THE SIGNIFICANCE OF COMORBID PHYSICAL CONDITIONS ON THE EXCESS MORTALITY OF PERSONS WITH SEVERE MENTAL ILLNESS

PhD dissertation

Anette Riisgaard Ribe

Faculty of Health
Aarhus University
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**PhD-student:**
MD, Anette Riisgaard Ribe, Mental Health in Primary Care (MEPRICA), The Research Unit for General Practice, Department of Public Health, Aarhus University.

**Supervisors:**
Professor, MD, PhD, Mogens Vestergaard, The Research Unit for General Practice and Section of General Medical Practice, Department of Public Health, Faculty of Health, Aarhus University.

Associate Professor, MSc, PhD, Thomas Munk Laursen, National Centre for Register-Based Research, Department of Economics and Business, School of Business and Social Sciences, Aarhus University.

Senior Researcher, MD, PhD, Morten Charles, Section of General Medical Practice, Department of Public Health, Faculty of Health, Aarhus University.

**Assessment committee:**
Professor, MD, PhD, Jane Gunn, Practice and Primary Health Care Academic Centre, Melbourne Medical School, Melbourne University, Australia.

Professor, MD, PhD, Jaana Suvisaari, Mental Health and Alcohol Research, National Institute for Health and Welfare, Helsinki University, Finland.

Associate Professor and Consultant in clinical epidemiology, MD, PhD, Reimar W. Thomsen, Department of Clinical Epidemiology, Faculty of Health, Aarhus University Hospital, Denmark.

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Sparle Christensen, great colleagues from the general practice, APU, for inspiring and encouraging me to enter into the fields of research. I would also like to thank Peter Vedsted for his thorough, bright and critically constructive reviews on our collaborating projects. I wish to thank Morten Fenger-Gron for excellent epidemiological and statistical support, for always challenging my intellectual capacity, for insightful conversations and great companionship in Seattle, and for being a good colleague. In addition, I would like to thank Henrik Søndergaard Pedersen for being a bright, patient, and hard-working statistician and colleague on our joint Seattle projects, and Anders Prior for being a great collaborator and colleague, for coffee swotting, fun, and live-music in Seattle. Also, I wish to thank Jakob Christensen for a fun collaboration, catching enthusiasm, and high spirits in Seattle.

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PREFACE
This PhD thesis is based on the project “The significance of comorbid, physical conditions on the excess mortality of persons with severe mental illness”. The project was carried out during my time as a research fellow at “Mental Health in Primary Care (MEPRICA)” at the Research Unit for General Practice, Aarhus University.

A description of the characteristics of persons with severe mental illness (SMI), the background on the excess mortality of persons with SMI as well as the connection between SMI and diabetes, breast cancer, infections and dementia, respectively, is provided in Chapter 1. Chapter 2 presents the aims of the PhD study. Chapter 3 describes the data sources, the study populations and the statistical analyses. Chapter 4 presents the main results of the four studies. Chapter 5-8 presents the four papers. Chapter 9 and 10 offer a general discussion of the methods used and the presented results. Chapter 11 presents the main conclusions and implications. Chapter 12 describes the perspectives raised by the present research and offers ideas for future research. Chapter 13 presents an English summary of the thesis. Chapter 14 presents the Danish summary of the thesis. The last chapter presents the references.
This PhD thesis is based on the following papers, which will be referred to by their Roman numerals:

I. "Long-term mortality of persons with severe mental illness and diabetes: a population-based cohort study in Denmark”¹

II. "Ten-year mortality after a breast cancer diagnosis in women with severe mental illness: a Danish population-based cohort study” (in review American Journal of Psychiatry, October 2015)

III. "Thirty-day mortality after infection among persons with severe mental illness: a population-based cohort study in Denmark”²

IV. "Long-term risk of dementia in persons with schizophrenia: a Danish population-based cohort study”³
ABBREVIATIONS

AF: atrial fibrillation or flutter
AP: attributable proportion
CCI: Charlson Comorbidity Index
CHF: congestive heart failure
CI: confidence interval
CIP: cumulative incidence proportion
CMP: cumulative mortality proportion
CNS: central nervous system
CRS: The Danish Civil Registration System
CVD: cardiovascular disease
DCR: The Danish Cancer Registry
DNDR: The Danish National Diabetes Register
DNPR: The Danish National Patient Register
DPCR: The Danish Psychiatric Central Register
DRCD: The Danish Register of Causes of Death
ICD-7: International Classification of Diseases, 7th Revision
ICD-8: International Classification of Diseases, 8th Revision
ICD-10: International Classification of Diseases, 10th Revision
IDA: The Danish Integrated Database for Labour Market Research
IHD: ischemic heart disease
IRR: incidence rate ratio
MR: mortality rate
MRR: mortality rate ratio
MS: metabolic syndrome
PPV: positive predictive value

PR: The Danish National Prescription Registry

PVD: peripheral vascular disease

SMI: severe mental illness

TMN system: tumor, node, metastasis staging system
CHAPTER 1:

INTRODUCTION
Persons with severe mental illness (SMI) comprise persons with schizophrenia and bipolar affective disorder. Although these two disorders display huge heterogeneity, some overlap in symptoms exists, such as psychosis, depressive symptoms, and cognitive impairment.\textsuperscript{4,5}

