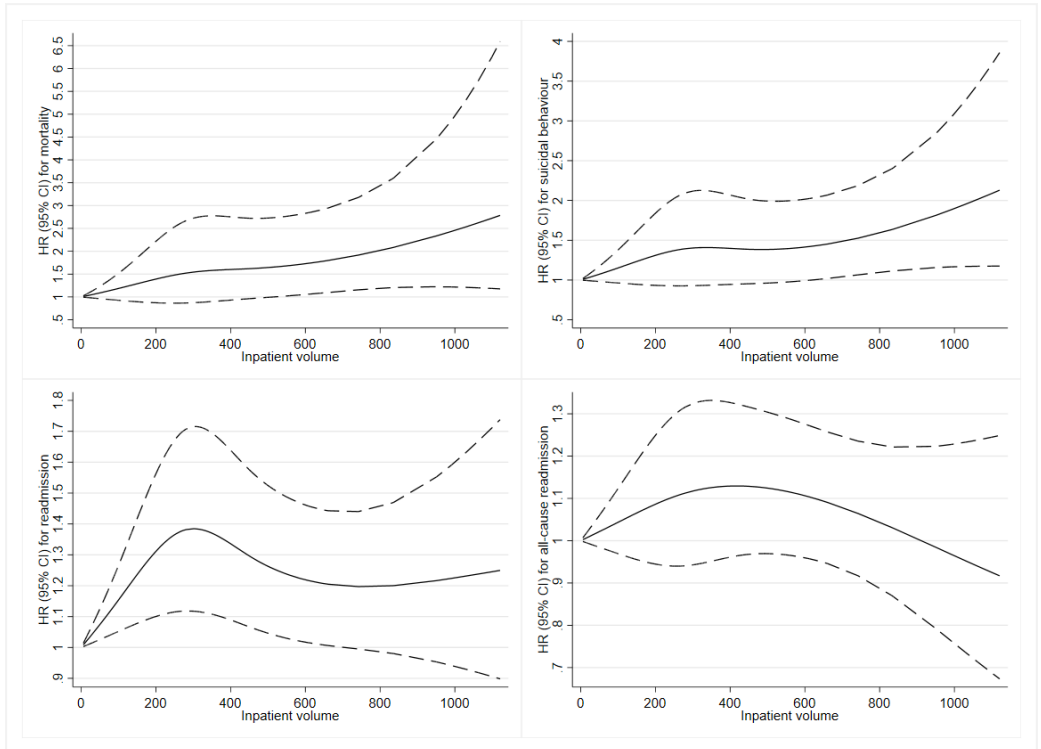
Table 6 Patient volume and all-cause 1-year mortality, suicidal behaviour, readmission for depression and all-cause readmission (93)

| | Unadjusted HR (95% CI) | Adjusted HR* (95% CI) | Adjusted HR+ (95% CI) |
|--|-----------------------------------|----------------------------------|----------------------------------|
| Inpatient volume and all-cause mortality | | | |
| Low volume | 1 (reference) | 1 (reference) | 1 (reference) |
| Medium volume | 1.14 (0.89 – 1.46) | 1.19 (0.86 – 1.64) | 1.20 (0.86 – 1.67) |
| High Volume | 1.26 (0.99 – 1.61) | 1.43 (1.07 – 1.92) | 1.49 (1.01 – 2.20) |
| Inpatient volume and suicidal behaviour | | | |
| Low volume | 1 (reference) | 1 (reference) | 1 (reference) |
| Medium volume | 0.98 (0.82 – 1.17) | 0.99 (0.83 – 1.18) | 1.04 (0.86 – 1.26) |
| High volume | 1.16 (0.98 – 1.38) | 1.20 (0.98 – 1.47) | 1.26 (0.97 – 1.65) |
| Inpatient volume and readmission for depression | | | |
| Low volume | 1 (reference) | 1 (reference) | 1 (reference) |
| Medium volume | 1.16 (1.08 – 1.24) | 1.16 (0.94 – 1.43) | 1.14 (0.94 – 1.38) |
| High volume | 1.01 (0.94 – 1.09) | 1.02 (0.85 – 1.22) | 1.01 (0.84 – 1.20) |
| Inpatient volume and all-cause readmission | | | |
| Low volume | 1 (reference) | 1 (reference) | 1 (reference) |
| Medium volume | 1.05 (0.99 – 1.11) | 1.05 (0.93 – 1.19) | 1.08 (0.96 – 1.21) |
| High volume | 1.01 (0.96 – 1.06) | 1.01 (0.90 – 1.14) | 1.00 (0.89 – 1.12) |

*Adjusted for age and sex.

