Quality of care for medical comorbidities among patients with schizophrenia

A Danish nationwide perspective

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A DANISH NATIONWIDE PERSPECTIVE

BY
METTE JØRGENSEN

DISSERTATION SUBMITTED 2017

AALBORG UNIVERSITY
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CIRRICULUM VITAE

Mette Jørgensen completed her Bachelor's degree in Nursing at the University College of Northern Denmark in 2011. Subsequently she graduated as a Master of Health Sciences in 2013 from Aarhus University, Denmark. In her Master's thesis, Mette Jørgensen examined the association between the patient volume of psychiatric hospital units and the quality of mental health care among patients diagnosed with schizophrenia in Denmark.

In 2014, Mette Jørgensen enrolled as a PhD student at the Faculty of Medicine, Aalborg University, Denmark, and began working as a clinical assistant for Professor Jan Mainz, Aalborg University Hospital, Psychiatry, Denmark.
While working on her PhD, Mette Jørgensen has worked as a Danish project manager for the Organisation for Economic Co-operation and Development (OECD) Health Care Indicator Project: Research & Development work on international suicide indicators in mental health, as well as taking part in a variety of projects. Moreover, she has been a reviewer for scientific journals and an assistant supervisor for Master students at Aarhus University, Denmark.

Mette Jørgensen has presented her PhD work at international scientific conferences, and she has published research within psychiatry and quality of care.

ENGLISH SUMMARY

BACKGROUND

Excess mortality in patients with schizophrenia is a well-established fact and the subject of widespread and growing concern. The literature indicates that diabetes, cardiovascular and respiratory diseases are major contributors to the reduced life expectancy of 10-20 year found in this vulnerable population. Yet, there is surprisingly sparse data available regarding the quality of care for their medical comorbidities. The overall objective of this thesis was therefore to determine the association between schizophrenia and the quality and predictors of care for diabetes, heart failure and chronic obstructive pulmonary disease (COPD) in Denmark, which has a free public health care system. Moreover, the thesis aimed to examine the clinical outcomes of heart failure and COPD among patients with schizophrenia. These goals were investigated in three nationwide population-based cohort studies.

METHOD

All three studies were based on individual-level data obtained from national Danish registries between 2004 and 2013. The quality of diabetes, heart failure and COPD care was defined as meeting guideline-recommended disease-specific process-performance measures of care in Danish public hospitals. Receiving at least 80% of the disease-specific performance measures of care was defined as meeting a high quality of care. Potential predictors of care for these medical comorbidities among patients with schizophrenia included factors related to patients (sex, age, abuse, Global Assessment of Functioning (GAF) score, duration of schizophrenia), to providers (quality of schizophrenia care) as well as system-related factors (contact volume defined as average contact volume of patients treated for diabetes, incident heart failure or COPD per year during the study period in hospital departments and/or outpatient clinics). The clinical outcomes of heart failure comprised 4-week all-cause readmission and 1-year all-cause mortality following a first-time hospital contact with incident heart failure. Clinical outcomes of COPD included 30-day all-cause readmission and 30-day all-cause mortality following an admission for exacerbation of COPD.

STUDY I

Study I included 83,813 diabetes hospital outpatients, of which 669 patients also had a diagnosis of schizophrenia. Results demonstrated that diabetes patients with schizophrenia had a lower chance of receiving 6 out of 11 examined individual process-performance measures of diabetes care, including blood pressure monitoring ((Relative risk) RR 0.98, 95% CI: 0.96-0.99), treatment with antihypertensive drugs (RR 0.83, 95% CI: 0.70-0.97) and ACE/ATII inhibitors (RR 0.72, 95% CI: 0.55-0.93), screening for albuminuria (RR 0.96, 95% CI: 0.93-0.99), eye examination at least every second year (RR 0.97, 95% CI: 0.94-0.99) and foot examination (RR 0.96, 95% CI: 0.93-0.99). The meeting of the high quality of diabetes care was also deficient

among this group (RR 0.91, 95% CI: 0.88-0.95) compared to diabetes patients without schizophrenia. Drug abuse and treatment at outpatient clinics with a low contact volume of diabetes patients were associated with an inadequate quality of diabetes care among diabetes patients with schizophrenia.

STUDY II

Study II comprised 36,718 hospital in- and outpatients with incident heart failure, of which 108 patients had comorbid schizophrenia. The results showed that patients with incident heart failure as well as schizophrenia had a lower chance of receiving 1 out of 7 assessed individual process-performance measures of heart failure care, including treatment with beta-blockers (RR 0.87, 95% CI: 0.79-0.97). These patients furthermore had a lower chance of meeting a high quality of heart failure care (RR 0.66, 95% CI: 0.48-0.91) than incident heart failure patients without schizophrenia. A low GAF score was associated with a deficient quality of heart failure care among incident heart failure patients with schizophrenia. Incident heart failure patients with schizophrenia had a higher risk of 1-year mortality (adjusted hazard ratio (HR) 2.85, 95% CI: 1.59-5.09), but not a higher risk of 4-week readmission compared to incident heart failure patients without schizophrenia.

STUDY III

Study III included 72,692 COPD hospital in- and outpatients, of which 621 patients also had a diagnosis of schizophrenia. The results showed that COPD patients with schizophrenia had a lower chance of receiving 1 out of 9 evaluated individual process-performance measures of COPD care, comprising treatment with long-acting muscarinic antagonists (LAMA) or long-acting β2- agonists (LABA) (RR 0.92, 95% CI: 0.87-0.98). This patient population had the same chance of meeting a high quality of COPD care (RR 0.95, 95% CI: 0.87-1.03) compared to COPD patients without schizophrenia. Male sex was associated with a poor quality of COPD care among COPD patients with schizophrenia. COPD patients with schizophrenia had an increased risk of 30-day mortality (adjusted odds ratio (OR) 1.27, 95% CI: 1.01-1.59), but not a higher risk of 30-day readmission than COPD patients without schizophrenia.

CONCLUSION

Patients with schizophrenia had a lower chance of meeting a number of process-performance measures for diabetes, heart failure and COPD care, although the absolute differences in general were small. The predictors of a poorer quality of care included patient- and system-related factors. However, patients with schizophrenia had a substantially higher risk of mortality following a first-time hospital contact with incident heart failure and after an admission for exacerbation of COPD. Additional interventions are therefore warranted to reduce the high mortality rates of heart failure and COPD among patients with schizophrenia.

DANSK RESUME

BAGGRUND

Overdødelighed blandt patienter med skizofreni er et område forbundet med stor bekymring. Litteraturen indikerer, at særligt diabetes, hjerte-kar-sygdomme og luftvejssygdomme bidrager til en 10-20 års reduceret levetid for denne sårbare population. Den eksisterende viden vedrørende kvaliteten af behandlingen for disse medicinske følgesygdomme er dog overraskende sparsom. Det overordnede formål med denne afhandling var derfor at undersøge associationen mellem skizofreni og kvalitet af behandling samt prædiktorer for behandling af diabetes, hjertesvigt og kronisk obstruktiv lungesygdom (KOL) i det danske gratis sundhedsvæsen. Desforuden sigtede afhandlingen mod at undersøge de kliniske udfald af hjertesvigt og KOL blandt patienter med skizofreni. Disse mål blev belyst i tre nationale, populationsbaserede kohortestudier.

METODE

Alle tre studier blev baseret på individbaserede data indhentet fra nationale danske registre mellem 2004 og 2013. Kvaliteten af behandlingen for diabetes, hjertesvigt og KOL blev vurderet ud fra, om patienterne modtog de anbefalede sygdomsspecifikke procesindikatorer på offentlige danske sygehuse. Såfremt patienterne modtog over 80% af de anbefalede sygdomsspecifikke indikatorer, blev dette anset som en høj behandlingskvalitet. Potentielle prædiktorer for behandling af disse medicinske følgesygdomme blandt patienter med skizofreni indbefattede faktorer relateret til patienten (køn, alder, misbrug, funktionsniveau vurderet ud fra en GAF-score, varighed af skizofreni), til udbyder (kvaliteten af behandlingen for skizofreni) og system-relaterede faktorer (kontaktvolumen beregnet på basis af gennemsnittet af det årlige antal kontakter med patienter med hhv. diabetes, nydiagnosticeret hjertesvigt og KOL på hver enkelt hospitalsafdeling og/eller ambulatorium i studieperioden). De kliniske udfald af hjertesvigt omfattede genindlæggelse indenfor 4 uger og mortalitet indenfor 1 år efter første hospitalskontakt med nydiagnosticeret hjertesvigt, uanset årsag. Derudover indbefattede de kliniske udfald af KOL genindlæggelse indenfor 30 dage samt mortalitet indenfor 30 dage efter indlæggelse for akut KOL-exacerbation, uanset årsag.

STUDIE I

Studie I inkluderede 83.813 ambulante diabetespatienter, hvoraf 669 tillige havde en diagnose med skizofreni. Resultaterne viste, at diabetespatienter med skizofreni havde en lavere risiko for at modtage 6 ud af 11 undersøgte procesindikatorer for diabetes, herunder blodtryksmåling (Relativ risiko (RR) 0.98, 95% CI: 0.96-0.99), antihypertensiv behandling (RR 0.83, 95% CI: 0.70-0.97) og ACE-hæmmer/ATII-receptor antagonist (RR 0.72, 95% CI: 0.55-0.93), undersøgelse for albuminuria (RR 0.72, 95% CI: 0.55-0.93), øjenundersøgelse mindst hvert andet år (RR 0.97, 95% CI: 0.94-0.99) og fodundersøgelse (RR 0.96, 95% CI: 0.93-0.99). Desuden havde denne

gruppe en lavere risiko for at modtage en høj behandlingskvalitet for diabetes (RR 0.91, 95% CI: 0.88-0.95) sammenlignet med diabetespatienter uden skizofreni. Stofmisbrug og behandling på ambulatorier med et lavt kontaktvolumen af diabetespatienter var associeret med en utilstrækkelig behandlingskvalitet for diabetes blandt diabetespatienter med skizofreni.

STUDIE II

Studie II omfattede 36.817 indlagte og ambulante patienter med nydiagnosticeret hjertesvigt, hvoraf 108 havde komorbid skizofreni. Resultaterne påviste, at nydiagnosticerede hjertesvigtpatienter med skizofreni havde en lavere risiko for at modtage 1 ud af 7 vurderede procesindikatorer for hjertesvigt, herunder behandling med betablokker (RR 0.87, 95% CI: 0.79-0.97). Disse patienter havde tillige en lavere risiko for at modtage en høj behandlingskvalitet for hjertesvigt (RR 0.66, 95% CI: 0.48-0.91) end nydiagnosticerede hjertesvigtpatienter uden skizofreni. En lav GAF-score var associeret med en mangelfuld behandlingskvalitet for hjertesvigt blandt nydiagnosticerede hjertesvigtpatienter med skizofreni. Nydiagnosticerede hjertesvigtpatienter med skizofreni havde en større risiko for 1-års mortalitet (justeret hasard ratio (HR) 2.85, 95% CI: 1.59-5.09), men ikke en større risiko for 4-ugers genindlæggelse sammenlignet med nydiagnosticerede hjertesvigtpatienter uden skizofreni.

STUDIE III

Studie III inkluderede 72.692 indlagte og ambulante KOL-patienter, hvoraf 621 også havde en diagnose med skizofreni. Resultaterne viste, at KOL-patienter med skizofreni havde en lavere risiko for at modtage 1 ud af 9 evaluerede procesindikatorer for KOL, herunder behandling med langtidsvirkende inhaleret bronkodilatator enten som LAMA eller LABA (RR 0.92, 95% CI: 0.87-0.98). Denne population havde den samme risiko for at modtage en høj behandlingskvalitet for KOL (RR 0.95, 95% CI: 0.87-1.03) sammenlignet med KOL-patienter uden skizofreni. Det mandlige køn var associeret med en utilstrækkelig behandlingskvalitet for KOL blandt KOL-patienter med skizofreni. KOL-patienter med skizofreni havde en større risiko for 30-dages mortalitet (justeret odds ratio (OR) 1.27, 95% CI: 1.01-1.59), men ikke en større risiko for 30-dages genindlæggelse end KOL-patienter uden skizofreni.

KONKLUSION

Patienter med skizofreni havde en lavere risiko for at modtage flere procesindikatorer for diabetes, hjertesvigt og KOL, men de absolutte forskelle var generelt beskedne. Prædiktorerne for denne mangelfulde behandlingskvalitet omfattede patient- og systemrelaterede faktorer. Patienter med skizofreni havde dog en betydelig højere risiko for mortalitet efter første hospitalskontakt med nydiagnosticeret hjertesvigt samt efter indlæggelse for akut KOL-exacerbation. Yderligere tiltag er derfor påkrævet for at reducere den høje mortalitet af hjertesvigt og KOL blandt patienter med skizofreni.

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Mette Jørgensen
Aalborg, January 2017

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LIST OF PAPERS

This thesis is based upon the following three papers:

I. Jørgensen M, Mainz J, Carinci F, Thomsen RW, Johnsen SP. Quality and predictors of diabetes care among patients with schizophrenia: a nationwide study (in review).

II. Jørgensen M, Mainz J, Egstrup K, Johnsen SP. Quality of care and clinical outcomes of heart failure among patients with schizophrenia under universal health care (in preparation).

III. Jørgensen M, Mainz J, Lange P, Johnsen SP. Chronic obstructive pulmonary disease care and outcomes in patients with schizophrenia (submitted).