Schizophrenia affects around 1\% of the population\textsuperscript{6} and is associated with disturbances in communication, perception and thought process as well as abnormalities in behaviour.\textsuperscript{4} These disturbances often lead to substantial social disability and functional impairment.\textsuperscript{7} Kraepelin named schizophrenia ‘dementia praecox’,\textsuperscript{8} as cognitive impairments, including deficits in memory, visuospatial orientation and attention, are hallmarks of the disorder.\textsuperscript{5}

Bipolar affective disorder affects around 0.5\% of the population,\textsuperscript{6} and the disorder is characterized by episodic recurrent pathological disturbances in mood that range from mania to severe depression.\textsuperscript{9} It is usually accompanied by disturbances in thinking and behavior and often by psychotic features, such as delusions and hallucinations.\textsuperscript{9} The psychosocial functioning in persons with bipolar disorder has huge variability. Many persons regain psychosocial functioning after a diagnosis of bipolar affective disorder, whereas other experience significant difficulties in managing tasks of daily living.\textsuperscript{10}
Persons with SMI have a two-to-three-fold increased risk of premature death,\textsuperscript{11-14} which is equivalent to a life-expectancy gap of 15-20 years compared to persons without SMI.\textsuperscript{12,13,15} The underlying causal mechanisms for this excess mortality are not fully clarified, but may be associated with higher prevalence of comorbid physical diseases,\textsuperscript{16-19} poor quality of medical health care,\textsuperscript{20-24} adverse health behaviors (i.e., tobacco use, sedentary lifestyle, obesity, and unhealthy diet),\textsuperscript{25} substance abuse,\textsuperscript{26,27} and suicide.\textsuperscript{27,28} The significance of antipsychotic medication for the excess mortality is controversial; although some metabolic disorders are known to be induced by antipsychotic medication (i.e., weight gain, dyslipidemia, diabetes and the metabolic syndrome (MS)),\textsuperscript{29,30} it is not clear whether antipsychotic medication increases,\textsuperscript{14,31,32} decreases,\textsuperscript{33} or does not affect\textsuperscript{34} the risk of premature death among persons with SMI. In addition, it has been suggested that individuals with schizophrenia are subject to an “accelerated aging” that contributes to their reduced life-expectancy.\textsuperscript{35} This theory is rendered plausible as schizophrenia is associated with premature death due to age-related disorders, such as diabetes, cancer, and cardiovascular disease (CVD),\textsuperscript{1,11,15,36} but also because of the existence of shared risk factors between schizophrenia and age-related disorders (i.e., advanced paternal age, low birth weight and specific genes).\textsuperscript{35}

While it has been established that the excess mortality from physical diseases contributes more to the reduced longevity in persons with SMI than the excess mortality due to external causes of death,\textsuperscript{15,37} little is known about which comorbid physical conditions play a role for the excess mortality. Previous literature has shown that deaths due to CVD,\textsuperscript{11,20} cancer,\textsuperscript{12,36} and suicide\textsuperscript{27,28} constitute predominant causes of death among persons with SMI. However, studies on causes of death, using information from death certificates, are known to be subject to certain methodological issues, such as cause-of-death-attribution-bias\textsuperscript{38} (i.e., the registration of cause of death is biased by physician knowledge about underlying diseases in the deceased) and bias due to varying
quality of information on causes of death.\textsuperscript{39} Therefore, these types of studies are less appropriate for evaluating the significance of comorbid physical conditions on the excess mortality for persons with an underlying disease, such as SMI. It has been documented, that persons with SMI are under-diagnosed and undertreated for comorbid CVD,\textsuperscript{16,19,20,22,24} and that these factors explain some of the reduced life-span of this group.\textsuperscript{15,20} Nevertheless, it remains unclear to what extent other physical diseases, in addition to CVD, contribute to the excess mortality among persons with SMI.

Common conditions, such as diabetes mellitus, breast cancer, and infections constitute either leading causes of death\textsuperscript{40-42} or important contributors to a reduced longevity\textsuperscript{43} in persons suffering from these disorders worldwide. Yet, although these conditions are known to be associated with SMI,\textsuperscript{44-49} the significance of these conditions for the excess mortality in persons with SMI remains unknown.
SMI AND DIABETES

Diabetes mellitus is an increasingly prevalent, chronic condition with a prevalence around 4% in Denmark. Diabetes is associated with an increased risk of macrovascular (i.e., CVD) and microvascular (i.e., retinopathy, nephropathy and neuropathy) complications and premature death. Recent research suggests that vascular as well as non-vascular causes contribute to the excess mortality of persons with diabetes.

Around 10-20% of persons with SMI suffer from diabetes, and the age of onset of diabetes seem to be 10-20 years lower among persons with SMI compared to persons without SMI. In addition, 70% of cases of diabetes is estimated to be undiagnosed among persons with SMI compared to 25-30% in the general population. The mechanisms underlying the association between diabetes and SMI are multifactorial, including genetic factors, life style factors (i.e., sedentary lifestyle, smoking and unhealthy diet), antipsychotic medication, and biological effects of SMI (i.e., inflammatory and neuroendocrine changes, which might increase insulin resistance).