+Adjusted for age, sex, ethnicity, income, educational level, CCI, substance misuse, place of residence.

Figure 3 Alternative distribution of hospital inpatient volume with restricted cubic splines (93)



*All adjusted for age, sex, ethnicity, income, educational level, CCI, substance misuse and place of residence.

4.3. STUDY III

For study III, 9,605 patients with a first-time hospitalization for depression between 2011-2016 were included. The socioeconomic status of patients varied across regions, with the Capital Region of Denmark having the largest share of employed (94).

The risks and the median relative risks for the clinical outcomes according to region is presented Table 7. The adjusted median relative risk was 1.18 (95% CI: 1.07-1.35) for 1-year all-cause mortality. The highest cumulative risk was observed in

Northern Denmark of 5% (4.1%-6.1%) and the lowest risk was seen in Region Zealand 3.1% (2.5%-3.9%). Figure 4 shows the variation between the regions (94).

The adjusted median relative risk for 1-year suicidal behaviour was 1.13 (1.07-1.26). The highest risk was seen in Northern Denmark 13% (11.3%-15.0%) and the lowest in Region Zealand 9.3% (8.0%-10.8%). For readmission due to depression the adjusted median relative risk was 1.06 (1.04-1.10). The highest risk was observed in Southern Denmark 55.0% (51.3%-59.0%) and the lowest risk was found in Region Zealand 45.5% (42.4%-48.8%). The adjusted median relative risk for all-cause readmission was 1.02 (1.01-1.03). Southern Denmark had the highest risk of all-cause readmission at 88.2% (85.8%-90.7%), whereas Northern Denmark had the lowest risk at 84.6% (82.3%-86.9%) (94).

When using stabilised weights and trimming in order to adjust for patients per general practitioner in each municipality, the study population was reduced to 7783 patients. The highest risk was found in Capital Region with a risk of 4.6% (3.6%-5.8%) and 11.7% (10.2%-13.3%) for all-cause mortality and suicidal behaviour, respectively. Southern Denmark had the highest risk of readmission due to depression at 56.9% (50.7%-63.9%). Conversely, for all-cause readmission the stabilised weights and trimming removed the variation across regions (94).

When the analysis was applied to the population with data on the Hamilton Depression Rating Scale, the Capital Region had the highest risk for all-cause mortality (4.1% (3.4%-5.0%)) and suicidal behaviour (10.7% (8.8%-13.0%)). Southern Denmark had the highest risk of readmission due to depression and all-cause readmission with a risk of 62.4% (56.6%-68.8%) and 87.9% (84.1%-91.9%), respectively (94).

With the alternative grouping of municipalities, the highest risk was observed in metropolitan municipalities for all-cause mortality 5.2% (4.4%-6.1%), suicidal behaviour 13.7% (12.2%-15.5%) and readmission due to depression 52.4% (50.8%-54.1%). These was observed no variation in risk for all-cause readmission across the grouping of municipalities (94).

Table 7 1-year absolute risk and median relative risk of clinical outcomes among patients with depression according to region of residence (94)