LIST OF ABBREVIATIONS

ACE	Angiotensin-converting enzyme
AMI	Acute myocardial infarction
ARB	Angiotensin II receptor blockers
ATII	Angiotensin II receptor
BMI	Body mass index
CABG	Coronary artery bypass graft
CC	Cardiac catheterization
CI	Confidence intervals
COPD	Chronic obstructive pulmonary disease
DADR	Danish Adult Diabetes Registry
DHFR	Danish Heart Failure Registry
DPP-4	Dipeptidyl peptidase -4
DrCOPD	Danish Registry for COPD
DSR	Danish Schizophrenia Registry
FEV_1 %	Forced expiratory volume in 1 second in percent
GAF	Global Assessment of Functioning
GLP-1	Glucagon-like peptide-1
GP	General practitioner
HbA_{1c}	Glycated haemoglobin
HDL	High-density lipoprotein

HR	Hazard ratio
ICD-10	International Classification of Diseases version 10
LABA	Long-acting β2-agonists
LAMA	Long-acting muscarinic antagonists
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LVEF	Left Ventricular Ejection Fraction
MRC	Medical Research Council
N	Number
NYHA	New York Heart Association
OPCRIT	Operational Criteria Checklist for Psychotic Illness
OR	Odds ratio
P	P value
PCI	Percutaneous coronary intervention
PCTA	Percutaneous transluminal coronary angioplasty
RR	Relative risk
SCAN	Schedules for Clinical Assessment in Neuropsychiatry
SGLT2	Sodium-glucose cotransporter 2
ULTRA-LABA	Ultra-long-acting β2-adrenoceptor agonists
VA	Veterans Health Administration

CHAPTER 1. INTRODUCTION

The substantial morbidity and disability experienced by patients with schizophrenia represent a major global health challenge. Improving the symptomatic treatment of the disorder has therefore received much needed attention since the term schizophrenia was introduced at the beginning of last century, and it remains an important goal (1,2). However, decades of neglecting the medical health in this vulnerable population has contributed to alarmingly high mortality rates. Patients with schizophrenia are estimated to have a reduced life expectancy of 10-20 years compared to the general population (3-9). Although intentional self-harm and accidents may partly explain the excess mortality, the dominant part is attributed to medical comorbidities, including diabetes, cardiovascular disease and respiratory disease (4-7,9). This emphasizes the crucial role of ensuring effective prevention, early diagnosis and optimal treatment of these potentially fatal medical comorbidities. There is, however, a shortage of published research, particularly from universal health care settings, to clarify whether patients with schizophrenia receive sufficient care for their comorbid diabetes, cardiovascular disease and respiratory disease. Despite emerging evidence indicating deficiencies in care (10-24), the magnitude of the problem varies considerably. In addition, the internal and external validity of the vast majority of existing studies is hampered by methodological limitations, including lack of detailed data on the care provided, non-population-based study designs and financial incentives.

For more than a decade, a nationwide multidisciplinary initiative has systematically monitored the quality and equity of care provided by the public and mainly tax-financed Danish health care system (25-27). The universal health coverage ensures, in principle, free and equal access to hospital care for all Danish residents regardless of their socioeconomic status (28). This singular setting creates a unique opportunity to elucidate whether equal access also implies equal and sufficient medical care for patients with a serious mental disorder such as schizophrenia. Based on comprehensive information from Danish nationwide registries, this thesis aims to examine the important interrelations between schizophrenia and the quality of care for diabetes, heart failure and chronic obstructive pulmonary disease (COPD) respectively.

CHAPTER 2. BACKGROUND

The following chapter will introduce schizophrenia and its association with medical comorbidities and increased mortality. Subsequently, a literature review will examine the existing evidence on the quality of care for diabetes, heart failure and COPD among patients with schizophrenia. Finally, limitations of the identified publications will be described, as well as the features that make Denmark a suitable setting for gaining further insight into the area.

2.1. SCHIZOPHRENIA

Schizophrenia is a severe and debilitating mental disorder. Approximately 1% of the population worldwide presents with the disorder, and the global incidence rate has been estimated to be 15.2 per 100,000 persons (29-32).
Although the etiology of schizophrenia remains complex and not fully clarified, genetic predisposition, including a family history of schizophrenia, and environmental factors, involving an urban place of birth and low social class, have been identified as the important determinants. The predisposing genes, the models of genetic transmission and the factors related to social class, however, need further verification (29-31,33).

The disorder affects roughly equal numbers of males and females. Males typically present with the first psychotic episode of schizophrenia between their early and mid-20s whilst females present in their late 20s (29-32). The course of the disorder varies, with an estimated duration of at least 6 months. About 25-45% of patients with schizophrenia recover after one or more episodes or show an almost complete remission; 35-50% display a moderate course with different lengths of exacerbations and degrees of remissions, whilst 20-25% experience increasing disability and chronic symptoms (29-31,34). The majority of patients with schizophrenia therefore require long-term maintenance care. Psychopharmacological treatment, including antipsychotic medication, is generally used to reduce symptoms of the disorder, whilst psychosocial interventions, comprising e.g. psychoeducation, cognitive behavioural therapy and family interventions, are provided to improve functioning and quality of life. Furthermore, treatment of schizophrenia often involves health monitoring and support programmes to promote recovery, although variations occur between mental health care systems (34-38).
As a consequence of its early onset and commonly chronic nature, schizophrenia imposes a high economic burden on society. Loss of productivity and unemployment due to morbidity and mortality, i.e. indirect costs, contribute most to the expenditures associated with the disorder. However, the amount spend on providing care, i.e. direct costs, are likewise significant, accounting for 1.5-3% of the total health care expenses (39,40).

2.1.1. MENTAL CONSEQUENSES

Schizophrenia has a wide range of psychological, social and cognitive symptoms. Although no symptom is entirely pathognomonic, a number of positive and negative symptoms generally characterize the disorder. The positive symptoms include distortion or exaggeration of normal brain functions such as disorganized speech and behaviour, hallucinations and delusions. In contrast, negative symptoms comprise loss or decrease of normal functions, such as inability to initiate and preserve in work or social activities, a diminished range of emotional expression and poverty of speech (29-31). Furthermore, patients with schizophrenia often experience deficits in several cognitive domains, including memory, attention and learning, which is a core feature of the disorder (41).

Concurrent with the characteristic symptoms, schizophrenia is commonly associated with additional mental comorbidities (29,42). Approximately 50% of all patients with schizophrenia are subject to comorbid depression and substance abuse, which further disturbs the clinical picture. Depressive symptoms can cause more psychotic relapses and secondary negative symptoms, whilst substance abuse can increase social disability and worsen positive psychotic symptoms (29,42). Schizophrenia is one of the leading causes of disability in the world (43,44).

2.1.2. MEDICAL CONSEQUENSES

In addition to the mental burden and suffering, the medical ramifications of schizophrenia likewise contribute to the debility. Of particular note is the increased risk of premature mortality associated with medical comorbidities. Compared to the general population, patients with schizophrenia have a 2-3 times higher mortality rate, which is equivalent to 10-20 years' shortened life expectancy (3-9). Over recent decades, this mortality gap has persisted, despite the fact that advances in e.g. public health and medical innovations have increased the lifespan of the general population (3,8,45,46).

The elevated mortality rates associated with schizophrenia are found for almost all causes (6,7,47,48). Overall, approximately one third can be explained by unnatural causes, including accidental death and suicide, whilst two thirds are attributable to natural causes involving medical comorbidities (4-7,9). In particular, diabetes, cardiovascular disease and respiratory disease, including COPD, have been identified as predominant and important contributors to the reduced longevity of patients with schizophrenia (5-9,49). The underlying causal mechanisms for these medical comorbidities are multifactorial, but often related to a higher prevalence of potentially modifiable risk factors.

Patients with schizophrenia are especially prone to weight gain and the metabolic syndrome, comprising hypertension, abdominal obesity, low high-density lipoprotein (HDL) cholesterol, hyperglycaemia and elevated triglycerides induced by their antipsychotic treatment (50-53). Unfavourable lifestyle behaviours, including poor diet, smoking, substance abuse and physical inactivity, are likewise more predominant in this group compared to the general population (29,54-57). This association is potentially explained by the characteristic symptoms of schizophrenia, cognitive impairment and low socioeconomic status. More recently, a genetic predisposition has been linked to the development of medical comorbidities. Biological markers, including e.g. diminished telomere length, might affect physiological changes occurring at an earlier stage. Schizophrenia may thus be a syndrome of accelerated aging, causing age-related disorders such as diabetes and cardiovascular disease (58,59). Shared susceptible genetic components between schizophrenia and Type 2 diabetes have also been suggested as potential risk factors (60,61). However, the pathogenetic association in schizophrenia is still elusive, and all the treatment, behavioural and genetic factors mentioned mainly serve to clarify the frequently observed medical comorbidities among patients with schizophrenia (48,62-64). What is certain is that this vulnerable population merit special health care attention in the management of their medical comorbidities. In particular, the leading and important medical causes to the devastating years of life lost, including diabetes, cardiovascular disease and respiratory disease, warrant an urgent call to action, and a duty for the health care systems to provide a better quality of care.

2.2. LITERATURE REVIEW

To clarify whether patients with schizophrenia receive the important treatment for their most critical medical comorbidities, a literature search was performed on the association between schizophrenia and the quality of care for diabetes, heart failure and COPD respectively.

2.2.1. SEARCH STRATEGY

Scientific publications were searched for in PubMed, Embase, PsycINFO and Cinahl based on a combination of free-text, MESH terms and Cinahl Headings, such as *Schizophrenia*, *Comorbidity* and *Healthcare disparities*. The search strategy included literature in English and Scandinavian languages with no restrictions on publication year (Appendix A). Studies located from the search strategy were initially excluded if the title, abstract or full text was considered non-relevant. Publications based on non-comparative results, weak and unclear designs or small study populations were further excluded (Appendix B). A literature checklist from the Danish Health Authority was used to critically assess the scientific content of the remaining identified relevant publications (65). Moreover, the reference lists of the included studies were browsed to identify further relevant publications. Additional literature and information not indexed were located from the internet, including google.com, who.com (World

Health Organization) and sundhed.dk (the public Danish Healthcare Services). The final search for scientific publications, literature and information was conducted in November 2016.

2.2.2. QUALITY OF DIABETES CARE

The literature search identified seven relevant publications examining the quality of diabetes care for a variety of mental disorders, including schizophrenia (10-14,66,67). An overview of the studies located, listed by publication year, is presented in Table 1. The assessed quality of care measures included a pathology test (glycated haemoglobin (HbA_{1c}), lipid, albuminuria, creatinine), body mass index (BMI) and blood pressure measurement, use of antidiabetic medication, flu vaccination provided, smoking cessation counselling as well as eye and foot examination.

Three studies from the USA, United Kingdom and Germany found that patients with and without a serious mental illness had a comparable or very similar chance of receiving tests for HbA_{1c}, lipid, albuminuria and creatinine, recordings for BMI, blood pressure, smoking history and smoking cessation counseling as well as retinal screening, flu vaccination and antidiabetic medication (14,66,67). An additional US study also detected no differences in diabetes care defined as offering test for HbA_{1c} as well as an eye and foot examination among patients with and without a major affective disorder, psychotic disorder or posttraumatic stress disorder. However, the study found that patients with a substance use disorder were less likely to receive retina (63.9% vs 71.0%) and foot sensory examination (74.7% vs 77.5%) compared to patients with no mental disorders (10). The three remaining studies from Australia and the USA documented an association between mental disorders and a deficient quality of diabetes care for all performance measures of care assessed (11-13). One of the publications set in USA demonstrated that patients with a mental disorder had a lower chance of receiving the four examined measures of diabetes care, including HbA_{1c} test (Odds ratio (OR) 0.88, 95% CI: 0.86-0.89), eye examination (OR 0.73, 95% CI: 0.72-0.74), low-density lipoprotein (LDL) screening (OR 0.88, 95% CI: 0.86-0.89) and medical attention for nephropathy (OR 0.96, 95% CI: 0.94-0.99) than patients with no mental disorders (13). Similar inequalities were shown in another study conducted in the USA, indicating insufficient quality of care for HbA_{1c} test and low-density lipoprotein cholesterol (LDL-C) measurement as well as eye examination (11). Failure to meet recommended testing for HbA_{1c}, microalbuminuria and blood lipid among mental health clients was likewise revealed in the Australian study (12).

Overall, the literature search demonstrated varying results and uncertainty about the quality of diabetes care among patients with a mental disorder, including schizophrenia.

Table 1 *Summary of the identified literature on the association between schizophrenia and the quality of care for diabetes*

Author, year	Study design and period	Study location and size	Quality of care measures	Main findings	Assessment
Desai et al. 2002 (10)	Cohort study January 1998 to December 1999	USA 38,020 outpatients with diabetes; 9,025 also had a psychiatric disorder.	Foot inspection, pedal pulses examination, foot sensory examination, examination of the retina, determination of glycated haemoglobin (HbA_{1c})	Only patients with comorbid substance use disorder were less likely to receive retina and foot sensory examination. No difference in care was found for patients with comorbid major affective disorder, psychotic disorder or posttraumatic stress disorder.	Limited to patients with at least three outpatient visits in the past year from the US Veterans Health Administration (VA). The VA is experienced in caring for the mentally ill. Differences in care might therefore be under-estimated compared to other health care settings.
Frayne et al. 2005 (11)	Cross-sectional study 1999	USA 313,586 out/primary care patients with diabetes; 76,799 also had a mental health condition.	HbA_{1c} testing, low-density lipoprotein cholesterol (LDL-C) testing, eye examination	Patients with comorbid mental health condition were less likely to receive testing for $HbA_{1c,}$ and LDL-C, and an eye examination.	Limited to predominantly male patients from the VA. Limited to the fiscal year 1999.
Krein et al. 2006 (66)	Case-control study October 1997 to September 1998	USA 36,546 patients with diabetes; 18,273 patients also had a serious mental illness.	Measurement of $HbA_{1c,}$ LDL-C and cholesterol	No difference in the quality of care for diabetes among patients with and without serious mental illnesses.	Limited to patients from the VA. No presentation of patient characteristics. Unclear whether the examined patient sample were in- or outpatients with diabetes or both.

Whyte et al. 2007 (67)	Cross-sectional study April 2002 to April 2005	United Kingdom 115,131 patients with diabetes seen at the general practitioner; 1,040 also had schizophrenia or bipolar disorder.	Recording of body mass index (BMI), smoking history, smoking cessation advice, $HbA_{1c,}$ blood pressure, creatinine, cholesterol, proteinuria, on acetylcholinesterase Provided retinal screening, test for microalbuminuria and flu vaccination	No difference was found for the quality of care measures for diabetes among patients with and without schizophrenia or bipolar disorder.	The diminished differences in care might be attributed to a GMS contract introduced on 1 April 2004. The contract provided major financial incentives to provide and record the provision of target levels of care. Target-related payments account for around 25% of the income of the average practice in the United Kingdom.
Mai et al. 2011 (12)	Cohort study January 1990 to June 2006	Western Australia 43,671 patients with diabetes; 17,045 also had a mental disorder.	HbA_{1c}, microalbuminuria, blood lipid	Patients with comorbid mental disorder were less likely to receive tests for HbA_{1c}, microalbuminuria and blood lipid.	Unclear whether the included patients with diabetes were inpatients, outpatients, or patients seen by the general practitioner. The strengths included the universal health care.