Although the prevalence of diabetes is high in persons with SMI, little is known about the long-term mortality of persons with SMI and diabetes. The association between diabetes and risk of premature death may be even stronger in persons with SMI, who experience increased rates of macrovascular and microvascular complications, and who tend to be less likely to meet diabetes performance measures. Two studies have found a higher mortality in persons with SMI and diabetes compared to persons with diabetes only or SMI only, whereas one study showed no difference in mortality for persons with SMI and diabetes compared to persons with diabetes only. No prior studies have evaluated the all-cause and cause-specific mortality of persons with SMI and diabetes compared to persons with neither of the two disorders.
Breast cancer constitutes the most frequently diagnosed cancer and the leading cause of cancer death in women worldwide. Still, it remains unclear whether higher mortality after a breast cancer diagnosis could partly explain the life-expectancy gap of 15 years in women with SMI. Women with SMI have been shown to present with more advanced stages of their breast cancer and to be less likely to receive mammography and treatment for breast cancer according to guidelines compared to those without SMI. Therefore, even though the survival after a breast cancer diagnosis has improved during the last decades, it is not clarified if women with SMI share these benefits equally with women without SMI.

Five studies have evaluated breast-cancer-related mortality in women with SMI. One found a five-year relative survival after breast cancer of 74% for women with schizophrenia compared to 79% for those without, and four studies found 1.2 to 2.9-fold higher risk of a breast cancer-specific death in women with SMI compared to women without SMI. The inconsistencies of the estimates could be explained by low sample size and statistical imprecision. Additionally, studies using information on causes of deaths from death certificates may be biased (see Chapter 1, Life-expectancy gap in persons with SMI). No prior studies have estimated the all-cause mortality after a breast cancer diagnosis in women with SMI compared to those without.
Infectious diseases are among the most frequent causes of acute hospital admission in both low- and high-income countries, and these conditions are associated with a markedly increased mortality.\textsuperscript{40,42} Prior studies have shown that infections predict subsequent development of SMI,\textsuperscript{61,62} and that persons with SMI have higher risk of specific infections.\textsuperscript{44,46} In an ongoing study, we found that persons with SMI have higher risk of being hospitalized for virtually all types of infections (Laursen TM et al., in manuscript).

Although infections are, thus, common conditions with a bidirectional link to SMI and additionally constitute leading causes of death, it remains unknown whether higher mortality after infection contributes to the reduced longevity of persons with SMI. Many hospitalizations for infections are potentially preventable and can be cured by affordable and readily available antibiotic treatment. The identification of higher mortality after infection in persons with SMI may, therefore, be the first step to develop health care interventions that could reduce the excess mortality for this group of patients. Studying the prognosis after hospitalization for infection is particularly interesting as a proxy for studying the effects of health care provision and health care adherence on mortality in persons with SMI and infections, since the infection has already been recognized and the health care contact established. Three studies found a three-to seven-fold higher risk of having an infection-related cause of death in persons with SMI compared to those without.\textsuperscript{12,44,46} However, studies using information on causes of deaths from death certificates may be biased (see \textit{Chapter 1, Life-expectancy gap in persons with SMI}). Furthermore, these types of studies seem to under-recognize the mortality accounted for by infections.\textsuperscript{42} No studies have evaluated the all-cause mortality after a hospitalization for infection in persons with SMI compared to those without.
Dementia affects around 6% of persons over the age of 60 years in the Western world, and is characterized by cognitive decline and impairment in activities of daily living. Due to increased life-expectancy and changes in population demographic, the prevalence of dementia is expected to double every 20 years through 2040. Therefore, the disorder poses a major current and future challenge to the health care system and society.

Although schizophrenia is associated with several age-related disorders and considerable cognitive impairment, it remains unclear whether the risk of dementia is higher among persons with schizophrenia compared to those without. Four prior studies have found a 2.4 to 16-fold higher risk of dementia in persons with schizophrenia. However, these studies either did not include individuals with onset of schizophrenia before the age of 30 years or did not have sufficient follow-up for the cohort to display a clinically significant risk of developing dementia. Furthermore, a review of 20 longitudinal studies, examining the risk of cognitive decline in persons with schizophrenia, found inconsistent results; 12 studies suggested a significant cognitive decline, whereas eight studies did not find a significant association. These inconsistencies may, in part, be due to the complexity of studying these highly age-related disorders in this vulnerable group. Persons with schizophrenia die on average 15-20 years prematurely compared to the general population. Consequently, those who live long enough to develop dementia would represent a selected group of more healthy persons, and thus studies on dementia in persons with schizophrenia need to take this issue into consideration.
INTRODUCTION AT A GLANCE

Persons with SMI have a two-to-three-fold increased risk of premature death, corresponding to a life-expectancy gap of 15-20 years compared to persons without SMI.

The excess mortality from physical diseases contributes more to the reduced longevity in persons with SMI than the excess mortality due to external causes of death, but little is known about which comorbid physical conditions play a role for the excess mortality.

Although 10-20% of persons with SMI have diabetes, the long-term mortality of persons with SMI and comorbid diabetes remains unknown.

Although breast cancer is the leading cause of cancer death in women worldwide, no studies have evaluated whether higher mortality after a breast cancer diagnosis contributes to the life-expectancy gap of 15 years in women with SMI.

Infections are common conditions and leading causes of death. Nevertheless, it remains unclear, whether higher mortality after infection contributes to the excess mortality among persons with SMI.

Schizophrenia is associated with several age-related disorders and considerable cognitive impairment. In addition, it has been suggested that individuals with schizophrenia are subject to an “accelerated aging” that contributes to their reduced life-expectancy. Yet, it is unknown, whether the risk of the ultimate age-related disorder, dementia, is higher among persons with schizophrenia compared to those without.
CHAPTER 2:

AIMS
The overall aim of this thesis is to study the significance of common comorbid physical conditions (i.e., diabetes, breast cancer and hospitalization for infection) on the excess mortality in persons with SMI, and to explore the risk of the ultimate age-related disorder, dementia, in persons with schizophrenia.