| Clinical outcomes | | Unadjusted | Adjusted model 1^a | Adjusted Model 2^b |
|--------------------------------------|----------------------|------------------------|-------------------------------------|-------------------------------------|
| | | Risk % (95% CI) | Risk % (95% CI) | Risk % (95% CI) |
| All-cause mortality | | | | |
| <i>Median</i> | <i>Relative Risk</i> | 1.00 (1.00-1.27) | 1.17 (1.07-1.34) | 1.18 (1.07-1.35) |
| | Northern Denmark | 4.1 (3.7-4.5) | 4.8 (4.0-5.9) | 5.0 (4.1-6.1) |
| | Central Denmark | 4.1 (3.7-4.5) | 4.1 (3.4-5.0) | 4.2 (3.4-5.1) |
| | Southern Denmark | 4.1 (3.7-4.5) | 3.6 (3.0-4.4) | 3.6 (2.9-4.4) |
| | Zealand | 4.1 (3.7-4.5) | 3.1 (2.6-3.8) | 3.1 (2.5-3.9) |
| | Capital | 4.1 (3.7-4.5) | 4.5 (3.7-5.4) | 4.4 (3.6-5.4) |
| Suicidal behaviour | | | | |
| <i>Median</i> | <i>Relative Risk</i> | 1.07 (1.00-1.22) | 1.12 (1.06-1.25) | 1.13 (1.07-1.26) |
| | Northern Denmark | 12.0 (10.5-13.8) | 12.6 (11.0-14.4) | 13.0 (11.3-15.0) |
| | Central Denmark | 11.3 (9.9-12.8) | 11.7 (10.3-13.5) | 11.9 (10.3-13.7) |
| | Southern Denmark | 10.9 (9.6-12.4) | 9.7 (8.5-11.2) | 9.6 (8.3-11.1) |
| | Zealand | 10.4 (9.1-11.9) | 9.3 (8.1-10.7) | 9.3 (8.0-10.8) |
| | Capital | 11.1 (9.9-12.5) | 11.7 (10.2-13.4) | 11.4 (9.9-13.2) |
| Readmission due to depression | | | | |
| <i>Median</i> | <i>Relative Risk</i> | 1.05 (1.03-1.08) | 1.06 (1.04-1.10) | 1.06 (1.04-1.10) |
| | Northern Denmark | 50.1 (45.8-54.8) | 49.0 (45.6-52.6) | 49.6 (46.2-53.2) |

| | | | |
|------------------|------------------|------------------|------------------|
| Central Denmark | 51.8 (47.8-56.0) | 52.2 (48.6-56.0) | 52.2 (48.7-56.0) |
| Southern Denmark | 54.6 (50.5-59.1) | 55.1 (51.3-59.1) | 55.0 (51.3-59.0) |
| Zealand | 47.3 (43.5-51.5) | 45.5 (42.3-48.8) | 45.5 (42.4-48.8) |
| Capital | 50.3 (46.9-54.0) | 50.0 (46.6-53.7) | 50.0 (46.6-53.6) |