Druss et al. 2012 (13)	Cross-sectional study 2003 to 2004	USA 657,628 patients with diabetes; 118,190 also had a comorbid mental condition.	HbA_{1c}, eye examination, low-density lipoprotein (LDL) screening, medical attention for nephropathy	Patients with a comorbid mental condition were less likely to have HbA_{1c} drawn, an eye examination, LDL screening and test for nephropathy.	Limited to Medicaid enrolees aged 65 or younger. The strength included data extractions from 50 states.
Rathmann et al. 2016 (14)	Case-control study January 2009 to December 2013	Germany 2,641 patients with Type 2 diabetes seen in primary care practices; 1,321 patients also had schizophrenia.	Metformin alone, metformin and sulfonylurea, sulfonylurea alone, novel antidiabetic agents (dipeptidyl peptidase -4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor antagonist or sodium-glucose cotransporter 2 (SGLT2) inhibitors), insulin	Patients with comorbid schizophrenia were less likely to receive prescriptions of metformin alone and novel antidiabetic agents, yet more likely to receive metformin and sulfonylurea, sulfonylurea alone and insulin in unadjusted analysis. In adjusted analysis, no difference was found in prescription use of novel antidiabetic agents among patients with and without comorbid schizophrenia.	No valid information on diabetes type. Only the association between schizophrenia and novel antidiabetic agents was explored using multivariable regression. Coverage of private health insurance differed between patient with diabetes only and patients with diabetes and schizophrenia.

2.2.3. QUALITY OF HEART FAILURE CARE

The literature search located no publications specifically assessing the quality of heart failure care in patients with schizophrenia. However, 11 relevant studies addressed the quality of care for a broader range of cardiovascular diseases among patients with mental disorders, including schizophrenia (15-24,68). Table 2 presents an overview of the literature identified, listed by publication year.

The quality of care measures examined included cardiovascular procedures and medication, laboratory health measurements and smoking cessation counseling. Of all the publications, only one study from the USA found no significant differences for any of the observed measures in the quality of care for acute coronary syndromes among patients with and without severe mental illness (68). The study compared the quality of care as receipt of cardiac catheterization (P value (p) =0.14), percutaneous coronary intervention (PCI) (p=0.10), coronary artery bypass graft (CABG) (p=0.61) and prescription rates for aspirin (p=0.38), angiotensin-converting enzyme inhibitors (ACE)/Angiotensin II receptor blockers (ARB) (p=0.31) and beta-blockers (p=0.19) at hospital discharge (68). Three other US studies found a difference in only one key area of care (16,18), or found mixed results (15). In these studies, patients with a mental disorder hospitalized with acute myocardial infarction (AMI) were less likely to undergo diagnostic angiography (Relative risk (RR) 0.90, 95% CI: 0.83-0.98) (18) and to receive reperfusion therapy at hospital discharge (RR 0.87, 95% CI: 0.79-0.95) (16) than patients without a mental disorder. These studies found no difference in care defined as receiving thrombolysis at arrival, percutaneous transluminal coronary angioplasty (PCTA), CABG and smoking cessation counseling during the index hospitalization, and cardiac medication, including beta-blockers, ACE inhibitors and aspirin at hospital discharge (15,16,18).

The remaining seven identified publications from Australia, Canada, Denmark, Israel and Taiwan demonstrated deficient quality of cardiovascular care in all (17,20-24) or almost all (19) examined measures of cardiovascular care among patients with a mental disorder. A Danish nationwide study compared the rates of invasive cardiac procedures after the first hospital contact for heart disease among patients with and without a severe mental disorder. Patients with a severe mental disorder younger than 70 years old received lower rates of CABG and PTCA within 1 month (1.6% vs 2.96%), 1 year (3.76% vs 7.90%) and 5 years (7.04% vs 12.27%) of contact compared to patients without a severe mental disorder. Similar results were found for patients with a severe mental disorder 70 years or older (20). The studies from Australia, Canada, Israel and Taiwan also found inadequate care defined as receiving CABG and PCTA as well as other cardiac procedures, including coronary artery obstruction, arterial implant, cardiac catheterization, cerebrovascular arteriography and percutaneous coronary intervention, in patients with mental disorder compared to those without (17,19,21-24).

In summary, the majority of the identified relevant publications suggested inferior quality of cardiovascular care among patients with mental disorders, although the magnitude varied.

Table 2 *Summary of the identified literature on the association between schizophrenia and the quality of care for cardiovascular disease*

Author, year	**Study design and period**	**Study location and size**	**Quality of care measures**	**Main findings**	**Assessment**
Druss et al. 2000 (15)	Cohort study February 1994 to July 1995	USA 111,653 patients hospitalized for acute myocardial infarction (AMI); 5,365 also had a mental disorder.	Cardiac catheterization (CC), percutaneous transluminal coronary angioplasty (PCTA), coronary artery bypass graft (CABG) surgery	Patients with comorbid mental disorders were less likely to undergo CC, PCTA or CABG. For patients having a CC, there was no difference in undergoing a PCTA or CABG among those with and without a mental disorder.	Limited to patients ≥65 years old who were Medicare beneficiaries. The specific location and number of the included acute care non-governmental hospitals in USA were unclear.
Druss et al. 2001 (16)	Cohort study February 1994 to July 1995	USA 83,557 patients hospitalized for AMI; 4,664 also had a mental disorder.	Reperfusion therapy, aspirin, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, smoking cessation counselling	Patents with comorbid mental disorders, classified as ideal candidates with clear indications for and without contraindications for the treatments, were less likely to have reperfusion. No difference was found for the remaining measures in this group.	Limited to patients ≥65 years old who were Medicare beneficiaries. The specific location, including the examined hospitals, in USA was unclear.
Lawrence et al. 2003 (17)	Cohort study 1980 to 1998	Western Australia 23,900 patients admitted for ischaemic heart disease; 1,807 were users of mental health services.	Removal of coronary artery obstruction, CABG or arterial implant	Patients with previous mental health service contacts, including schizophrenia, had lower rates of coronary artery obstruction and CABG or arterial implant.	No presentation of patient characteristics. No information on the clinical decision-making, which could potentially explain the differing rates of cardiac procedures. The strength included the universal health care.

Petersen et al. 2003 (18)	Cohort study January 1994 to September 1995	USA 4,340 patients admitted for AMI; 859 also had a mental disorder.	Angiography, PCTA, CABG. Thrombolysis, beta-blockers, ACE inhibitors, aspirin	Patents with comorbid mental disorders were less likely to undergo angiography. No difference was found for the remaining measures in this group.	Limited to patients from the Veterans Health Administration (VA). A criterion for free care in the VA includes an income qualification, which limits generalization.
Plomodon et al. 2007 (68)	Cohort study October 2003 to September 2005	USA 14,194 patients admitted for acute coronary syndromes; 2,623 also had a severe mental illness.	CC, percutaneous coronary intervention (PCI) and CABG. ACE inhibitors/Angiotensin II Receptor Blockers (ARB), aspirin and beta-blockers	No difference in the quality of care for acute coronary syndromes among patients with and without severe mental illness.	Limited to predominantly male patients from the VA. Mental illness is common among veterans, which might reduce physician bias and thus diminish a difference in care.
Kisely et al. 2009 (19)	Cohort study 1995 to 2001	Nova Scotia, Canada 49,248 patients admitted for ischaemic heart disease; 1,284 also had a history of psychosis. 15,791 patients admitted for stroke; 594 also had a history of psychosis.	Ischaemic heart disease: CC, PTCA or CABG, beta-blockers, ACE inhibitors, statins, ARB, clopidogrel Stroke: cerebrovascular arteriography, carotid endarterectomy, ticlopidine, warfarin, clopidogrel	Ischaemic heart disease patients with comorbid psychosis were less likely to receive CC, PCTA, CABG, beta-blockers, statins. Stroke patients with comorbid psychosis were less likely to receive cerebrovascular arteriography, warfarin.	No presentation of patient characteristics. Information on access to prescriptions was only available for patients over 65 years old. The strength included the universal health care.

Laursen et al. 2009 (20)	Cohort study January 1994 to January 2007	Denmark 605,649 patients admitted with heart disease; 4,997 also had a severe mental disorder.	CABG, PCTA	Patients with comorbid mental disorders had the lower rates of CABG and PCTA after the first heart disease contact.	No presentation of patient characteristics. The strengths included the nationwide study and the universal health care.
Kurdyak et al. 2012 (21)	Cohort study January 2002 to December 2006	Ontario, Canada 27,025 patients admitted with AMI; 203 also had schizophrenia.	CABG, PCTA	Patients with comorbid mental disorders were less likely to receive CABG and PCTA.	No validation of the diagnostic code for schizophrenia, although a similar algorithm identified most cases of schizophrenia in another province in Canada. The strength included the universal health care.
Bresee et al. 2012 (22)	Cohort study January 1995 to December 2006	Alberta, Canada 38,232 patients hospitalized with coronary artery disease; 350 also had schizophrenia.	PCI and CABG	Patients with comorbid mental disorders were less likely to undergo PCI and CABG.	No information on the severity of the coronary artery disease, which might determine whether patients were assessed as eligible to undergo revascularization. The strength included the universal health care.

Wu et al. 2013 (23)	Case-control study 1996 to 2007	Taiwan 2,527 inpatients with AMI; 834 also had schizophrenia or bipolar disorder.	CC, PCTA, CABG	Patients with comorbid schizophrenia and bipolar disorder were less likely to receive CC, PCTA and CABG.	Limited to patients with schizophrenia or bipolar disorder previously seen only in psychiatric inpatient care. The strength included the near-universal health care provision system.
Gal et al. 2016 (24)	Case-control study 2000 to 2009	Israel 5,931 patients with cardiovascular disease; 2,277 also had schizophrenia.	Annual health measures: LDL, HbA_{1c}, stress test, chest X-ray. Surgical interventions: CC, CABG, cardiac pacemaker implantation. Utilisation of cardiovascular drugs: Most frequently utilized drugs, total numbers of drugs utilized, statins and antihypertensive	Patients with comorbid schizophrenia were less likely to receive any of the health measures, surgical interventions and cardiovascular drugs.	No information on the severity of the cardiovascular disease. An Israeli rehabilitation act for persons with mental disabilities entitles these patients to a basket of services, including the appointment of a treatment coordinator of all services. The strength included the universal health care.

2.2.4. QUALITY OF COPD CARE

The literature search identified no publications on the quality of COPD care in patients with mental disorders in general, just as no studies examining the quality of care for other respiratory disorders were identified. It therefore remains unknown whether patients with schizophrenia receive adequate care for their COPD comorbidity.

2.2.5. SUMMARY AND LIMITATIONS OF THE LITERATURE IDENTIFIED

In summary, the existing evidence on the association between schizophrenia and the quality of care for diabetes, heart failure and COPD is sparse, inconclusive or lacking. The literature search identified seven relevant studies assessing the care adequacy for diabetes, including four publications demonstrating equal or almost comparable levels of care among patients with and without mental disorders (10,14,66,67), and three studies showing suboptimal care for patients with a mental disorder (11-13). However, organizational and financial differences in the health care systems as well as methodological limitations need to be taken into consideration when interpreting the results. In the four studies with no appreciable differences in diabetes care, one German publication also included patients covered by private health insurance (14), whilst two US studies comprised patients from the US Veterans Health Administration only (10,66). The fourth study from the United Kingdom examined patients seen by general practitioners (67). Of the remaining three publications demonstrating insufficient diabetes care for patients with a mental disorder, only one Australian study was conducted in a universal health care system (12). The other two publications originated in the USA and included members aged 65 years or younger (13) or predominantly male patients receiving care in the Veterans Health Administration (11). These factors may therefore partly explain the inconsistencies between the studies and affect the generalizability of the results. The main limitations of the existing publications in diabetes care include the non-population-based study designs (only one Australian study examined the population of Western Australia (12)), the more than 10 years old data (10,11,66,67), the limited follow-up period (10,11,13,66), and the potential influence of unaccounted-for confounding factors.
Similar financial differences between the health care systems and methodological limitations characterize the 11 located relevant studies addressing the quality of cardiovascular care, including four publications demonstrating no differences in care or diverging results between patients with and without mental disorders (15,16,18,68), and seven studies indicating deficient quality of care for patients with a mental disorder (17,19-24). Of the four US studies with no or inconclusive differences in cardiovascular care, two publications included only patients aged 65 years or older (15,16), whilst the other two studies covered mainly male patients with access to care through the US Veterans Health Administration (18,68), which complicates generalizability across health care systems. The remaining seven studies originating in Australia, Canada, Denmark, Israel and Taiwan showing inadequate quality of care for patients with a mental disorder were all executed in universal or near-universal

health care systems (17,19-24). Different inclusions of cardiovascular disease, quality measures and psychiatric disorders, however, complicate a direct comparison across the studies. Overall, the methodological limitations include lack of information on patient characteristics, including severity of cardiovascular disease or clinical decision-making on cardiac procedures in some studies as well as shortage of detailed data on the care provided and population-based study designs. Of the 11 identified publications in cardiovascular care, only one Danish study based their results on an entire population (20).
Finally, no publications were found elucidating the quality of care for COPD or other respiratory diseases among patients with a mental disorder, including schizophrenia. The literature identified therefore strongly suggests a continued need for population-based studies with detailed data on the care provided, in particular from universal health care settings, to clarify the association between schizophrenia and the quality of care for diabetes, heart failure and COPD.

2.3. DENMARK AS A SETTING FOR STUDYING MEDICAL CARE FOR PATIENTS WITH SCHIZOPHRENIA

In Denmark, health equity is a stated priority of the public and mainly tax-financed health care system that covers the entire population of 5.7 million residents. The universal health coverage ensures free and equal access to care in public health services for all Danish citizens regardless of their socioeconomic status (28). The health care system consists of a primary and secondary sector. While general health problems are typically treated by general practitioners in the primary sector, patients requiring specialized treatment are referred to public hospitals defined as the secondary sector. The public hospitals cover both in- and outpatients as well as emergency room contacts (69).