Specific aims:

1) To study the long-term mortality in persons with SMI and diabetes, in persons with SMI only and in persons with diabetes only compared to persons with neither of the two disorders, while taking into account the interaction between SMI and diabetes and the attributable proportion due to diabetes.

2) To study the ten-year mortality after a breast cancer diagnosis in women with SMI compared to women without SMI, while taking into account tumor stage and comorbidity.

3) To study the thirty-day mortality after a hospitalization for infection in persons with SMI compared to persons without SMI, while taking into account comorbidity and the type of infection causing the hospitalization.

4) To study the long-term risk of dementia in persons with schizophrenia, while taking into account established dementia risk factors.
CHAPTER 3:

METHODS
The thesis consists of four population-based cohort studies, which are all based on information from Danish nationwide registers. Table 3.1 gives an overview of the study population, the data sources and the outcomes of the four papers in the thesis. A further detailed description of methods is given in Chapters 5-8.

**Table 3.1. Characteristics of Papers I-IV**

<table>
<thead>
<tr>
<th>Paper</th>
<th>Study population</th>
<th>Follow-up period</th>
<th>Data sources</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>All persons born in Denmark, registered in the CRS between 1968 and 2010 and alive at some point during follow-up.</td>
<td>1997-2010</td>
<td>CRS, DPCR, DNDR, DRCD</td>
<td>The long-term all-cause and cause-specific mortality in persons with SMI and diabetes, in persons with SMI only, in persons with diabetes only compared to persons with neither SMI nor diabetes.</td>
</tr>
<tr>
<td>II</td>
<td>All women born in Denmark, registered in the CRS, registered with breast cancer in the DCR between 1980 and 2012 and alive at some point during follow-up.</td>
<td>1980-2012</td>
<td>CRS, DPCR, DCR, DRCD, DNDR, DNPR</td>
<td>The ten-year all-cause and breast cancer-specific mortality after a breast cancer diagnosis in women with SMI compared to women without SMI.</td>
</tr>
<tr>
<td>III</td>
<td>All persons above age 15 years, born in Denmark, registered in the CRS and registered with a hospitalization for infection in the DNPR between 1995 and 2011 and alive at some point during follow-up.</td>
<td>1995-2011</td>
<td>CRS, DPCR, DNPR, DRCD, DNDR, IDA</td>
<td>The 30-day all-cause and infection-related mortality after a hospitalization for an infection in persons with SMI compared to persons without SMI.</td>
</tr>
<tr>
<td>IV</td>
<td>All persons above age 50 years, born in Denmark, registered in the CRS between 1968 and 2013 and alive at some point during follow-up.</td>
<td>1995-2013</td>
<td>CRS, DPCR, DNPR, PR, DNDR, IDA</td>
<td>The long-term incidence of dementia for persons with schizophrenia compared to persons without schizophrenia.</td>
</tr>
</tbody>
</table>
The Danish Civil Registration System (CRS)
The Danish Psychiatric Central Register (DPCR)
The Danish National Diabetes Register (DNDR)
The Danish Register of Causes of Death (DRCD)
The Danish Cancer Registry (DCR)
The Danish National Patient Register (DNPR)
The Danish Integrated Database for Labour Market Research (IDA)
The Danish National Prescription Registry (PR)
DATA SOURCES

Four longitudinal population-based cohorts were established using information on Danish citizens from nationwide Danish registries. All data are recorded with reference to a civil registration (CPR) number, which is a unique personal identification number assigned to all Danish residents. This number permits accurate linkage of recorded information at the personal level. Until December 31, 1993, the diagnostic system used in the Danish registers was the Danish version of the International Classification of Diseases, 8th Revision (ICD-8). From January 1, 1994, the Danish version of the ICD-10 was used. The ICD-9 has never been used in Denmark.

The Danish Civil Registration System (CRS)

The CRS includes information on gender, date of birth, place of residence, identity of parents and spouse and continuously updated information on vital status and migration since April 1, 1968.

The Danish Psychiatric Central Register (DPCR)

The DPCR contains information on all admissions to psychiatric hospitals in Denmark since 1969 and outpatient mental health contacts (comprising all contacts with psychiatric ambulatory care and emergency rooms) since 1995.

The Danish National Patient Register (DNPR)

The DNPR contains information on all Danish medical inpatient hospital contacts since 1977 and outpatient contacts since 1995.

The Danish National Diabetes Register (DNDR)

This DNDR was established by linking information from the following registers: the DNPR, the Danish National Health Service Register, and the Danish National Prescription Registry (PR). The DNDR does not contain information on the values for the measured blood glucose, and therefore the identification of persons with diabetes relies on a validated algorithm: Individuals are classified as having diabetes on the day where at least one of the
following six criteria is met: 1) A diagnosis of diabetes made at the DNPR (ICD-8: 249, 250 and ICD-10: E10-14, H36.0, O24, excluding O24.4). 2) Registered in the Danish National Health Service Register with either a referral to chiropody for diabetic patients, five blood glucose measurements within one year or two blood glucose measurements per year for five consecutive years. 3) Registered with the PR with either two redemptions of oral glucose-lowering drugs within six months or two redemptions of prescribed insulin. The DNDR has been registering persons with diabetes since 1990. The register does not separate type 1 and type 2- diabetes.