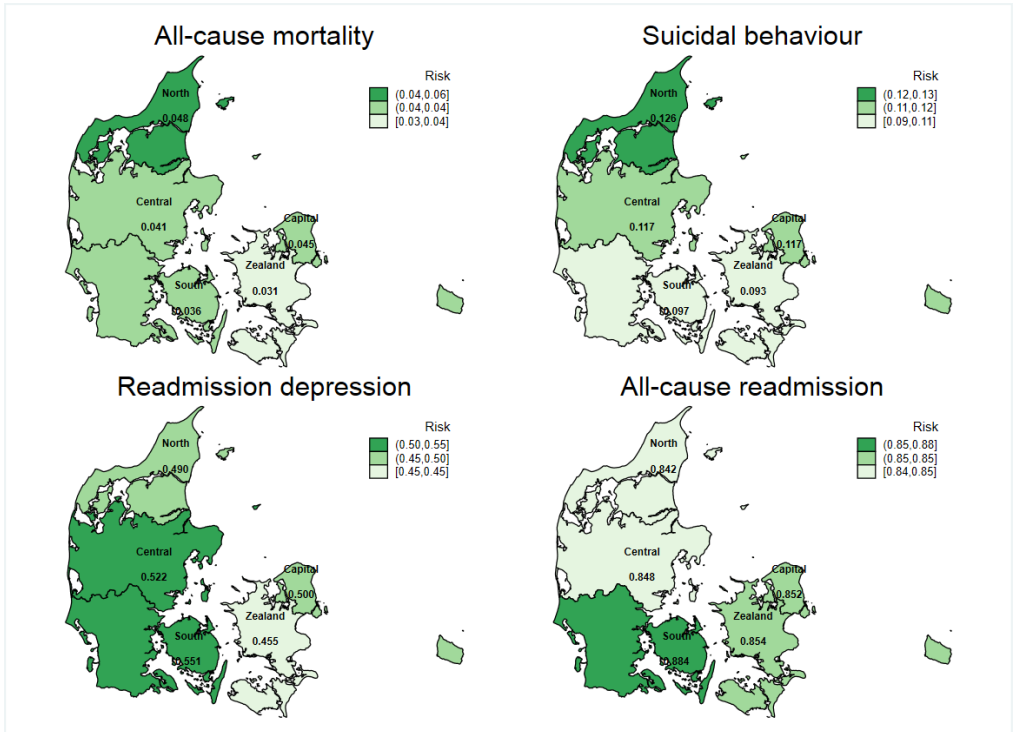
All-cause readmission

| | | | | |
|--------------------|------------------|-------------------------|-------------------------|-------------------------|
| <i>Median Risk</i> | <i>Relative</i> | <i>1.00 (1.00-1.02)</i> | <i>1.02 (1.01-1.03)</i> | <i>1.02 (1.01-1.03)</i> |
| Northern Denmark | 85.7 (83.8-87.5) | 84.2 (81.8-87.6) | 84.6 (82.3-86.9) | |
| Central Denmark | 85.7 (83.8-87.5) | 84.8 (82.4-87.2) | 84.8 (82.5-87.2) | |
| Southern Denmark | 85.7 (83.8-87.5) | 88.4 (85.9-90.9) | 88.2 (85.8-90.7) | |
| Zealand | 85.7 (83.8-87.5) | 85.4 (83.0-87.9) | 85.4 (83.1-87.8) | |
| Capital | 85.7 (83.8-87.5) | 85.2 (82.8-87.6) | 85.2 (82.8-87.6) | |

^a Adjusted for age, sex, ethnicity, income, educational level, CCI, substance misuse, inpatient volume.

^b Adjusted for age, sex, ethnicity, income, educational level, CCI, substance misuse, inpatient volume and Hamilton Depression Rating Scale.

Figure 4 Risk of all-cause mortality, suicidal behaviour, readmission due to depression and all-cause readmission for regions (94)



CHAPTER 5. DISCUSSION

5.1. SUMMARY OF FINDINGS

This thesis shows that older inpatients with depression had a higher chance of receiving most individual process performance measures and high overall quality of care compared to younger inpatients. In addition, disparities of all-cause mortality and suicidal behaviour among inpatients, i.e., inpatients admitted to high-volume psychiatric hospitals had an increased risk of all-cause mortality and suicidal behaviour. Further, variation regarding all-cause mortality and suicidal behaviour were found between regions in Denmark.

5.2. COMPARISON OF RESULTS WITH THE EXISTING LITERATURE

5.2.1. STUDY I

The aim of study I was to investigate the quality of inpatient care based on sex and age among patients hospitalized with depression. The study reported an association between increasing age and a higher likelihood of receiving high overall quality of care as well as a number of recommended process performance measures, such as examination by a psychiatrist, somatic examination, assessment by a social worker, assessment with the Hamilton Depression Scale at discharge, contact with relatives and planned psychiatric aftercare (82).

Direct comparison with previous studies may be difficult due to the differences in the definition of quality of care, study design and sampling of the study population. However, the findings of disparities in the quality of care among patients with depression are in accordance with those observed by one American study (74). The study reported no sex-related disparities in the quality of care, and odds of receiving medical treatment in accordance with the standards were higher for older age (74). Why the quality of depression care received among the elderly is higher, is uncertain, however it can be hypothesized that concerns regarding elderly patients having a higher risk of adverse outcomes such as longer duration of depression and increased risk of suicide is driving additional attention (101).

The findings of disparities in the quality of mental health care in study I (82), however, are inconsistent with previous studies which have showed that, compared to younger patients, elderly patients had poorer access to recommended mental health care (70,71,73,75). Two studies on outpatient care have found that women

had a statistically significant higher likelihood than men of receiving treatment in accordance with clinical guidelines (70,72). In contrast, one study showed that men had a higher likelihood of receiving treatment in accordance with guidelines compared to women (71). Women being more likely to use mental health services for outpatients, men expressing depression more atypically and less frequent endorsement of core depressive symptoms like depressed mood and anhedonia by men, are some of the reasons argued to explain the sex disparities in the above studies (70-72). In study I (82) no sex disparities were found for inpatients with depression regarding the receipt of overall quality of care; thus, in a Danish setting, in relation to process performance measures assessed in this study, these argued reasons do not seem to be the cause of any disparities in mental health care. However, in line with previous studies, for the process performance measure psychiatric aftercare, study I showed that men were less likely to fulfil it (70,72,82).

Only 20% or less of the relevant process performance measures were received by approximately one-third of patients, which indicates an urgent need to enhance and increase the quality of inpatient care for patients with depression in Denmark as well as to ensure equally high quality across age groups (82).

5.2.2. STUDY II

The aim of study II was to examine disparities in 1-year all-cause mortality, suicidal behaviour, and readmission among patients with depression based on the hospital inpatient volume (93).