All Danish residents are assigned a unique ten-digit civil registration number, which follows the persons forever (70,71). This number is used to record each patient contact with the health care system in public registries and ensures unambiguous linkage of information at the individual level across various data sources. The variables collected in relation to the care provided include e.g. date of contact, diagnostic and procedure codes as well as the quality of care defined as receiving guideline-recommended disease-specific performance measures of care (25,72). This setting and the availability of comprehensive health care datasets in Denmark create an exceptional opportunity to examine whether equal access also implies equal and sufficient medical care for patients with serious mental disorders such as schizophrenia.

CHAPTER 3. AIMS AND HYPOTHESES

The thesis aims to examine the association between schizophrenia and the quality of care for diabetes, heart failure and COPD in Denmark. This goal is investigated in three nationwide population-based cohort studies with the following objectives:

3.1. STUDY I

i. To compare the quality of diabetes care as reflected by meeting guideline-recommended process-performance measures of care among patients with and without schizophrenia
ii. To identify potential patient-, provider- and system-related predictors of quality of diabetes care among patients with schizophrenia

3.2. STUDY II

i. To compare the quality of heart failure care as reflected by meeting guideline-recommended process-performance measures of care among patients with and without schizophrenia
ii. To identify potential patient-, provider- and system-related predictors of quality of heart failure care among patients with schizophrenia
iii. To compare 4-week readmission and 1-year mortality following a first-time hospital contact with heart failure among patients with and without schizophrenia

3.3. STUDY III

i. To compare the quality of COPD care as reflected by meeting guideline-recommended process-performance measures of care among patients with and without schizophrenia
ii. To identify potential patient-, provider- and system-related predictors of quality of COPD care among patients with schizophrenia
iii. To compare 30-day readmission and 30-day mortality following admission for an exacerbation of COPD among patients with and without schizophrenia

It is hypothesized that patients with schizophrenia are less likely to receive guideline-recommended diabetes, heart failure and COPD care compared to patients without schizophrenia, and that specific factors can predict these quality gaps. Moreover, schizophrenia is hypothesized to be associated with increased readmission and mortality rates of heart failure and COPD.

CHAPTER 4. METHODS

The three studies included in the thesis were approved by the Danish Data Protection Agency (J.no. 2008-58-0028) and based on information from national population-based registries.

4.1. DATA SOURCES

A description of the data sources applied is provided in the following, including the Danish Clinical Registries (the Danish Schizophrenia Registry (DSR), the Danish Adult Diabetes Registry (DADR), the Danish Heart Failure Registry (DHFR) and the Danish Registry for COPD (DrCOPD)), the Danish National Patient Register, the Danish Psychiatric Central Research Register and the Danish Civil Registration System (25-27,70-82). It is mandatory for all Danish public hospitals to report to these registries.

4.1.1. THE DANISH CLINICAL REGISTRIES

In 2000, a nationwide multidisciplinary quality improvement initiative was initiated with the objective to routinely monitor and continuously audit the quality of care delivered by the Danish health care system (25-27). During the subsequent years, population-based clinical registries were established to document and improve the care for selected important diseases, including schizophrenia (DSR), diabetes (DADR), heart failure (DHFR) and COPD (DrCOPD) (73-80). These diseases were prioritized on the basis of high incidence, severity and expenditure for the Danish health care services (26,27). For each disease, a number of specific performance measures of care set in accordance with recommendations from national clinical guidelines are collected at the level of the individual in the registries. A multidisciplinary expert group appointed by professional organizations and scientific societies developed the disease-specific performance measures of care and relevant prognostic factors also monitored in the registries. Potential changes, additions or omissions of the quality measures of care are discussed regularly to ensure the continued relevance of the standards to be met in clinical practice (25-27,73-80).

All data in the DSR, DADR and DHFR are collected prospectively from documentation in medical records by using standardized registration forms with precise, simple and feasible data instructions (73-78). For patients with schizophrenia, the registration form is completed for inpatients at discharge from psychiatric hospitals, and once a year for outpatients treated at hospital outpatient clinics. The DSR provides a high coverage: records are available for 93% of all hospital inpatients and 92% of every hospital outpatient with schizophrenia. Almost all patients with schizophrenia seen in the secondary health care system can therefore be identified

from the DSR since its introduction in 2004 (73,74).
Outpatients with diabetes have their registration form filled in once a year at the hospital specialized outpatient clinics responsible for their care. The DADR was initiated in 2005 and approximately 90% of all hospital outpatients with diabetes are recorded in the registry. General practitioners collect similar diabetes data; however, completeness is currently low (75,76).
Quality of care data for heart failure in- and outpatients are recorded at their first-time hospital admission or hospital outpatient contact with heart failure as the primary diagnosis. The DHFR includes records of 84% of all hospital in -and outpatients with incident heart failure. Due to a high proportion of missing data in the DHFR in its first year of launching in 2003, this thesis only included data from 2004 onwards (77,78).
All of the collected data on patients treated with schizophrenia, diabetes and incident heart failure at Danish public hospitals are securely transmitted via the internet to each disease-specific clinical registry (26,27).

In contrast to the DSR, DHFR and DADR, data on COPD care are not directly reported to a separate clinical registry. The DrCOPD has been operative since 2008, and data are prospectively recorded at discharge, hospital transmission or death for inpatients with COPD, and as part of daily clinical routine for outpatients with COPD seen at hospital outpatient clinics. The COPD diagnosis in the DrCOPD has a positive predictive value of 92% for hospital inpatients and 86% for hospital outpatients. Outpatient data from general practitioners can also be obtained; however, data coverage remains incomplete. All data in the DrCOPD are reported entirely through diagnosis codes and codes for clinical procedures in the Danish National Patient Register (72,79,80). The DSR also decided to collect data via the Danish National Patient Register from 2012 onwards (73).

4.1.2. THE DANISH NATIONAL PATIENT REGISTER

The Danish National Patient Register has collected information on all somatic inpatient hospital contacts in Denmark since its establishment in 1977. From 1995 onwards, all outpatient, emergency room and psychiatric hospital contacts have also been included in the registry. Data records include date and time of hospital contact, identification of the specific place of treatment, diagnoses and type of examination, treatment or surgical procedure. Each variable is allocated a structured and limited set of codes (72).

4.1.3. THE DANISH PSYCHIATRIC CENTRAL RESEARCH REGISTER

Since 1969, all psychiatric inpatients treated at Danish psychiatric hospitals have been recorded in the Danish Psychiatric Central Research Register. The register was expanded in 1995 to also include psychiatric patients seen at hospital outpatient clinics and emergency rooms, simultaneously becoming an integrated part of the Danish National Patient Register. The psychiatric data are transmitted monthly from the

Danish National Patient Register to the Danish Psychiatric Central Research Register. For each psychiatric patient treated, the register contains all diagnoses, dates of start and end of any treatment as well as the specific location of treatment (81,82).

4.1.4. THE DANISH CIVIL REGISTRATION SYSTEM

The Danish Civil Registration System was founded in 1969 and assigns a unique civil registration number to all Danish residents at birth or when taking up residence. The system maintains daily updated information on date and place of birth, location of residence, emigration or immigration and vital status (70,71).

4.2. STUDY POPULATION

The study populations of all three studies were identified from the Danish Clinical Registries.

4.2.1. STUDY I

Study I comprised all outpatients (≥18 years old) treated for diabetes at a hospital diabetes specialized outpatient clinic and recorded in the DADR between 1 January 2005 and 31 December 2013. All diabetes contacts for each patient were included in the analysis. Diabetes referred to Type 1 diabetes, Type 2 diabetes, other types of diabetes and diabetes without specification defined according to the International Classification of Diseases version 10 (ICD-10) (E10.0-E11.9, E13.0-E14.9). At each diabetes contact, the patient was assigned the current clinical diagnosis by the treating outpatient clinic (75,76,83).

4.2.2. STUDY II

Study II included all in- and outpatients (≥18 years old) registered in the DHFR at first-time hospital contact (admission or outpatient contact) with heart failure as the primary diagnosis between 1 January 2004 and 31 December 2013. Each incident heart failure patient was thus only included once in the analysis, whether treated at a hospital department or outpatient clinic. Based on diagnoses made by cardiologists using the guidelines of the European Society of Cardiology, the DHFR includes the following ICD-10 codes for heart failure: I11.0, I13.0, I13.2, I42.0, I42.6, I42.7, I42.9, I50.0, I50.1, I50.9 (77,78,83).

4.2.3. STUDY III

Study III covered all in- and outpatients (≥30 years old) treated for COPD or an acute exacerbation of COPD at any hospital department and hospital outpatient clinic and recorded in the DrCOPD between 1 January 2008 and 31 December 2013. All COPD contacts for in- and outpatients were included in the analysis. The DrCOPD includes

inpatients with the following ICD-10 codes: DJ44.X as a primary diagnosis or DJ96.X or DJ13.X-DJ18.X as a primary diagnosis in combination with DJ44.X as a secondary diagnosis. For outpatients, the DrCOPD includes DJ44.X or DJ96.X in combination with DJ44.X as a secondary diagnosis. The physicians responsible for the care of the individual COPD patient performed the coding of the diagnosis (79,80,83).

4.3. PATIENTS WITH SCHIZOPHRENIA

By linkage with the DSR, all patients in the three study populations who also had comorbid schizophrenia were identified. Schizophrenia was defined as a recording in the DSR between 1 January 2004 and 31 December 2011 as either an in -or outpatient with schizophrenia (ICD-10 codes: F20.0-F20.99). A psychiatrist or a specialist clinical psychologist made the diagnosis of schizophrenia (73,74,83).
Patients were excluded if schizophrenia was not recorded before their first recording of diabetes (N=29), incident heart failure (N=26) or COPD contact (N=16). To ensure coherence, patients were moreover excluded if they had >5 years between the recording for schizophrenia in the DSR and the subsequent registration in the DADR (N=23), DHFR (N=6) and DrCOPD (N=36).

4.4. PREDICTORS OF MEDICAL CARE

In all three studies, factors related to patients, providers and health care system were examined as potential predictors of the quality of care for diabetes, heart failure and COPD respectively.

4.4.1. PATIENT-RELATED FACTORS

The patient-related predictors were collected from the DSR, DADR, DHFR, DrCOPD and the Danish Psychiatric Central Research Register and included sex, age, abuse (alcohol or drug abuse (defined as illegal drugs, benzodiazepines or central stimulants)), duration of schizophrenia at the hospital contact for either diabetes, incident heart failure or COPD, and the Global Assessment of Functioning (GAF) scale ranging from 1 to 100. The GAF scale evaluates the overall psychosocial functioning of patients with schizophrenia, with 1 representing the poorest functioning and 100 the best functioning (73-82,84,85).

4.4.2. PROVIDER-RELATED FACTORS

To elucidate whether receiving an inadequate quality of care for schizophrenia is potentially associated with a subsequent deficient quality of care for diabetes, heart failure or COPD, the provider-related predictor included the quality of schizophrenia care delivered before the contact for diabetes, heart failure or COPD. Obtained from the DSR, Table 3 lists the definitions of the 12 process-performance measures of schizophrenia care assessed, covering the areas: diagnosing schizophrenia,

antipsychotic medical treatment, family intervention, psychoeducation, suicide risk assessment and post-discharge support (73,74). These process-performance measures were relevant for hospital in- and outpatients with schizophrenia, including incident patients. Patients with incident schizophrenia were defined as individuals diagnosed with schizophrenia within the past year. The quality of schizophrenia care was evaluated overall by dividing the number of process-performance measures of care received with the number of relevant measures for each patient with schizophrenia.

Table 3 *Definitions of the process-performance measures of schizophrenia care for hospital in- and outpatients with schizophrenia*

Process-performance measure	**Definition**
Assessment of psychopathology by a specialist in psychiatry	Incident patients who are assessed for psychopathological characteristics by a specialist in psychiatry.
Assessment of psychopathology by interview form	Incident patients who receive a diagnostic interview with an established interview instrument, such as the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) or the Operational Criteria Checklist for Psychotic Illness (OPCRIT).
Assessment of cognitive function	Incident patients who are administered cognitive testing by a psychologist.
Assessment by a social worker	Incident patients who are assessed for need for social support by a social worker, e.g. financial help to purchase medicine, help with changing housing or application for disability benefits.
Antipsychotic medical treatment	Patients who are prescribed antipsychotic medical treatment.
Outpatient antipsychotic medical treatment	Outpatients who are in medical treatment with more than one antipsychotic.
Benzodiazepine medical treatment	Outpatients who are in medical treatment with benzodiazepines, exclusive of benzodiazepine-related drugs (zolpidem, zopiclon, zaleplon).
Contact with relatives	Staff contact with the patient's relatives.
Psychoeducation	Patients who receive psychoeducation.
Professional support	Patients with a GAF score ≤30 who are referred to post-discharge professional support in the patient's own home, residential facilities or care homes.
Psychiatric aftercare	Patients who are referred to psychiatric aftercare, including outpatient treatment, contact to general practitioner or a private specialist, after discharge.
Suicide risk assessment	Patients who are assessed for suicide risk at discharge.

4.4.3. SYSTEM-RELATED FACTORS

The system-related predictor comprised the contact volume of patients treated for diabetes, incident heart failure or COPD in the hospital departments and/or outpatient clinics.

4.4.3.1 Study I

Drawn from the DADR, the contact volume in Study I was defined as the average number of diabetes contacts in each hospital outpatient clinic per year from 2005 to 2013 (75,76). The contact volume was divided into 4 quartiles, including low-volume contact (quartile 1, ≤519 diabetes contacts per year), medium-volume (quartile 2, >519-895 diabetes contacts per year), high-volume (quartile 3, >895-1620 diabetes contacts per year) and very high-volume contact (quartile 4, >1620 diabetes contacts per year).

4.4.3.2 Study II

The contact volume in Study II was collected from the DHFR and referred to as the average number of incident heart failure patients in the hospital departments and outpatient clinics per year from 2004 to 2013 (77,78). The four quartiles of the contact volume comprised: low-volume contact (quartile 1, ≤78 incident heart failure patients per year), medium-volume (quartile 2, >78-103 incident heart failure patients per year), high-volume (quartile 3, >103-120 incident heart failure patients per year) and very high-volume contact (quartile 4, >120 incident heart failure patients per year).