The Danish Cancer Registry (DCR)

The DCR\textsuperscript{79} contains information on cancer diagnoses in Denmark since 1943, classified according to a modified version of the ICD-7\textsuperscript{80} between 1943 and 1977, whereas data from 1978 to 2003 were converted to ICD-10, and data from 2004 and onwards were classified according to the ICD-10.\textsuperscript{79,80} The DCR also holds information on tumor stage, i.e., ‘extent of disease’, categorized into localized, regional, distant (i.e., metastasis) or unknown.\textsuperscript{79} Since 2004, information on tumor stage in the DCR was based on the Tumor, Node, Metastasis (TNM) classification codes.\textsuperscript{81}

The Danish Register of Causes of Death (DRCD)

The DRCD\textsuperscript{39} contains information on deaths of Danish citizens and residents, place of death and cause of death since 1970.

The Danish National Prescription Registry (PR)

The PR\textsuperscript{78} contains information on all prescriptions dispensed at Danish pharmacies since 1995, including information on day of purchase and classification of drugs according to the Anatomical Therapeutic Chemical Classification System.\textsuperscript{82}
The Danish Integrated Database for Labour Market Research (IDA)

Statistics Denmark maintains a data bank, IDA\textsuperscript{83,83} with socioeconomic information, including data on income, employment status, educational level and civil status on all citizens in Denmark from 1980 onwards.
STUDY POPULATION

The specific diagnostic codes and algorithms defining the exposure, outcome and covariate variables included in the four studies can be found in the Appendices of this chapter.

**Paper I**

We used the CRS to establish our study cohort consisting of all persons who were born in Denmark and alive at some point during follow-up between January 1, 1997 and January 1, 2010. These individuals were censured on the day of death, on the day of emigration or on January 1, 2010, whichever came first. All cases of prevalent diabetes between 1990 and 1997 were excluded to ensure inclusion of incident cases of diabetes only.76

We obtained information on SMI (defined as those with schizophrenia and bipolar affective disorders) from the DPCR, information on diabetes from the DNDR using a validated algorithm,80 information on all-cause death from the CRS and information on causes of death from the DRCD.

**Paper II**

We used the CRS and the DCR to establish a population-based cohort consisting of all women, who were born in Denmark, alive on January 1, 1980 and who had a first-time diagnosis of breast cancer between 1980 and 2012. These women were censured on the day of death, on the day of emigration or on January 1, 2012, whichever came first. All women with a breast cancer diagnosis before January 1, 1980 were excluded to ensure inclusion of incident cases only.

We obtained information on SMI (defined as those with schizophrenia and bipolar affective disorders) from the DPCR, information on breast cancer and tumor stage of breast cancer from the DCR, information on all-cause deaths from the CRS, information on causes of death from the DRCD, information on diabetes from the DNDR, information on chronic diseases included in the Charlson Comorbidity Index (CCI)84 from the DNPR and information on substance abuse (excluding tobacco abuse) from the DPCR and the DNPR.
Paper III

We used the CRS and the DNPR to establish our study cohort consisting of all persons who were born in Denmark, were at least 15 years old, were alive and had a first-time hospitalization for infection at some point during follow-up between January 1, 1995 and April 30, 2011. These individuals were censored 30 days after the admission, on the date of death, on the date of emigration or on April 30, 2011, whichever came first. To avoid including re-hospitalizations, we excluded persons admitted with an infection during the year preceding the start of follow-up.

We obtained information on SMI (defined as those with schizophrenia and bipolar affective disorders) from the DPCR, information on all-cause deaths after a hospitalization for an infection from the CRS, information on causes of death from the DRCD, information on medical comorbid conditions (i.e., diabetes, CVD and chronic diseases included in the CCI) from the DNPR and the DNDR, information on substance abuse from the DNDR and the DPCR and information on educational level from IDA.

Paper IV

We used the CRS to establish our study cohort consisting of all persons who were born in Denmark, at least 50 years of age, were alive at some point during follow-up between 1995 and 2013. These individuals were censored on the date of a diagnosis for dementia, on the day of death, on the day of emigration, on the person’s 100th birthday or on January 1, 2013, whichever came first. All cases of prevalent dementia before January 1, 1995 were excluded to ensure inclusion of incident cases of dementia only.

We obtained information on schizophrenia from the DPCR, information on dementia diagnoses from the DNPR and the DPCR using a validated algorithm,\textsuperscript{85} information on anti-dementia drugs (i.e., cholinesterase inhibitors and memantine) from the PR, information on comorbid medical conditions (i.e., diabetes, ischemic heart disease (IHD), congestive heart failure (CHF), atrial fibrillation and flutter (AF), peripheral vascular disease (PVD) and cerebrovascular disease) from the DNPR and the DNDR, information on
substance abuse from the DNPR and the DPCR and information on civil status from IDA.
STATISTICAL ANALYSES

For all four cohort studies, data were analyzed by using log-linear Poisson regression analysis. Data were analyzed with the logarithm of the person-years as an offset variable, using Stata, version 13 (StataCorp, College Station, Tex.). The analyses were, thus, performed as time-to-event survival analyses and included varying follow-up periods and censorings. Poisson regression is equivalent to a Cox Regression model. All variables, except gender and tumor stage of breast cancer, were treated as time-dependent variables. We used two-sided significance tests for all analyses with statistical significance set at P < 0.05.