Study II found no association between hospital inpatient volume and readmission rates, which differs from pre-existing studies (76-78,93); one examining readmission rates based on hospital volume and two based on volume per psychiatrist. Whereas this study found no clear association between patient volume and readmission risk, a previous study from Taiwan found a positive association between hospital volume and 30-day readmission rates for patients with major depressive disorders admitted to medium- and high-volume hospitals (76). However, direct comparison is challenging due to the size of hospitals and definitions of high-volume. Likewise, two previous studies investigating the association between inpatient volume per psychiatrist and the risk of readmission found that patients admitted with depression and mood disorders at a hospital with high volume had a higher risk of readmission (77,78,93).

Study II found that admission to high-volume hospitals were associated with higher all-cause mortality within a year from admission among psychiatric inpatients with depression. Furthermore, patients admitted to a high-volume hospital had a

statistical non-significantly increased risk for suicidal behaviour. No previous studies investigating this association has been identified (93).

An argument for centralization is centred around the hypothesis that high inpatient volume, i.e., increased care volume, provides better quality and the thought that "practice makes perfect". Particularly within surgery, studies have shown that high inpatient volume has an impact on better clinical outcome, however some of the studies can be criticized for their method (46-49,93). Consequently, it appears that the benefits of high-volume hospitals and centralizing of patient care could be limited to highly specialized treatments, however, since studies in other medical specialities, including psychiatry, is sparse, it is difficult to conclude anything about the advantages and disadvantages of centralizing in those specialities. Our findings of higher mortality rates in larger hospitals may seem counterintuitive and surprising. However, this finding is not entirely unprecedented; an earlier Danish study found that high-volume units were associated with higher 30-day mortality (50,93). The higher mortality rate in high-volume hospitals could not be explained by the available data. One could speculate that psychiatric inpatient care quality could be a contributing factor to the higher mortality rate; but according to a study published in 2018, patients in high volume wards were more likely to receive care that met a panel of process performance measures than patients in low volume wards, which contradicts this hypothesis (93,102). It remains unclear to what extent differences in quality of care contribute to the differences in clinical outcomes observed in our study. This is because many aspects of care would not be captured by a simple set of performance measures (93).

5.2.3. STUDY III

The aim of study III was to investigate the geographical variation in clinical outcomes such as 1-year all-cause mortality, suicidal behaviour, and readmission among patients with depression in Denmark. The study reported variation between regions in Denmark regarding all-cause mortality and suicidal behaviour for incident patients (94). Although no previous studies have examined geographical variation in clinical outcomes among patients with depression for an entire country, one study reports regional differences in death rates from depression among US residents (103).

Differences in health care outcomes such as all-cause mortality, suicidal behaviour, and readmission between administrative units appear to be present and may potentially be the result of inequalities in the quality of health care delivery and treatment among inpatients with depression (94,104). This is the case even though the health care system is universal and somewhat uniform and despite that the population of the five regions in Denmark is substantially homogeneous in terms of

sociodemographic and health-related characteristics (94,104). The Danish Depression Database was established to monitor the quality of treatment and care for patients with depression. All Danish psychiatric hospitals are required to submit data to the registry, which includes data on process performance measures that are in line with national clinical guidelines (8,9,84). In general, psychiatric patients in Denmark are admitted to the nearest psychiatric hospital rather than being triaged according to the severity of their depression or other characteristics (94).

Identifying unwarranted variation in all-cause mortality and suicidal behaviour may also be essential in other settings and populations, particularly considering the ongoing increase in the worldwide incidence and disease burden of depression. The differences in clinical outcomes found in a somewhat uniform health care system like the Danish system suggest that unwarranted variation in quality-of-care measures and the causes of the unwarranted variation must be addressed in subsequent research (94).

5.2.4. DISCUSSION ACROSS STUDIES

In general, the existing studies on disparities in quality of care and clinical outcomes including mortality, suicidal behaviour, and readmission among inpatients with depression is sparse and lacking; only one study was identified on the association between inpatient volume and clinical outcomes, and no previous studies were identified on geographical variation.