4.4.3.3 Study III

In Study III, the contact volume was obtained from the DrCOPD and defined as average COPD contacts in hospital departments and outpatient clinics per year from 2008 to 2013 (79,80). The contact volume was distributed into the four qualities: low-volume contact (quartile 1, ≤244 COPD contacts per year), medium-volume (quartile 2, >244-424 COPD contacts per year), high-volume (quartile 3, >424-585 COPD contacts per year) and very high-volume contact (quartile 4, >585 COPD contacts per year).

4.5. QUALITY OF MEDICAL CARE

The quality of diabetes, heart failure and COPD care was defined as fulfillment of the individual disease-specific process-performance measures of care. Table 4, 5 and 6 present the included performance measures of care by medical disease (75-80). Furthermore, the quality of care for each medical disease was summarized using an overall composite measure determined by dividing the number of received disease-specific process-performance measures of care with the number of relevant measures

for each diabetes, incident heart failure and COPD patient.
Throughout the study period, the set of disease-specific performance measures of care was modified as some performance measures were added whilst others were omitted. Therefore, the time periods for the measures varied, which was taken into account in the analysis.

4.5.1. STUDY I

Collected from the DADR, the quality of diabetes care was evaluated by 11 process-performance measures of care relevant to hospital outpatients with diabetes (Table 4). The areas of diabetes care covered metabolic or glycemic regulation, monitoring and medical treatment for hypertension, lipids and albuminuria as well as eye and foot examination (75,76).

Table 4 *Definitions of the process-performance measures of diabetes care for hospital outpatients with diabetes*

Process-performance measure	**Definition**
Glycemic monitoring	Patients who have their glycated haemoglobin (HbA_{1c}) level monitored, at least once a year.
Medication: anti-diabetics	Type 2 diabetes patients with $HbA_{1c} \geq 53$ mmol/mol [7%] who are treated with anti-diabetic medication.
Blood pressure monitoring	Patients who have their blood pressure monitored, at least once a year.
Medication: antihypertensive	Patients with a blood pressure of >140/90 mmHg who are treated with antihypertensive medication.
Cholesterol monitoring	Patients over 30 years old who have their low-density lipoprotein (LDL) cholesterol monitored, at least every second year.
Medication: lipid-lowering	Type 2 diabetes patients over 40 years old with a LDL cholesterol > 2.5 mmol/l who are treated with lipid-lowering medication.
Screening for albuminuria	Patients who are screened for albuminuria, at least every second year.
Medication: ACE/ATII inhibitors	Patients with micro- or macroalbuminuria who are treated with angiotensin-converting enzyme (ACE)/ angiotensin II receptor (ATII) inhibitors.
Eye examination I	Patients receiving an eye examination, at least every second year.
Eye examination II	Patients receiving an eye examination, at least every fourth year.
Foot examination	Patients receiving a foot examination, at least every second year.

4.5.2. STUDY II

The quality of heart failure care was assessed using seven process-performance measures of care obtained from the DHFR and related to hospital in- and outpatients with incident heart failure (Table 5). The variables included diagnostic test, severity of symptoms, medical treatment, physical training and patient education (77,78).

Table 5 *Definitions of the process-performance measures of heart failure care and the clinical outcomes of heart failure for hospital in- and outpatients with incident heart failure*

Process-performance measure	**Definition**
Echocardiography	Patients who undergo echocardiography.
NYHA classification	Patients who undergo New York Heart Association (NYHA) classification.
Medication: ACE/ATII inhibitors	Patients with reduced systolic function (Left Ventricular Ejection Fraction (LVEF) ≤ 40%) who are treated with angiotensin-converting enzyme (ACE)/angiotensin II receptor (ATII) inhibitors.
Medication: beta-blockers	Patients with reduced systolic function (LVEF ≤ 40%) who are treated with beta-blockers.
Medication: aldosterone	Patients with reduced systolic function (LVEF ≤ 35%) who are treated with aldosterone.
Physical training	Patients with reduced systolic function (LVEF ≤ 40%) who are referred to individual physical training.
Patient education	Patients with reduced systolic function (LVEF ≤ 40%) who start a structured patient education programme (including e.g. nutrition, physical training and medical treatment).
Clinical outcome	**Definition**
Readmission	Patients who are acutely (i.e. not planned) readmitted for any cause within 4 weeks of discharge from a hospital department admission or outpatient clinic contact.
Mortality	Patients who die from any cause within 1 year of discharge from a hospital department admission or outpatient clinic contact.

4.5.3. STUDY III

The quality of COPD care was examined using nine process-performance measures of care relevant to COPD hospital outpatients only (Table 6). Classification of severity of disease, nutrition status, smoking history and cessation, COPD rehabilitation, medical treatment and inhalation technique were the measures assessed (79,80).

Table 6 *Definitions of the process-performance measures of COPD care and the clinical outcomes of COPD for hospital in- and outpatients with COPD*

Process-performance measure	**Definition**
Lung function	Outpatients who have their forced expiratory volume in 1 second in percent of predicted (FEV_1 %) measured and recorded, at least once a year.
Nutrition status	Outpatients who have their body mass index (BMI) calculated and recorded, at least once a year.
Dyspnea measurement	Outpatients who have their dyspnea measured and recorded using the Medical Research Council (MRC) scale, at least once a year.
Smoking status	Outpatients who have their smoking status determined and recorded, at least once a year.
Smoking cessation	Active smokers or recently stopped smoking outpatients who are encouraged to stop smoking, at least once a year.
COPD rehabilitation	Outpatients with an MRC level ≥ 3 who are offered participation in COPD rehabilitation, at least once every third year.
Medication: LAMA/LABA	Outpatients with an MRC level ≥ 2 who are treated with long-acting muscarinic antagonists (LAMA) or long-acting β2-agonists (LABA) including ultra-long-acting β2-adrenoceptor agonists (ULTRA-LABA).
Medication: inhaled steroids	Outpatients with an MRC level ≥ 2 in a long-acting inhaled bronchodilator treatment and with a FEV_1 <60% who are treated with inhaled steroids.
Inhalation technique	Outpatients in inhaled medication treatment who have their inhalation technique checked with the relevant inhalers, at least once a year.
Clinical outcome	**Definition**
Readmission	Inpatients acutely admitted with a COPD exacerbation who are readmitted for any cause within 30 days of discharge.
Mortality	Inpatients acutely admitted with a COPD exacerbation who die from any cause within 30 days of admission.

4.6. CLINICAL OUTCOMES

Data on the clinical outcomes of heart failure and COPD are also shown in Table 5 and 6. The DADR does not document clinical outcomes for patients with diabetes (75,76).

4.6.1. STUDY II

Drawn from the DHFR and the Danish Civil Registration System, the clinical outcomes of heart failure comprised 4-week all-cause readmission and 1-year all-cause mortality following a first-time hospital contact (admission or outpatient contact) with incident heart failure (Table 5) (70,71,77,78).

4.6.2. STUDY III

Information on clinical outcomes of COPD, including 30-day all-cause readmission and 30-day all-cause mortality following an admission for exacerbation of COPD, were obtained from the DrCOPD and the Danish Civil Registration System (Table 6) (70,71,79,80).

4.7. STATISTICAL ANALYSIS

All statistical analyses in the three studies were performed using STATA (version 11.2 Special Edition). The 95% confidence intervals (CI) were corrected for clustering of each patient with diabetes, incident heart failure or COPD within the treating hospital department and/or outpatient clinic using robust estimates of variance. A two-sided p-value ≤ 0.05 was considered to be significant.

4.7.1. ANALYSIS OF QUALITY OF MEDICAL CARE

For all three studies, binary regression was used to estimate the RR of adherence to the individual disease-specific process-performance measures of care and the overall composite measure among diabetes, incident heart failure and COPD patients with and without schizophrenia. Only patients recorded as relevant for the disease-specific performance measures of care according to the definitions were included in analysis. A high overall quality of diabetes, heart failure and COPD care was defined as having fulfilled at least 80% of the relevant recommended disease-specific process-performance measures of care. This analysis was repeated to assess the robustness of the findings by using alternative cut points ranging from 60-90%.

All analysis were stratified according to patient characteristics, including sex, age, HbA_{1c} level (for patients with diabetes), Left Ventricular Ejection Fraction (LVEF) level (for patients with incident heart failure) and dyspnea using the Medical Research Council (MRC) scale (for patients with COPD).

4.7.2. ANALYSIS OF PREDICTORS OF MEDICAL CARE

Binary regression was used in all three studies to examine separately the association between patient-, provider- and system-related predictors and the quality of care for each medical disease among diabetes, incident heart failure and COPD patients with schizophrenia. The potential predictors of medical care included sex, age, abuse, GAF score, duration of schizophrenia, quality of schizophrenia care and contact volume. Only predictors statistically significantly associated with the quality of diabetes, heart failure or COPD care in the univariable analysis were included in the mutually adjusted multivariable analysis. A high overall quality of schizophrenia care was defined as receiving at least 80% of the relevant process-performance measures of schizophrenia care.

4.7.3. ANALYSIS OF CLINICAL OUTCOMES

4.7.3.1 Study II

In Study II, logistic regression was used to estimate the OR for 4-week all-cause readmission, whilst cox proportional hazards regression analysis was used to calculate the hazard ratio (HR) for 1-year all-cause mortality. The ORs and HRs were adjusted for patient characteristics, including sex, age, LVEF level, previous acute myocardial infarction (AMI), stroke or COPD, diabetes, treatment for hypertension, alcohol intake and smoking habits, to control for confounding. Due to several missing data, New York Heart Association (NYHA) classification was excluded from the adjusted multivariable analysis. The Kaplan-Meier estimator was used to plot cumulative mortality curves for 1-year all-cause mortality among incident heart failure patients with and without schizophrenia.

4.7.3.2 Study III

Logistic regression was also used in Study III to examine the OR for 30-day all-cause readmission and 30-day all-cause mortality. To control for confounding factors, ORs were adjusted for sex, age and the Charlson Index, which scores the number and severity of comorbidities for each patient (86).

CHAPTER 5. RESULTS

The main results from the three studies included in the thesis will be presented in the following chapter. A detailed description of the results is reported in the appended papers for each study (Appendix C-E).

5.1. STUDY I

Study I comprised 83,813 diabetes patients with 302,638 diabetes contacts. A total of 669 (0.79%) diabetes patients with 1,681 diabetes contacts also had schizophrenia recorded prior to their contact for diabetes. Compared to diabetes patients without schizophrenia, diabetes patients with schizophrenia were overrepresented with Type 2 diabetes, were younger, more likely to be smokers and had higher HbA_{1c} levels and BMI.

5.1.1. QUALITY OF DIABETES CARE

Table 7 presents the association between schizophrenia and the individual process-performance measures of care as well as the overall quality of diabetes care (≥ 80% of all relevant process-performance measures of diabetes care fulfilled). Compared to diabetes patients without schizophrenia, diabetes patients with schizophrenia were less likely to receive 6 out of 11 individual process-performance measures, including blood pressure monitoring (RR 0.98, 95% CI: 0.96-0.99), treatment with antihypertensive drugs (RR 0.83, 95% CI: 0.70-0.97) and ACE/ATII inhibitors (RR 0.72, 95% CI: 0.55-0.93), screening for albuminuria (RR 0.96, 95% CI: 0.93-0.99), eye examination at least every second year (RR 0.97, 95% CI: 0.94-0.99) and foot examination at least every second year (RR 0.96, 95% CI: 0.93-0.99) than diabetes patients without schizophrenia. The remaining process-performance measures were equally distributed among diabetes patients with and without schizophrenia. Meeting a high overall quality of diabetes care was also less likely among diabetes patients with schizophrenia (RR 0.91, 95% CI: 0.88-0.95) than among diabetes patients without schizophrenia. When applying alternative cut points of 60-90% to describe a high overall quality of diabetes care, the pattern remained, with RRs ranging between 0.94 (95% CI: 0.91-0.97) and 0.82 (95% CI: 0.76-0.88). No systematic interaction was found when the individual process-performance measures and a high overall quality of diabetes care were stratified according to sex, age and HbA_{1c} (data not shown).

Table 7 *The relative risk (RR) of receiving the individual process-performance measures and a high overall quality of diabetes care among diabetes hospital outpatients with and without schizophrenia*

	Diabetes contacts with schizophrenia, N (%)	**Diabetes contacts without schizophrenia, N (%)**	**Unadjusted RR (95 % CI)**
Individual performance measure			
Glycemic monitoring	1,227 (96)	241,955 (97)	0.98 (0.96-1.00)
Medication: anti-diabetics	321 (98)	48,533 (98)	1.00 (0.99-1.02)
Blood pressure monitoring	1,178 (93)	234,424 (95)	0.98 (0.96-0.99)
Medication: antihypertensive	86 (66)	28,228 (80)	0.83 (0.70-0.97)
Cholesterol monitoring	1,108 (94)	221,457 (95)	0.99 (0.97-1.01)
Medication: lipid-lowering	38 (70)	7,161 (64)	1.09 (0.89-1.35)
Screening for albuminuria	1,108 (88)	221,920 (91)	0.96 (0.93-0.99)
Medication: ACE/ATII inhibitors	27 (59)	7,656 (82)	0.72 (0.55-0.93)
Eye examination I	1,075 (86)	214,593 (88)	0.97 (0.94-0.99)
Eye examination II	1,155 (92)	226,515 (93)	0.99 (0.96-1.01)
Foot examination	1,097 (87)	220,702 (91)	0.96 (0.93-0.99)
Overall quality of care			
High*	956 (66)	197,412 (72)	0.91 (0.88-0.95)

* Receiving 80-100% of relevant performance measures of diabetes care

5.1.2. PREDICTORS OF DIABETES CARE

Drug abuse reduced the chance of receiving foot examination (adjusted for age: RR 0.88, 95% CI: 0.79-0.99), whilst a very high clinic contact volume increased the chance of meeting a high overall quality of diabetes care (adjusted for age: RR 1.44, 95% CI: 1.18-1.75) and treatment with ACE/ATII inhibitors (adjusted for duration of schizophrenia: RR 3.19, 95% CI: 1.80-5.65) among diabetes patients with schizophrenia. Young age and short duration of schizophrenia were also associated with a poorer quality of diabetes care, although the correlations were not as clear (data not shown).

5.2. STUDY II

Study II included a total of 36,718 incident heart failure patients, of which 108 (0.29%) patients also had a diagnosis of schizophrenia before their first-time hospital contact with incident heart failure. The patient characteristics demonstrated that incident heart failure patients with schizophrenia were more likely to be smokers, younger and have a higher alcohol intake as well as a lower LVEF (≤ 35) than incident heart failure patients without schizophrenia.