Paper I

For persons with SMI only, for persons with diabetes only and for persons with SMI and diabetes compared to those with neither of the disorders, we evaluated the mortality rate ratios (MRRs) and corresponding confidence intervals (CIs) for the all-cause mortality, for the mortality due to natural and unnatural (i.e., suicide, accident and homicide) causes and for the cause-specific mortality. We tested for statistical interaction between SMI and diabetes on a multiplicative scale and on an additive scale. We calculated the attributable proportion (AP) due to interaction between SMI and diabetes (i.e., a measure of the MRR for persons with both diseases not explained by the independent effects of SMI or diabetes), the AP due to diabetes among persons with SMI and diabetes (i.e., the proportion of deaths that would not have occurred, if persons with SMI and diabetes had had the same mortality as persons with SMI alone) and the numbers of hypothetically preventable deaths due to diabetes among persons with both diseases. All MRRs were adjusted for age, gender and calendar period. Adjustments for age and calendar period were performed using 5-year age bands and 2-year time bands, respectively. Cumulative mortality proportions (CMPs) were estimated for persons with SMI and diabetes and for persons with diabetes in three age categories. These estimates were plotted with time since a diagnosis of diabetes as a time scale, using Kaplan-Meier curves for the all-cause mortality outcome and using Aalen-Johansen curves for the natural
causes of death mortality outcome (taking into account competing risk from unnatural causes of death).

**Paper II**

For women with SMI compared to those without, we evaluated the all-cause MRRs within ten years after a breast cancer diagnosis. We fitted four models of survival analysis to describe the ten-year all-cause mortality outcome and evaluated these for SMI, schizophrenia and bipolar affective disorder, respectively. The first model included demographic characteristics (i.e. age and calendar period), the second model added tumor stage, the third model added medical comorbidity (i.e. diabetes and the CCI score), while the fourth model added substance abuse. We performed four sub-analyses by evaluating: 1) the ten-year all-cause MRRs associated with SMI in subgroups characterized by demographics, tumor stage, medical comorbidity and substance abuse, 2) the ten-year all-cause MRRs associated with SMI for four calendar periods (i.e., 1980-1987, 1988-1995, 1996-2003, 2004-2011), stratified for stage of breast cancer at diagnosis, 3) the ten-year breast cancer-specific MRRs associated with SMI and 4) the conditional all-cause MRRs associated with SMI for six different time periods after a breast cancer diagnosis (i.e., <1, 1-4, 5-9, 10-14, 15-19, >20 years). All MRRs were adjusted for age, gender, and calendar period. All adjustments for age and calendar period were performed using two-year age -and time bands.

**Paper III**

For persons with SMI compared to those without, we evaluated the 30-day all-cause MRRs after a hospitalization for any infection and did six sub-analysis for this outcome: 1) for persons with schizophrenia only, 2) for persons with bipolar affective disorder only, 3) for the periods before and after discharge from the hospital, 4) for different time periods within the 30-day period, 5) for each month of the first year after an admission for infection and 6) for different subgroups categorized by comorbidity and demographics. We fitted three models of survival analysis to the all-cause mortality outcome after admission for any infection for four different time periods during the 30-day period after
admission for an infection and adjusted stepwise for demographics (age, gender, and calendar period), clinical comorbidity (diabetes, CVD, and the CCI score), and substance abuse. Adjustment for educational level was included as a sensitivity analysis. We evaluated the 30-day all-cause mortality for different categories of infections causing the hospitalization, and the MRRs for death due to infectious causes, as stated in the death certificate, within 30 days after a hospitalization for infection. All MRRs were adjusted for age, gender, and calendar period. Adjustments for age and calendar period were performed using 5-year age bands and 4-year time bands, respectively. CMPs were estimated for persons with and without SMI in three age categories for up to 30 days after the date of admission with time since admission as a time scale, using Kaplan-Meier curves.

**Paper IV**

For persons with schizophrenia compared to those without, we evaluated the all-cause dementia incidence rate ratio (IRR) and did three sub-analysis for this outcome: 1) for subgroups characterized by demographics, civil status and comorbidity, 2) for a restriction of the dementia definition to diagnoses from the registers/diagnoses from the DPCR and 3) for the impact of early- and late-onset schizophrenia (before/after age 40). All IRRs were adjusted for age, gender, and calendar period. We fitted four survival analysis models to the all-cause dementia outcome and adjusted stepwise for demographics (i.e., age, gender, and calendar period), civil status, medical comorbidity (i.e., a diagnosis of diabetes, IHD, CHF, AF, PVD, and cerebrovascular disease), and substance abuse. Adjustments for age and calendar period were performed using two-year age bands and one-year time bands, respectively. Cumulative incidence proportions (CIPs) for the all-cause dementia outcome were estimated for persons with and without schizophrenia with age as the time scale, using Aalen-Johansen curves, which take into account competing risk of death.
APPROVAL AND ETHICS

This study was approved by the Danish Data Protection Agency and the Danish Health and Medicines Authority. No informed consent from participants was needed, as data were analyzed anonymously. Since the study is entirely based on register data, no ethical permission is required according to Danish law.
APPENDICES FOR VARIABLES

Definitions of exposure variables:

Table 3.2.1. Severe mental illness (Exposure variable in Paper I-IV)