The design, sample size, and how the quality-of-care process performance measures are defined, varies across the existing studies. Previous studies have almost solely focused on the quality in primary care and on the quality of outpatient treatment after discharge and in primary care, in contrast to this thesis, which explored sex- and age-related disparities in relation to the quality of care among inpatients with depression (82). This study, which is one of the first to investigate the quality of mental health care among inpatients with depression, highlights the general paucity of data and research on potential disparities in this field. Further, the lacking data among inpatients with depression includes studies investigating the quality of mental health care in relation to clinical outcomes as well as disparities in clinical outcomes across hospital volume and geographical variation. It is difficult to completely understand the possible clinical consequences of the disparities in receiving the process performance measures examined in this thesis, due to the lack of such data (82). The relationship between quality-of-care measures or proxy measures and clinical outcomes has only been briefly studied: According to a Canadian study, getting at least one minimally acceptable depression treatment in the previous 12 months was linked to higher reductions in depression symptoms at both the 6- and 12-month mark (82,105). Similarly, an American study showed that improved

fulfilment on process performance quality measures was associated with lower 12- and 24-month mortality in patients with co-occurring substance use and mental disorders (82,106).

Overall, the findings in this thesis did not support findings from the few existing studies. It should be noted, however, that most of the identified literature are more than ten years old, used data from the last century, had small study populations, were cross-sectional studies and did not necessarily focus on patients with depression. Further, differences between health care systems and settings may complicate a comparison of findings. Finally, the inclusion criteria used in this thesis to only examine the associations for first-time admissions with depression may play some role.

5.3. METHODOLOGICAL CONSIDERATIONS

All three studies in the thesis were observational nationwide population-based cohort studies designed to investigate disparities in the quality of inpatient care for inpatients with depression and in clinical outcomes. However, due to potential systemic or random errors the observational design can have affected the validity and accuracy of the results; therefore, methodological considerations in terms of internal and external validity are considered below.

5.3.1. SELECTION BIAS

A systematic error in a study that results from the techniques used to select subjects as well as factors that impact study participation is referred to as selection bias (107). It occurs when the relationship between exposure and disease varies between participants and those who do not complete the study. As the association between nonparticipants' exposure and disease is not known, the presence of selection bias must usually be deduced rather than observed (107).

In this thesis the study population of all three studies and the process performance measures were identified from the Danish Depression Database (84). It is mandatory to report to the Danish Clinical Registries for all public hospitals. This ensures a generally high coverage and almost complete follow-up of every patient treated for depression in the secondary Danish health care system. No formal validation studies have been done on the completeness of the patient registration, however, all patients with a relevant diagnose in The Danish National Patient Registry will also be included in the Danish Depression Database, i.e., it is administratively not possible to be admitted with a diagnosis of depression in a psychiatric hospital without the

patient also appearing in the Danish Depression Database. As mentioned in the Introduction Section treatment in public hospitals is free of charge for Danish residents, due to tax funding (33), meaning that the chance of systematic excluding patients with depression in the clinical registries is limited.

Only hospital in-patients with depression were included in the three thesis studies. As a result, the disparity in quality of care and clinical outcomes remains unknown for outpatients and patients with depression seen exclusively by their general practitioner (GP).

It should be noted that, in this context, the majority of patients with mild depression is commonly treated at the GP and is therefore not included in the study populations for this thesis.

Consequently, since only first-time admissions and admissions with a time-period longer than 24 ours are included in the study populations in the thesis, it may affect the generalizability of the findings.

5.3.2. INFORMATION BIAS

A systematic error in a study can occur when information about or from the study subjects is incorrect. If the variable is measured on a categorical scale and the error causes a person to be placed in the wrong category, this information is often referred to as misclassified. Subject misclassification can be differential or nondifferential. A nondifferential misclassification is one that is unrelated to other variables in the study. In contrast, with differential misclassification, the misclassification varies depending on the value of other study variables. In terms of misclassification, the two most important variables to consider are exposure and disease (107).

All three studies in this thesis were based on data recorded prospectively in Danish registries and were collected independently of the studies hypotheses, reducing differential misclassification. Still, in registry-based studies, data validity is always a concern. The reporting of data to the Danish Depression Database involves a lot of health care professionals in clinical practice, which can lead to differences in coding or registration practices and errors, as well as intra- and inter-observer variation, may occur. To ensure data standardization, each hospital department and outpatient clinic have designated essential health care professionals to be in charge of data accuracy and collection (8-10). Even though, those extensive efforts are made, some geographical areas in Denmark, particularly Eastern Denmark, have problems with low indicator fulfilment, which have been noted in yearly reports for several years. All data on the process performance measures are registered through codes for procedures and diagnosis, thus, they are only available as being performed or not.