5.2.1. QUALITY OF HEART FAILURE CARE

The association between schizophrenia and the individual process-performance measures of care as well as the overall quality of heart failure care is illustrated in Table 8. Incident heart failure patients with schizophrenia were less likely to receive 1 out of 7 individual process-performance measures, including treatment with beta-blockers (RR 0.87, 95% CI: 0.79-0.97) than incident heart failure patients without schizophrenia. No difference in heart failure care was found for the remaining process-performance measures among incident heart failure patients with and without schizophrenia. Incident heart failure patients with schizophrenia were less likely to receive a high overall quality of heart failure care (RR 0.66, 95% CI: 0.48-0.91) compared to those without schizophrenia. However, this pattern was not significant when a high overall quality of heart failure care was defined using alternative cut points ranging between 60% (RR 0.87, 95% CI: 0.75-1.01) and 90% (RR 0.65, 95% CI: 0.40-1.05). Stratifying the individual process-performance measures of care and a high overall quality of heart failure care by age, sex and LVEF displayed no evidence of systematic interaction (data not shown).

Table 8 *The relative risk (RR) of meeting the individual process-performance measures and a high overall quality of heart failure care among incident heart failure hospital in- and outpatients with and without schizophrenia*

	Incident heart failure patients with schizophrenia, N (%)	**Incident heart failure patients without schizophrenia, N (%)**	**Unadjusted RR (95 % CI)**
Individual performance measure			
Echocardiography	84 (86)	26,801 (87)	0.99 (0.91-1.07)
NYHA classification	75 (74)	25,104 (73)	1.00 (0.89-1.13)
Medication: ACE/ATII inhibitors	69 (93)	20,415 (93)	1.00 (0.94-1.06)
Medication: beta-blockers	56 (76)	18,892 (87)	0.87 (0.79-0.97)
Medication: aldosterone	20 (37)	4,874 (35)	1.06 (0.75-1.49)
Physical training	10 (13)	4,785 (21)	0.62 (0.36-1.08)
Patient education	50 (68)	17,083 (76)	0.89 (0.75-1.05)
Overall quality of care			
High*	26 (25)	13,188 (39)	0.66 (0.48-0.91)

* Receiving 80-100% of relevant performance measures of heart failure care

5.2.2. PREDICTORS OF HEART FAILURE CARE

A GAF score ≥ 75 increased the chance of receiving treatment with beta-blockers (adjusted for age: RR 1.42, 95% CI: 1.15-1.76) and a high overall quality of heart failure care (adjusted for age: RR 3.41, 95% CI: 2.17-5.35) among incident heart failure patients with schizophrenia. The remaining potential predictors of heart failure care, including sex, age, abuse, duration of schizophrenia, quality of schizophrenia care and contact volume, were not independently associated with the chance of receiving treatment with beta-blockers and a high overall quality of heart failure care (data not shown).

5.2.3. CLINICAL OUTCOMES OF HEART FAILURE

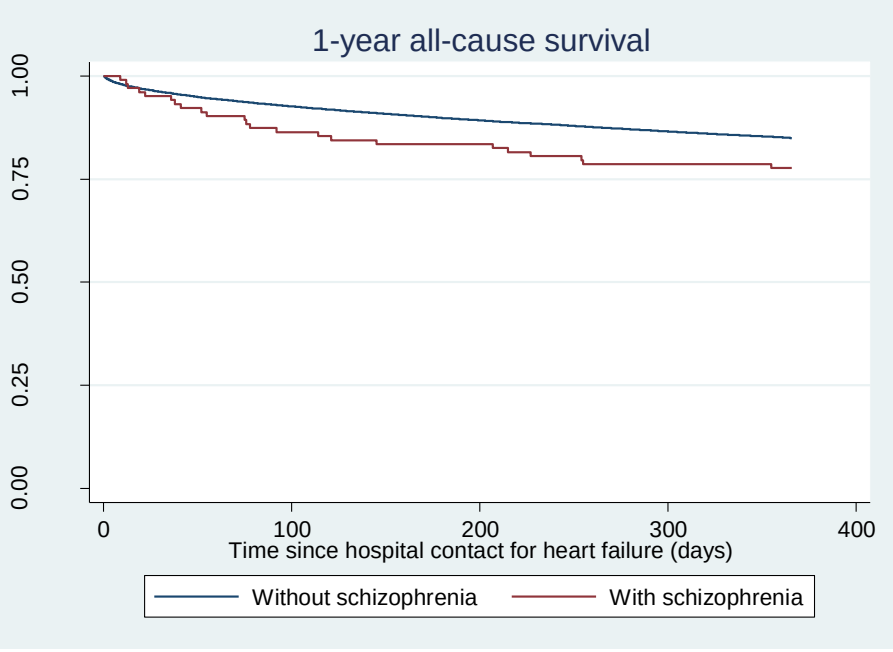
In the adjusted analysis for age, sex, LVEF, previous AMI, stroke and COPD, diabetes, in treatment for hypertension, alcohol intake and smoking habits, incident heart failure patients with schizophrenia did not have any statistically significantly increased risk of 4-week all-cause readmission (adjusted OR 1.77, 95% CI: 0.79-3.92) following a first-time hospital contact with incident heart failure compared to incident heart failure patients without schizophrenia. However, incident heart failure patients with schizophrenia had an increased risk of 1-year all-cause mortality (adjusted HR 2.83, 95% CI: 1.59-5.04) (Table 9). A higher cumulative 1-year all-cause mortality for incident heart failure patients with schizophrenia compared to incident heart failure patients without schizophrenia is illustrated in Figure 1.

Table 9 *The odds ratio (OR) of 4-week all-cause readmission and the hazard ratio (HR) of 1-year all-cause mortality following a first-time hospital contact with incident heart failure among hospital in- and outpatients with and without schizophrenia*

Clinical outcome	**Incident heart failure patients with schizophrenia, N (%)**	**Incident heart failure patients without schizophrenia, N (%)**	**Unadjusted OR/HR (95 % CI)**	**Adjusted[*] OR/HR (95 % CI)**
4-week readmission	13 (17)	2,445 (10)	OR= 1.84 (1.09-3.08)	OR= 1.77 (0.79-3.92)
1-year mortality	23 (22)	5,194 (15)	HR= 1.57 (0.94-2.59)	HR= 2.83 (1.59-5.04)

[*] Adjusted for age, sex, LVEF, previous AMI, stroke and COPD, diabetes, in treatment for hypertension, alcohol intake and smoking habits

Figure 1 *The Kaplan-Meier curves for 1-year all-cause mortality following a first-time hospital contact for heart failure among incident heart failure hospital in- and outpatients with and without schizophrenia*



5.3. STUDY III

Study III contained 72,692 COPD patients with a total of 211,868 COPD contacts. Within this sample, 621 (0.85%) COPD patients with 1,502 COPD contacts also had a diagnosis of schizophrenia prior to their COPD contact. The characteristics indicated that COPD patients with schizophrenia had a higher BMI and were more likely to be younger, smokers and inpatients admitted for acute COPD exacerbation compared to COPD patients without schizophrenia.

5.3.1. QUALITY OF COPD CARE

Table 10 shows the association between schizophrenia and the individual process-performance measures of care as well as the high overall quality of COPD care. Compared to COPD outpatients without schizophrenia, those with schizophrenia were less likely to receive 1 out of 9 process-performance measures, including treatment with long-acting muscarinic antagonists (LAMA) or long-acting β2-agonists (LABA) (RR 0.92, 95% CI: 0.87.-0.98). COPD outpatients with and without

schizophrenia had the same chance of receiving a high overall quality of COPD care (RR 0.95, 95% CI: 0.87-1.03), also when applying alternative cut points of 60-90% for defining a high overall quality of COPD care, with RRs ranging between 0.97 (95% CI: 0.90-1.04) and 0.91 (95% CI: 0.79-1.04). When stratifying the individual process-performance measure of care and the high overall quality of COPD care by sex, age and the MRC scale, no evidence of systematic interaction was found (data not shown).

Table 10 *The relative risk (RR) of the adherence to the individual process-performance measures and a high overall quality of COPD care among COPD hospital outpatients with and without schizophrenia*

	COPD contacts with schizophrenia, N (%)	**COPD contacts without schizophrenia, N (%)**	**Unadjusted RR (95 % CI)**
Individual performance measure			
Lung function	261 (72)	62,687 (75)	0.95 (0.88-1.02)
Nutrition status	267 (73)	62,413 (75)	0.98 (0.91-1.04)
Dyspnea measurement	261 (72)	61,082 (73)	0.97 (0.91-1.04)
Smoking status	263 (72)	60,942 (73)	0.98 (0.92-1.06)
Smoking cessation	173 (91)	17,746 (92)	0.99 (0.94-1.05)
COPD rehabilitation	162 (90)	38,180 (90)	1.00 (0.95-1.06)
Medication: LAMA/LABA	123 (87)	24,484 (95)	0.92 (0.87-0.98)
Medication: inhaled steroids	91 (95)	17,734 (90)	1.05 (0.99-1.11)
Inhalation technique	116 (75)	23,664 (77)	0.97 (0.88-1.08)
Overall quality of care			
High*	244 (67)	58,686 (70)	0.95 (0.87-1.03)

* Receiving 80-100% of relevant performance measures of COPD outpatient care

5.3.2. PREDICTORS OF COPD CARE

Female sex increased the chance of receiving treatment with LAMA/LABA (adjusted for contact volume: RR 1.19, 95% CI: 1.02-1.39) among COPD patients with schizophrenia. The remaining predictors of COPD care were not independently associated with the chance of receiving LAMA/LABA treatment (data not shown).

5.3.3. CLINICAL OUTCOMES OF COPD

In the adjusted analysis for age, sex and Charlson index, COPD inpatients with schizophrenia did not have a statistically significantly increased risk of 30-day all-cause readmission (adjusted OR 1.08, 95% CI: 0.92-1.28) following an admission for exacerbation of COPD. However, they had an increased adjusted risk of 30-day all-cause mortality (adjusted OR 1.27, 95% CI: 1.01-1.59) compared to COPD inpatients without schizophrenia (Table 11).

Table 11 *The odds ratio (OR) of 30-day all-cause readmission and 30-day all-cause mortality following an admission for exacerbation of COPD among COPD hospital inpatients with and without schizophrenia*

Clinical outcome	**COPD contacts with schizophrenia, N (%)**	**COPD contacts without schizophrenia, N (%)**	**Unadjusted OR (95 % CI)**	**Adjusted[*] OR (95 % CI)**
30-day readmission	216 (21)	22,509 (20)	OR= 1.07 (0.90-1.26)	OR= 1.08 (0.92-1.28)
30-day mortality	101 (9)	12,739 (10)	OR= 0.87 (0.69-1.08)	OR= 1.27 (1.01-1.59)

[*] Adjusted for age, sex and Charlson index

CHAPTER 6. DISCUSSION

The findings from the three studies will be summarized in the following and methodological considerations will be discussed. Finally, the findings will be compared to the existing literature.

6.1. SUMMARY OF FINDINGS

Overall, in all three studies patients with schizophrenia appeared to have a worse physical health status and more unfavorable lifestyle behaviors than patients without schizophrenia. In addition, patients with schizophrenia had a lower chance of receiving diabetes, heart failure and COPD care measured by a number of clinical guideline recommendations than patients without schizophrenia, although the absolute differences in general were small. The predictors of not meeting the recommended care among patients with schizophrenia included drug abuse and low contact volume in diabetes care, a low GAF score in heart failure care, and male sex in COPD care. Patients with schizophrenia did not have a higher risk of early readmission, but experienced a substantially higher risk of mortality from both heart failure and COPD compared to patients without schizophrenia.

6.2. METHODOLOGICAL CONSIDERATIONS

All three studies in the thesis were designed as nationwide population-based cohort studies. The observational design may, however, have affected the accuracy and validity of the results due to potential systematic or random errors. Internal and external methodological considerations therefore need to be taken into account.

6.2.1. INTERNAL VALIDITY

6.2.1.1 Selection bias

The study populations of all three studies were identified from national clinical registries (73-80). It is mandatory for all public hospitals to report to these registries, which ensures a generally high coverage of every patient treated for schizophrenia, diabetes, incident heart failure and COPD in the secondary Danish health care system, and an almost complete follow-up. Due to tax funding, treatment in public hospitals is free of charge for Danish residents (28). The probability of a systematic exclusion of patients with schizophrenia, diabetes, incident heart failure and COPD in the clinical registries is therefore considered to be limited.

Only hospital outpatients with diabetes, in- and outpatients with incident heart failure and in- and outpatients treated for acute COPD exacerbation or COPD were included

in the three thesis studies. As a result, the quality of care remains unknown for diabetes, incident heart failure and COPD patients with schizophrenia seen exclusively by their general practitioner (GP). In this context, it should be noted that the majority of patients with Type 2 diabetes as well as patients with a primarily mild symptom severity of schizophrenia, heart failure and COPD are commonly treated by their GP and therefore potentially not included in the three study populations. Moreover, the interpretation of the results in the thesis should be considered taking into account that the impact of schizophrenia on diabetes, heart failure and COPD care may be considerable larger than reported in the three studies as patients with schizophrenia are frequently undiagnosed or untreated for their medical comorbidities (11,17,20,48,87). Consequently, the study populations included in the thesis may affect the generalizability of the findings.
From the entire study population of patients with diabetes in Study I, 52 (0.06%) diabetes patients with comorbid schizophrenia were omitted from analysis due to exclusion criteria. In Study II, 32 (0.09%) incident heart failure patients with schizophrenia were excluded, whilst 52 (0.07%) COPD patients with schizophrenia were omitted from analysis in Study III. These small differences are considered not to have affected the results presented and therefore to be insignificant.

6.2.1.2 Information bias

All three studies in the thesis were based on information registered prospectively in Danish registries and independently of the study hypotheses, which reduces differential misclassification. However, data validity can always be called into question in registry-based studies. A large number of health professionals in routine clinical practice are involved in the data reporting to the DSR, DHFR, DADR and DrCOPD, which means that intra-and inter-observer variation as well as errors and differences in registration or coding practice may occur. However, extensive efforts are made to ensure data uniformity by designating key health care professionals in each hospital department or outpatient clinic to be responsible for data collection and accuracy. Moreover, validity is secured by detailed instructions and explicit data definitions, just as multidisciplinary structured audits are carried out regularly on a local, regional and national basis. The audits assess the quality of data critically and provide continuous feedback to hospital departments and outpatient clinics (25-27,73-80).