<table>
<thead>
<tr>
<th>Information on schizophrenia and bipolar affective disorders obtained from the Danish Psychiatric Central Register</th>
<th>ICD-8</th>
<th>ICD-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia and Schizoaffective disorders</td>
<td>295, 296.8</td>
<td>F20, F25</td>
</tr>
<tr>
<td>Bipolar affective disorders</td>
<td>296.19, 296.39</td>
<td>F30, F31</td>
</tr>
</tbody>
</table>

Table 3.2.2. Diabetes (Exposure variable in Paper I and covariate in paper II-IV)

<table>
<thead>
<tr>
<th>Information on diabetes obtained from the Danish National Diabetes Register</th>
</tr>
</thead>
<tbody>
<tr>
<td>Algorithm: Individuals were classified as having diabetes on the date when at least one of the following six criteria was met:</td>
</tr>
<tr>
<td>A diagnosis of diabetes made at any Danish hospital registered in the Danish National Patient Register (ICD-8:249, 250; ICD-10:E10-14, H36.0, O24, excluding O24.4).</td>
</tr>
<tr>
<td>A referral to chiropody of diabetic patients as registered in the Danish National Health Service Register.77</td>
</tr>
<tr>
<td>Five blood glucose measurements within one year registered in the Danish National Health Service Register.</td>
</tr>
<tr>
<td>Two blood glucose measurements per year for five consecutive years registered in the Danish National Health Service Register.</td>
</tr>
<tr>
<td>Two redemptions of oral anti-diabetic drugs within six months registered in the Danish National Prescription Registry.</td>
</tr>
<tr>
<td>Two redemptions of prescribed insulin registered in the Danish National Prescription Registry.</td>
</tr>
</tbody>
</table>
Table 3.2.3. Breast cancer (Exposure variable in Paper II)

<table>
<thead>
<tr>
<th>Information on breast cancer diagnoses obtained from the Danish Cancer Registry</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD-10</td>
</tr>
<tr>
<td>Breast cancer</td>
</tr>
<tr>
<td>C50</td>
</tr>
</tbody>
</table>

Table 3.2.4. Infections (Exposure variable in Paper III)

<table>
<thead>
<tr>
<th>Information on hospital contacts for infections obtained from the Danish National Patient Register</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection categories</td>
</tr>
<tr>
<td>ICD-10</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>A40.0-41.9</td>
</tr>
<tr>
<td>Respiratory infections</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>J12.0-18.9, A48.1, A70.9</td>
</tr>
<tr>
<td>Other respiratory infections</td>
</tr>
<tr>
<td>J00.0-11.9</td>
</tr>
<tr>
<td>Gastrointestinal infections</td>
</tr>
<tr>
<td>A00.0-09.9, K35.0-35.9</td>
</tr>
<tr>
<td>Urinary tract infections</td>
</tr>
<tr>
<td>N10.0-10.9, N30.0, N39.0</td>
</tr>
<tr>
<td>Central nervous system infections</td>
</tr>
<tr>
<td>A17.0-17.9, A32.1, A39.0, A81.0-81.9, A83.0-89.9, B00.3, B00.4, B01.0, B01.1, B02.0, B02.1 B05.0, B05.1, B06.0, B26.1, B26.2, B58.2, G00.0-01.9, G02.0, G02.1, G02.8, G03.0-04.9, G05.0, G05.1, G05.2, G05.8, G06.0-07.9</td>
</tr>
<tr>
<td>HIV or hepatitis infections</td>
</tr>
<tr>
<td>B15.0-19.9, B20.0-24.9</td>
</tr>
<tr>
<td>Other infections</td>
</tr>
<tr>
<td>A00.0-B99.9 (excluding all the above-mentioned codes), L00.0-08.9, M00.0-00.9, N45.0-45.9, N70.0-72.9, N76.0-77.9, O23.0-23.9, O26.4, O85.0-86.9, O98.0-98.9</td>
</tr>
</tbody>
</table>
**Definitions of outcome variables:**

**Table 3.3.1. Causes of death (Outcome variable in Paper I)**

<table>
<thead>
<tr>
<th>Causes of death</th>
<th>ICD-10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unnatural causes</strong></td>
<td></td>
</tr>
<tr>
<td>Suicide</td>
<td>X60-84, Y87.0</td>
</tr>
<tr>
<td>Accidents</td>
<td>V01-X59, Y10-Y86, Y87.2, Y88-Y89</td>
</tr>
<tr>
<td><strong>Natural causes</strong></td>
<td></td>
</tr>
<tr>
<td>Old age and apoplexy,</td>
<td>I60-I72, R54, F03.9</td>
</tr>
<tr>
<td>Malignant neoplasms</td>
<td>C00-D09</td>
</tr>
<tr>
<td>Myocardial infarction (MI)</td>
<td>I21</td>
</tr>
<tr>
<td>Cardiac death, non-MI</td>
<td>I00-I25 (excluding I21), I27, I30-I52</td>
</tr>
<tr>
<td>Respiratory diseases</td>
<td>J00-J99</td>
</tr>
<tr>
<td>Endocrine and metabolic conditions</td>
<td>E00-E07, E10-E90</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>A00-A09, A15-99, B00-B99</td>
</tr>
<tr>
<td>Other deaths¹</td>
<td>The remaining causes of death</td>
</tr>
</tbody>
</table>

¹Also including homicide (ICD-10: X85-Y09, Y87.1)
Table 3.3.2. Breast cancer-specific cause of death (Outcome variable in Paper II)