Thus, missing data are reported as the process performance measure not being fulfilled, which makes it impossible to distinguish between if the individual patient has not received the performance measure or if it just has not been registered, which can lead to misclassification. Due to this, the association found in the analyses could be a conservative estimate of the true association or the findings could be biased if the proportion of patients with missing data on quality of inpatient care differs on sex and age. However, the missing data in the Danish Depression Database are most likely non-differentially distributed at patient-level. Furthermore, detailed instructions and clear data definitions ensure validity, as well as clinical multidisciplinary structured audits are performed on a regular basis at the local, regional, and national levels. These audits provide continuous feedback to hospital departments with analyses of the data quality (8-10).

Missing data on socioeconomic and demographic variables were generally very low, as the use of the unique personal identifier enabled linkage between public registries with high data completeness (26) and where the data validity and coverage are considered to be high (85,88,90). Most sociodemographic variables were categorized according to formal standards.

Hospital inpatient volume was calculated based on patients admitted with depression per year. However, since patients with depression are admitted to psychiatric hospitals with patients treated for other psychiatric disorders as well, it is possible that some hospitals can have been misclassified in terms of inpatient volume. Even though the exact extent of misclassification is unknown, the most likely source of bias will be non-differential misclassification, which will result in an underestimation of the association. Complete data related to follow-up on clinical outcomes, data on diagnosis and data on date and time of admission and readmission were ensured by the use of the Danish National Patient Registry with nationwide coverage (26) and the Danish Register of Causes of Death with a very high completeness of data (87), complete data on time and date of admission and remission, on diagnosis and on data related to follow-up on clinical outcomes was ensured. Therefore, the risks of information bias should be considered limited for these variables.

5.3.3. CONFOUNDING

Confounding is a critical consideration in the design of epidemiologic studies. Confounding can be defined as confusion of effects, which implies that the exposure effect is mixed with the effect of another variable, resulting in a bias (107).

Due to their observational design, confounding is a relevant concern in all three studies in the thesis. This issue has been addressed in the statistical analysis by stratification, adjustment for possible confounding factors and to some extent,

efforts have also been made to address this by restricting the inclusion to patients hospitalized for more than 24 hours. Explicit criteria were specified for the inclusion of the patients with depression as well as for the process performance measures in the Danish Depression Database (84), which means that all patients are qualified to receive the recommended process performance measures of care and equal care, irrespective of the treating hospital or hospital department, place of residence or patient characteristics. Therefore, confounding is considered to be of minor importance for the study findings. A broad range of potential confounders of quality of care, 1-year all-cause mortality, suicidal behaviour and readmission, including sex, age, severity of depression, quality of inpatient depression care, socioeconomic variables, place of residence and hospital inpatient volume were taken into account in the studies. However, the associations may still be confounded and influenced by additional potential underlying and complex mechanisms and possible residual confounding due to uncontrolled factors cannot be disregarded.

After adjustment for several possible confounders, some of the point estimates for increased mortality among patients with depression in Studies II and III moved.

However, residual confounding from misclassification may still have an impact on the results, and unaccounted-for confounding from unknown factors, such as the length of stay at the hospital, cannot be disregarded. Readmission can also be an expression for severity of the disease and relapse of depression is not uncommon, and since the Hamilton score were missing for approximately half of the patients, adjustment could not be done for the whole population. However, the sensitivity analysis where only patients with a Hamilton Depression Rating Scale were included confirmed the association found in the main analysis.

Due to the important characteristics that has been accounted for, the overall results are considered to be valid within reason. In all three studies, robust estimates of variance were used to account for patient clustering within hospital departments; thus, including unmeasured hospital departments characteristics that potentially could be associated with both the quality of care and the clinical outcomes.

5.3.4. PRECISION

The statistically precision in all three studies is improved by the large sample sizes acquired from population-based nationwide registries. Furthermore, the 95% CI utilized throughout the thesis to reflect the random errors underlying the risk estimations were relatively narrow, indicating a high level of precision. However, some of the analysis with few events of mortality and suicidal behaviour showed relatively broad CIs, which causes lower precision of the estimates and may have caused a type II-error (finding a difference, where there is none). Therefore,

additional care should be taken while interpreting the point estimations. Likewise, the statistically significant findings in the studies had a 5% risk of being coincidental. Further, the absolute differences for the analysed process performance measures of inpatient care and to some extent the clinical outcomes among patients with depression in general were small, which indicates that the differences observed in the quality of care could be of less clinical importance. The main objective of this thesis was to examine potential disparities among patients admitted with depression and since the same general pattern was observed across all studies it is not likely that the findings in this thesis can be explained by random errors. Though the point estimates may not be exact, the directions of the associations are likely valid.