The primary exposure of interest in all three studies was the dichotomous presence of schizophrenia (yes/no). A possible inclusion of other psychiatric diagnoses in the comparison group of patients without schizophrenia may have diminished differences in the quality of diabetes, heart failure and COPD care as well as the differences in the clinical outcomes of heart failure and COPD. Disparities in care have also been demonstrated among diabetes patients with bipolar disorder and depression (12,13), and among patients with cardiovascular disease and bipolar disorder as well as affective disorder (15,23). Increased early readmission rates for ambulatory-care

sensitive conditions, including congestive heart failure exacerbation and COPD/adult asthma exacerbation, have also been shown among patients with a serious mental illness, including bipolar disorder (88).
The secondary objective of interest, including patient-, (sex, age, abuse, duration of schizophrenia and GAF score), provider- (quality of schizophrenia care) and system-related predictors (contact volume) of the quality of diabetes, heart failure and COPD care among patients with schizophrenia, was primarily categorized according to predefined cut points in all three studies. This may have introduced an additional potential bias towards the null if patients at a high risk of receiving the disease-specific process-performance measures of care were subcategorized together with patients at a low risk. The cut points may, in contrast, also have caused Type 2 errors. Different cut points were tested to reduce these biases. Furthermore, it should be noted that the patient-related predictor "duration of schizophrenia" may potentially be underestimated for some patients due to a restricted follow-up time in the registries used, including the DSR, DHFR, DADR, DrCOPD and the Danish Psychiatric Central Research Register (73-82). As a consequence of registration only starting in 1969, the maximum duration of schizophrenia for any patient was 44 years.

The individual disease-specific process-performance measures of care and the high overall quality of diabetes, heart failure and COPD care were analysed dichotomously (received/not received) in all three studies in the thesis, as were the clinical outcomes of heart failure and COPD in Studies II and III, including readmission (yes/no) and mortality (dead/alive). Any potential errors in these performance measures are considered most likely to be non-differential misclassifications that bias the results presented toward the null value. However, it must be pointed out that the recording practice in standardized registration forms in Studies I and II could have caused missing data on the process-performance measures of care. Differential misclassification could potentially occur in these studies if the staff providing care were affected by e.g. difficulties in handling patients with a serious mental disorder such as schizophrenia in a somatic department or outpatient clinic. In this scenario, data on process-performance measures of care would be more likely to be missing among patients with schizophrenia. The results would therefore be biased and potentially underestimate differences in the quality of care between patients with and without schizophrenia. No particular differences in the missing performance measures were, however, found in Studies I and II.
As all data are reported entirely through diagnosis codes and codes for clinical procedures in the DrCOPD, the process-performance measures of COPD care are only registered as being performed or not. This also means that it is not possible to determine whether a particular clinical procedure was not being performed or simply not being reported. However, Study III showed a similar percentage of missing data for the reported characteristics between COPD patients with and without schizophrenia as did Studies I and II. The missing values for the clinical outcome "readmission" were likewise almost equally distributed among patients with and without schizophrenia in Studies II and III. Data on the other clinical outcome

"mortality" in Studies II and III were obtained from the Danish Civil Registration System, which updates information daily on vital status of all Danish residents (70,71). Missing data on mortality were minimal, and misclassification of this outcome was therefore considered highly unlikely. Hence, the potential information biases in the thesis would most likely lead to non-differential misclassification and bias the presented results toward the null.

6.2.1.3 Confounding

Confounding is inevitably a relevant concern in all three studies included in the thesis due to their observational design. To address this issue, possible confounding factors were handled in the statistical analysis by stratification and adjustments.

Explicit criteria were specified for the inclusion of diabetes, incident heart failure and COPD patients as well as for the performance measures in the DSR, DHFR, DADR and the DrCOPD (73-80). In principle, this means that all patients qualified as relevant to be provided with the recommended disease-specific processes-performance measures of care, irrespective of patient characteristics, psychiatric diseases and the treating hospital department and/or outpatient clinic. Confounding is therefore considered to be of minor importance for the study findings. Additional precautions were, however, undertaken by stratifying the analysis for sex, age and severity of the medical disease, including diabetes, heart failure or COPD, which did not considerably change the results resented in the thesis studies.

A broad range of predictors of quality of care, including patient-, (sex, age, abuse, duration of schizophrenia and GAF score), provider- (quality of schizophrenia care), and system-related predictors (contact volume) were taken into account in all three studies. Nonetheless, several additional plausible underlying and complex mechanisms may influence and confound the quality of diabetes, heart failure and COPD care among patients with schizophrenia. Difficulties navigating between the psychiatric and somatic hospital departments and outpatient clinics, impaired or altered perception of physical symptom awareness, lack of strength to manage a somatic disease concurrent with a severe mental disorder, deficient communication skills or social vulnerability such as homelessness or isolation may constitute particular challenges among patients with schizophrenia. Fear, mistrust or a problematic relationship with the treating physician can also cause disengagement from care. The physician barriers may include provider variability, minimal experience with psychiatric patients or prejudice against these patients, whilst differences in the resources available, geographical variation as well as coordination and time constraints may serve as system-specific factors (89-91). These uncontrolled-for factors must consequently be taken into consideration when interpreting the results.

The clinical outcomes in Studies II and III, including readmission and mortality, were adjusted for several important patient characteristics. After doing so, both the non-significant crude estimates for increased mortality among patients with schizophrenia in Studies II and III changed to be significant after the adjustments. Still, the findings

may be affected by residual confounding due to misclassification or use of categorical variables while unaccounted-for confounding of unknown characteristics, e.g. length of hospital stay, cannot be disregarded. Nonetheless, the overall results are considered to be reasonably valid due to the accounted-for important characteristics.
In all three studies, clustering of patients within the hospital departments and outpatient clinics was taken into account by the use of robust estimates of the variance. This was done to include unmeasured characteristics of the hospital departments and outpatient clinics potentially associated with both the quality and predictors of care as well as clinical outcomes.

6.2.1.4 Precision

The large sample sizes obtained from nationwide population-based registries improve the statistical precision in all three studies. Moreover, the 95% CI used throughout the thesis to express the random errors underlying the risk estimates were quite narrow, which indicates a high level of precision. However, some of the analysis of the predictors of care and clinical outcomes demonstrated relatively broad CIs. The point estimates should therefore be interpreted with more caution. The statistically significant results in all three studies also had a 5% risk of being chance findings.

It should be noted that the absolute differences for the examined process-performance measures of diabetes, heart failure and COPD care among patients with and without schizophrenia in general were small in all studies included in the thesis. This indicates that the differences observed in care could be random. The sum of differences was, nonetheless, considerable in Studies I and II when all process-performance measures of care were taken into account. Furthermore, the clinical outcome, including mortality, yielded substantial differences in survival among patients with and without schizophrenia in Studies II and III. Overall, the findings in the thesis are therefore not likely to be explained by random errors.

6.2.1.5 Summary of the internal validity

The main strengths of all three studies include the nationwide population-based design, the large sample sizes and the comprehensive prospective data collection of the quality of diabetes, heart failure and COPD care. In addition, only patients relevant for the specific process-performance measures of care were included in the analysis, which reduces the risk of selection and information bias. Any potential misclassification in the thesis is most likely considered non-differential and biasing the findings toward the null. However, the results presented may be affected by residual or unaccounted-for confounding due to the observational study designs whilst some of the risk estimates had a moderate statistical precision. All findings in the thesis should therefore be interpreted only as associations and not as evidence of a causal relationship.

6.2.2. EXTERNAL VALIDITY

All three studies were conducted under a universal and free-of-charge health care system using national registries with a generally high data coverage and completeness of patient recording as well as explicit data definitions. Population characteristics and management of medical comorbidities in patients with schizophrenia may differ across countries. These factors must be taken into consideration when comparing the findings presented in the thesis with previous publications from other health care settings.

6.3. COMPARISON WITH THE EXISTING LITERATURE

6.3.1. STUDY I

Study I reported an association between schizophrenia and reduced risk of receiving a number of recommended process-performance measures of care, including treatment with antihypertensives, screening for albuminuria, blood pressure monitoring, eye and feet examination as well as a high quality of diabetes care. The findings of disparities in the quality of diabetes care among patients with schizophrenia are inconsistent with approximately half of the previous studies (10,14,66,67), but are in alignment with findings from the other half (11-13) (Table 1). Only one of these publications, an Australian study, was conducted in a comparable universal health care setting (12). The authors of the Australian study reported that mental health clients were less likely to receive recommended routine pathology tests, including HbA_{1c}, microalbuminuria and blood lipid, both at 1-year and during the entire follow-up period from 1990 to 2006 compared to non-mental health clients (12), which is in accordance with the inequalities reported in Study I. It can therefore be hypothesised that patients with schizophrenia may find the long intervals of time between diabetes follow-up checks particularly challenging to maintain, just as cognitive and social dysfunctions may hamper engagement, attendance and adherence in care (92,93).

Study I showed that patient- and system-related factors were associated with the insufficient quality of diabetes care among diabetes patients with schizophrenia, including young age, drug abuse, short duration of schizophrenia and low contact volume. The clearest association was, however, found for drug abuse and contact volume, which might indicate that being a diabetes patient with schizophrenia and a concomitant drug abuse may engender major attendance issues with diabetes follow-up checks. Moreover, outpatient clinics with a very high contact volume of diabetes patients may be characterized by better specialization, more resources and experience in managing psychiatric patients with special needs. Although the association between mental illness and the organizational structure of a health care system as a predictor of quality of care was not confirmed in other studies on diabetes care, similar findings have been shown for cardiovascular care. Previous US studies found that mentally ill patients were more likely to be admitted to low-quality somatic hospitals and to be

treated by low-quality cardiac surgeons for their cardiovascular comorbidities than non-mentally ill patients (94-96). Another US publication indicated that both patient-, county- and state-specific factors predicted the quality of diabetes care among patients with diabetes and mental comorbidities. In this regard, young age, male sex, non-Hispanic race/ethnicity, low numbers of medical comorbidities (patient-specific factors), living in urban settings or primary care shortage areas (county-specific factors) and low reimbursement rates for physicians (state-specific factors) were associated with inadequate quality of diabetes care (13). It must, however, be pointed out that differences in financing and organization may complicate the generalizability of these findings across health care systems.

Only patient- and system-related factors were identified as independent predictors of quality of care among diabetes patients with schizophrenia in this study. A recent Danish nationwide study documented improvements in the quality of schizophrenia care provided to inpatients with schizophrenia in Denmark between 2004 and 2011 (97). In this period, the overall quality of schizophrenia care, reflected in the proportion of all relevant recommended process-performance measures of care provided to the patients, increased from 64% to 76% (97). This relatively high quality of schizophrenia care may potentially explain why the provider-related factor in this current study was not observed as a predictor of diabetes care.

6.3.2. STUDY II

Study II demonstrated an association between schizophrenia and reduced risk of receiving treatment with beta-blockers and a high quality of heart failure care. The majority of previous studies support similar findings of disparities in cardiovascular care among patients with a mental disorder, including schizophrenia (17,19-24) (Table 2). One of these publications, a Canadian study, likewise reported that ischaemic heart disease patients with comorbid psychosis were less likely to receive beta-blockers under universal health care compared to those without comorbid psychosis (19). The remaining process-performance measures of heart failure care explored in Study II were equally distributed among incident heart failure patients with and without schizophrenia. However, the differences in applied quality of care measures between this current study and the other publications in cardiovascular care complicate further direct comparison.

Study II found that a high GAF score was associated with increased chance of receiving treatment with beta-blockers and a high quality of heart failure care among incident heart failure patients with schizophrenia. These findings may reflect that patients with a high GAF score usually experience a high level of functioning with only slight impairment, which may imply greater mental resources, understanding and ability to adhere to recommended medical treatment. This assumption is in accordance with previous studies indicating that positive attitudes toward medication and illness insight are associated with better medication adherence among patients with schizophrenia-spectrum disorders (93). Still, other issues need to be clarified before an actual conclusion can be drawn in this regard.

The finding of no early readmission among incident heart failure patients with schizophrenia is inconsistent with previous studies (88,98,99). It is, however, important to note that only one of these publications was conducted in a universal health care setting (88). This recent Danish nationwide study found an association between serious mental illness and increased risk of 30-day readmission for ambulatory-care sensitive conditions, including congestive heart failure exacerbation (88). In contrast, the finding of a higher 1-year mortality among incident heart failure patients with schizophrenia in this study is in accordance with several previous publications assessing the mortality rates of cardiovascular disease in patients with a mental illness (16,18-20). The most comparable study included a Danish publication demonstrating that patients with severe mental disorders had a higher risk of 1-year mortality following discharge from the first hospital contact with heart disease than patients without severe mental disorders (20).

6.3.3. STUDY III

Study III depicted an association between schizophrenia and reduced risk of receiving treatment with LAMA/LABA. However, COPD patients with and without schizophrenia had an equal risk of meeting the remaining process-performance measures of care included as well as a high quality of COPD care. Although no previous studies have examined the quality of care for COPD patients with and without schizophrenia, previous studies in primary care have demonstrated that compared to non-psychiatric patients, psychiatric patients were less likely to be asked about smoking status and to receive smoking cessation interventions as well as having BMI recorded (100-102). However, the magnitude of these differences varies considerably, with some studies finding no such deficits in the preventive care (103,104).

It must be taken into consideration that only one process-performance measure of COPD care was found inadequate among patients with schizophrenia in this current study. Moreover, the difference in care for LAMA/LABA treatment between patients with and without schizophrenia was modest, which might indicate a chance finding. If the association genuinely reflects less probability of receiving LAMA/LABA treatment among COPD patients with schizophrenia, it points to the importance of improving the recommended pharmacological therapy in this group.

Female sex was identified as an independent predictor of receiving LAMA/LABA among COPD patients with schizophrenia. It is possible, though not confirmed, that male patients in general may be more likely than female patients to lack energy, attention or willingness to attend regular COPD follow-up checks and therefore fail to meet the medical recommendations.