5.3.5. EXTERNAL VALIDITY

All three studies were conducted using national registries with specific data definitions, a generally high data completeness and coverage of patient recording and in the context of a universal and free-of-charge health care system. The treatment and management of patients with depression and the population characteristics may differ across countries, hence, the findings may not be generalized to countries with insurance-based health care systems. These factors must be considered when comparing previous publications from other health care settings with the results reported in this thesis. However, if disparities are found among inpatients with depression in countries with free access to health care it could be a concern that countries with insurance-based health care or other barriers have a some of the same challenges in a larger scale.

CHAPTER 6. CONCLUSION

This thesis provides greater insight into the disparities in the quality of depression inpatient care and the clinical outcomes 1-year all-cause mortality, suicidal behaviour and readmission among patients admitted with depression in Denmark through three nationwide population-based cohort studies.

Despite of a universal health care system, this thesis reported higher likelihood of receiving high quality of inpatient care with increasing age, both overall and for 6 out of 9 individual process performance measures; examination by a psychiatrist, somatic examination, assessment by a social worker, assessment with the Hamilton Depression Scale at discharge, contact with relatives and planned psychiatric aftercare.

Moreover, admission to high-volume hospitals were associated with higher all-cause mortality within a year from admission among psychiatric inpatients with depression. Patients admitted to a high-volume hospital also had a statistical non-significantly increased risk for suicidal behaviour. No clear association between patient volume and readmission risk was observed.

Finally, this thesis reported variation between regions in Denmark regarding all-cause mortality and suicidal behaviour for incident patients.

CHAPTER 7. PERSPECTIVES

The findings of this thesis indicate the presence of disparities in the fulfilment of recommended quality of care process performance measures for patients admitted with depression according to age. This requires clinicians to be more aware of the need to treat patients equally, as required by Danish law and the code of ethics. As the literature search showed there is an extensive lack of studies on disparities in quality of care in the mental health care sector. Further studies are needed to illuminate the extent of disparities in the quality of care among mental health illnesses. Further, this thesis also finds disparities on the clinical outcomes 1-year all-cause mortality, and suicidal behaviour based on hospital inpatient volume and region of residence.

Overall, the quality of care received among inpatients with depression was low, which should be of concern. However, alterations in the general quality level do not necessarily result in a decrease in disparities (40). An improved understanding of what comprises best care for these more vulnerable groups is required in order to attain the same level of care for all groups. Professionals may be able to provide better care by having a better understanding of the patient's health literacy, cultural perspectives and social circumstances. The potential differences between the health care professionals' perspective and the patient's perspective can be significant for the outcome of the treatment, why it is important to identify the aspects of care that are important for the patients' mental health care. This knowledge can assist the health care professionals in prioritizing their efforts to deliver the right treatment, to the right patient, at the right time. Similarly, examining the perspectives of health care professionals could be helpful in identifying potential obstacles in taking care of vulnerable groups, such as lack of resources and time. More information is also needed on medical care after discharge from hospitalization, which may be insufficient given the risk of higher mortality for patients with depression who were admitted to a high-volume hospital and the variation across regions in Denmark. Interventions aimed at improving the survival of patients with depression are therefore required and research of the possible challenge with managing patients with depression after discharge from both psychiatric and somatic hospitals would be meaningful.

The current measures used to monitor the quality of care, might not be sufficient enough to reflect the impact of the health care system. Due to the findings of disparities in the clinical outcomes 1-year all-cause mortality, and suicidal behaviour based on hospital inpatient volume and region of residence, monitoring the entire patient pathway, including hospital structures and transitions between secondary and primary sector may be crucial.

Other areas of interest for future research could include an exploration of the impact of quality of care on the clinical outcomes.

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APPENDICES

Appendix A: Article of study I: Gender- and age-related differences in the quality of mental health care among inpatients with unipolar depression: a nationwide study – see separate file.

Appendix B: Article of study II: Hospital inpatient volume and clinical outcomes among patients with incident depression: a nationwide study – see separate file.

Appendix C: Article of study III: Geographical variation in clinical outcomes among patients with depression: a nationwide study – see separate file.

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