Study III did not detect any increased risk of early readmission, after adjusting for age, sex and Charlson Index, among COPD patients with schizophrenia. This finding is inconsistent with previous publications (88,99), including a Danish nationwide study that demonstrated an association between serious mental illness and increased risk of 30-day readmission for ambulatory-care sensitive conditions, including

COPD/adult asthma exacerbation, after adjusting for demographics (age, sex and calendar year) or socio-economic factors (marital/partnered status, educational level, comorbidities) (88). The additional inclusion of adult asthma exacerbation in the analysis in the previous Danish study potentially explains the discrepancy between the results. Nonetheless, the finding of a higher risk of 30-day mortality among COPD patients with schizophrenia is in line with another population-based Danish study. In this particular study, patients with severe mental illness were found to have an increased risk of 30-day mortality after hospitalization for an infection, including pneumonia, compared with patients without a severe mental illness (105).

6.3.4. SUMMARY OF COMPARISON WITH THE EXISTING LITERATURE

In general, the findings in the existing literature is consistent with the findings from this thesis regarding a deficient quality of diabetes, heart failure and COPD care on specific parameters among patients with schizophrenia. However, the magnitude varies considerably and different quality of care measures and health care settings complicate a direct comparison. Moreover, other studies examining predictors of the quality of care in this population are sparse. The findings of no early readmission in Studies II and III among patients with schizophrenia are not in accordance with previous studies; however, the increased rates of mortality are supported by several previous publications.

CHAPTER 7. CONCLUSION

This thesis provides greater insight into the interrelations between schizophrenia and the quality of diabetes, heart failure and COPD care in Denmark, which has a universal health care system. Based upon the findings from the three nationwide population-based cohort studies included in the thesis, the following conclusions can be drawn.

7.1. STUDY I

Schizophrenia was associated with a lower chance of receiving 6 out of 11 examined process-performance measures of diabetes care, including blood pressure monitoring, treatment with antihypertensive drugs, including ACE/ATII, screening for albuminuria, eye examination at least every second year and foot examination, as well as a high quality of diabetes care. Predictors of deficient quality of care among diabetes patients with schizophrenia included drug abuse and low diabetes clinic contact volume.

7.2. STUDY II

Schizophrenia was associated with a lower chance of meeting 1 out of 7 assessed process-performance measures of heart failure care, including treatment with beta-blockers, as well as a high quality of heart failure care. A predictor of inadequate quality of care among incident heart failure patients with schizophrenia included a low GAF score. Incident heart failure patients with schizophrenia experienced a higher 1-year mortality following the first-time hospital contact with incident heart failure, but not an increased risk of 4-week readmission.

7.3. STUDY III

Schizophrenia was associated with a lower chance of receiving 1 out of 9 examined process-performance measures of COPD care, including treatment with LAMA/LABA. The chance of meeting a high quality of COPD care was comparable among COPD patients with and without schizophrenia. A predictor of insufficient quality of care among COPD patients with schizophrenia included male sex. COPD patients with schizophrenia had no increased risk of 30-day readmission; however, they had a higher risk of 30-day mortality following admission for an exacerbation.

In conclusion, the results showed that patients with schizophrenia had a lower chance of receiving a number of process-performance measures of diabetes, heart failure and COPD care compared to patients without schizophrenia. However, in general the absolute differences in care were small. Predictors of poorer quality of care included patient- and system-related factors among diabetes, incident heart failure and COPD

patients with schizophrenia. Patients with schizophrenia had a substantially increased risk of mortality following a first-time hospital contact with incident heart failure and after an admission for exacerbation of COPD. Interventions are therefore warranted to improve the survival of heart failure and COPD among patients with schizophrenia. Overall, the hypotheses of the studies included in this thesis were therefore partly confirmed.

CHAPTER 8. PERSPECTIVES

For more than 50 years, it has been well-established that compared to the general population, patients with schizophrenia have substantially high mortality rates (4). Emerging evidence indicates that the major part of this mortality excess is due to medical comorbidities (4-7,9). Still, the findings of this thesis demonstrate a continuing health disparity in the survival of heart failure and COPD among patients with schizophrenia, even in a universal health care system with equity as a stated priority.

Several questions, however, need to be further explored regarding the quality and predictors of care as well as the clinical outcomes of medical comorbidities among patients with schizophrenia. For instance, more information is needed to clarify whether this group receives deficient preventive care or experiences delays in medical screening and diagnostics of e.g. diabetes, heart failure and COPD. Moreover, it could be interesting to look into the health-seeking (or lack of) behaviour of patients with schizophrenia.

Although the findings of this thesis suggest an almost sufficient fulfilment of heart failure and COPD treatment recommendations, the increased mortality rates of these medical comorbidities may indicate that patients with schizophrenia need more intensive and specialized care in the public somatic hospitals. Areas of interest for future research could therefore include an exploration of both the perspectives of the health care professionals and of the patients on the medical care provided. Potentially, the health care professionals in somatic hospitals may find that more time and resources as well as training in handling the specific needs of psychiatric patients are required in order for them to deliver ideal care. Likewise, patients with schizophrenia might state that the medical care provided does not fit their specific needs. Such an improved understanding of what constitutes optimal medical care could bring new insights into the area.

More information is also warranted on the post-discharge medical care, which could prove to be inadequate since incident heart failure and COPD patients with schizophrenia did not experience any increased risk of early readmission despite increased mortality. Targeted interventions to improve the survival of patients with schizophrenia are highly needed, and it would therefore be relevant to examine the potential challenges of managing patients with schizophrenia after discharge from somatic hospitals. Such challenges might include concomitant drug or alcohol abuse, severe psychotic symptoms or social vulnerability, e.g. homelessness, as well as a range of other factors affecting the quality of post-discharge medical care among patients with schizophrenia. A further examination of the specific causes of death among incident heart failure and COPD patients with schizophrenia is needed to clarify the exact cause of death.

The need to focus attention on the medical ramifications of schizophrenia appears to apply to primary, secondary as well as tertiary care. This calls for an effectively collaborating and coordinated health care system in order to reduce the excess mortality in this vulnerable population. The Danish health care system is divided into psychiatric and somatic hospitals, with no integrated co-operation between the mental health care providers and the health care providers, neither in the somatic hospitals nor in the primary care settings, which is likely to complicate the management of medical comorbidities in patients with schizophrenia. Establishment of liaison somatic departments or outpatient clinics in the psychiatric hospitals would therefore be highly relevant as a means to coordinate and, to the extent possible, treat medical comorbidities, including e.g. diabetes, heart failure and COPD, among patients with schizophrenia.

Finally, it must be noted that the latest version of Danish clinical guidelines for schizophrenia from 2004 was declared outdated in 2006 (34). Updated treatment recommendations are therefore warranted, including a greater focus on the medical comorbidities among patients with schizophrenia.

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APPENDICES

Appendix A. Literature search

Table A1 *The performed search strategies in PubMed, Embase, PsycINFO and Cinahl including English and Scandinavian language literature with no restriction on the publication year*

Database	Search strategy
PubMed	**#1:** Schizophren*[tiab] **#2:** Schizophrenia[Mesh] **#3: #1 OR #2** **#4:** Metabolic syndrome X[Mesh] **#5:** Metabolic syndrome*[tiab] **#6:** Cardiovascular diseases[Mesh] **#7:** Cardiovascular disease*[tiab] **#8:** Diabetes mellitus[Mesh] **#9:** Diabet*[tiab] **#10:** Pulmonary disease, chronic obstructive[Mesh] **#11:** Copd[tiab] **#12:** Chronic obstructive disease*[tiab] **#13:** Comorbidity[Mesh] **#14:** Comorbidit*[tiab] **#15: #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14** **#16:** Medical errors[Mesh] **#17:** Outcome assessment(Health care)[Mesh] **#18:** Healthcare disparities[Mesh] **#19:** Disparit*[tiab] **#20**: Inequalit*[tiab] **#21:** Inadequacy[tiab] **#22:** Diagnostic error*[tiab] **#23:** Underdetect*[tiab] **#24:** Misclassif*[tiab] **#25:** Misinterpret*[tiab] **#26: #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25** **#27: #3 AND #15 AND #26** **Total literature from search: 492**
Embase	**#1:** Exp schizophrenia **#2:** Metabolic syndrome **#3:** Chronic obstructive lung disease **#4:** Exp diabetes mellitus

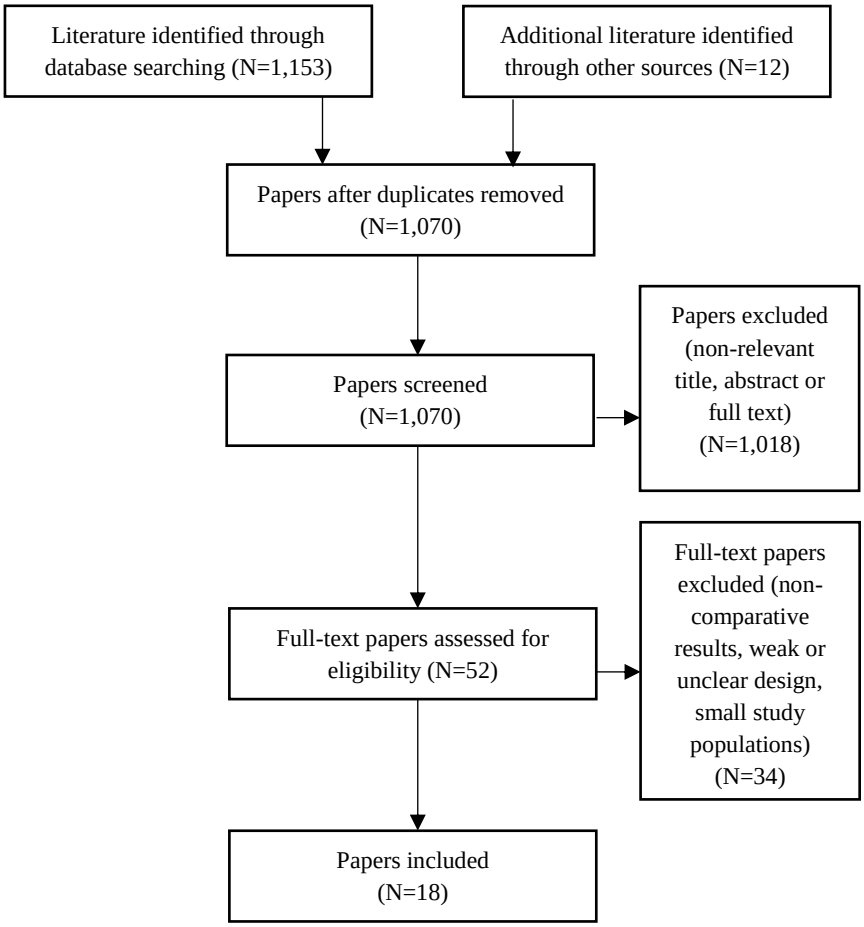
	#5: Exp diabetic angiopathy **#6:** Exp experimental diabetes mellitus **#7:** Exp pregnancy diabetes mellitus **#8: #4 OR #5 OR #6 OR #7** **#9:** Exp cardiovascular disease **#10:** Exp comorbidity **#11: #2 OR #3 OR #8 OR #9 OR #10** **#12: #1 AND #11** **#13:** Exp medical error **#14:** Outcome assessment **#15:** Health care disparity **#16:** Disparit* **#17:** Inequalit* **#18:** Inadequacy **#19:** Diagnostic error* **#20:** Underdetect* **#21:** Misclassif* **#22:** Misinterpret* **#23: #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 (ti,ab,kw)** **#24: #13 OR #14 OR #15 OR #23** **#25: #12 AND #24** **Total literature from search: 536**
PsycINFO	**#1:** Exp schizophrenia **#2:** Schizophren*.ti,ab **#3: #1 OR #2** **#4:** Metabolic syndrome **#5:** Metabolic syndrome*.ti,ab **#6:** Cardiovascular disease*.ti,ab **#7:** Diabetes Mellitus **#8:** Diabet*.ti,ab **#9**: Exp chronic obstructive pulmonary disease **#10:** Copd **#11:** Chronic obstructive pulmonary disease* **#12: #10 OR #11 (ti,ab)** **#13:** Exp cardiovascular disorders **#14:** Exp comorbidity **#15:**Comorbidit*ti,ab **#16: #14 OR #15** **#17: #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #12 OR #13 OR #16**

	#18: #3 AND #17 **#19:** Exp treatment outcomes **#20:** Health disparities **#21:** Disparit* **#22:** Inequalit* **#23:** Inadequacy **#24:** Diagnostic error* **#25:** Undertetect* **#26:** Misclassif* **#27:** Misinterpret* **#28:** Medical error* **#29: #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 (ti,ab)** **#30: #19 OR #20 OR #29** **#31: #18 AND #30** **Total literature from search: 97**
Cinahl	**#1:** MH "schizophrenia" **#2:** Schizophren* **#3: #1 OR #2** **#4:** MH "metabolic syndrome X" **#5**: Metabolic syndrome* **#6:** MH "cardiovascular diseases+" **#7:** Cardiovascular disease* **#8:** MH "Diabetes Mellitus+" **#9:** Diabet* **#10:** MH "pulmonary disease, chronic obstructive+" **#11:** Copd **#12:** Chronic obstructive pulmonary disease* **#13: #11 OR #12** **#14:** MH "Comorbidity" **#15: #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #13 OR #14** **#16: #3 AND #15** **#17:** MH "health care errors+" **#18:** MH "outcome assessment" **#19:** MH "healthcare disparities" **#20:** Disparit* **#21:** Inequalit* **#22:** Inadequacy **#23:** Diagnostic error*

	#24: Undertetect* **#25:** Misclassif* **#26:** Misinterpret* **#27: #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26** **#28: #16 AND #27** **Total literature from search: 28**

Appendix B. Flow diagram of the literature identification

Figure A1 *A flow diagram of the identified papers from the literature search*



Appendix C. Study I

Quality and predictors of diabetes care among patients with schizophrenia: a nationwide study

Jørgensen M, Mainz J, Carinci F, Thomsen RW, Johnsen SP

In review

Appendix D. Study II

Quality of care and clinical outcomes of heart failure among patients with schizophrenia under universal health care

Jørgensen M, Mainz J, Egstrup K, Johnsen SP

In preparation

Appendix E. Study III

Chronic obstructive pulmonary disease care and outcomes in patients with schizophrenia

Jørgensen M, Mainz J, Lange P, Johnsen SP

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