<table>
<thead>
<tr>
<th>Information on death due to breast cancer obtained from the Danish Register of Causes of Death</th>
<th>ICD-8</th>
<th>ICD-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>174.00-174.09</td>
<td>C50</td>
</tr>
</tbody>
</table>

Table 3.3.3. Infection-related causes of death (Outcome variable in Paper III)

<table>
<thead>
<tr>
<th>Information on death due to infections obtained from the Danish Register of Causes of Death</th>
<th>ICD-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection categories</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>A40.0-41.9</td>
</tr>
<tr>
<td>Respiratory infections</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>J12.0-18.9, A48.1, A70.9</td>
</tr>
<tr>
<td>Other respiratory infections</td>
<td>J00.0-11.9</td>
</tr>
<tr>
<td>Gastrointestinal infections</td>
<td>A00.0-09.9, K35.0-35.9</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>N10.0-10.9, N30.0, N39.0</td>
</tr>
<tr>
<td>Central nervous system infections</td>
<td>A17.0-17.9, A32.1, A39.0, A81.0-81.9, A83.0-89.9, B00.3, B00.4, B01.0, B01.1, B02.0, B02.1 B05.0, B05.1, B06.0, B26.1, B26.2, B58.2, G00.0-01.9, G02.0, G02.1, G02.8, G03.0-04.9, G05.0, G05.1, G05.2, G05.8, G06.0-07.9</td>
</tr>
<tr>
<td>HIV or hepatitis infections</td>
<td>B15.0-19.9, B20.0-24.9</td>
</tr>
<tr>
<td>Other infections</td>
<td>A00.0-B99.9 (excluding all the above-mentioned codes), L00.0-08.9, M00.0-00.9, N45.0-45.9, N70.0-72.9, N76.0-77.9, O23.0-23.9, O26.4, O85.0-86.9, O98.0-98.9</td>
</tr>
</tbody>
</table>
**Table 3.3.4. Dementia (Outcome variable in Paper IV)**

<table>
<thead>
<tr>
<th>Information on dementia obtained from the Danish Psychiatric Central Research Register, the Danish National Patient Register and the Danish National Prescription Registry</th>
</tr>
</thead>
<tbody>
<tr>
<td>A diagnosis of dementia was identified if at least one of the following criteria was met:</td>
</tr>
<tr>
<td>Registration of a diagnosis of dementia in the Danish Psychiatric Central Register or the Danish National Patient Register.</td>
</tr>
<tr>
<td>And/or</td>
</tr>
<tr>
<td>Registration of at least one prescription of anti-dementia drug redeemed in the Danish National Prescription Registry.</td>
</tr>
<tr>
<td>Diagnosis according to a record of dementia in the Danish Psychiatric Central Register or the Danish National Patient Register.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>ICD-8</th>
<th>ICD-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD (Alzheimer’s disease)</td>
<td>290.10</td>
<td>F00.0, F00.1, F00.2, F00.9, G30.0, G30.1, G30.8, G30.9</td>
</tr>
<tr>
<td>VaD (vascular dementia)</td>
<td>293.09-19</td>
<td>F01.0, F01.1, F01.2, F01.3, F01.8, F01.9</td>
</tr>
<tr>
<td>FTD (frontotemporal dementia)</td>
<td>290.11</td>
<td>F02.0</td>
</tr>
<tr>
<td>Dementia without specification</td>
<td>290.09-19</td>
<td>F03.9</td>
</tr>
</tbody>
</table>

**Diagnosis according to a record of prescriptions for anti-dementia drugs in the Danish National Prescription Registry:**

<table>
<thead>
<tr>
<th>Name</th>
<th>Drug name</th>
<th>ATC-codes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticholinesterases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tacrine</td>
<td>N06DA01</td>
<td></td>
</tr>
<tr>
<td>Donepezile</td>
<td>N06DA02</td>
<td></td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>N06DA03</td>
<td></td>
</tr>
<tr>
<td>Galantamine</td>
<td>N06DA04</td>
<td></td>
</tr>
<tr>
<td>Donepezile and Memantine</td>
<td>N06DA52</td>
<td></td>
</tr>
<tr>
<td><strong>Other anti-dementia drugs</strong></td>
<td></td>
<td>Memantine</td>
</tr>
</tbody>
</table>
**Definitions of covariates:**

**Table 3.4.1. Tumor stage (covariate in Paper II)**

<table>
<thead>
<tr>
<th></th>
<th>Tumor</th>
<th>Node</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Localized</strong></td>
<td>T1-4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1-2</td>
<td>N0</td>
<td>Mx</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>Nx</td>
<td>M0x</td>
</tr>
<tr>
<td><strong>Regional</strong></td>
<td>T1-4,x</td>
<td>N1-3</td>
<td>M0</td>
</tr>
<tr>
<td><strong>Metastasis</strong></td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
<td>T2-4,x</td>
<td>Nx</td>
<td>M0-x</td>
</tr>
<tr>
<td></td>
<td>T3-4,x</td>
<td>N0</td>
<td>Mx</td>
</tr>
<tr>
<td></td>
<td>T1-4,x</td>
<td>N1-3</td>
<td>Mx</td>
</tr>
<tr>
<td></td>
<td>T0</td>
<td>N1-3</td>
<td>M0-1x</td>
</tr>
<tr>
<td></td>
<td>T0</td>
<td>N0,x</td>
<td>M1</td>
</tr>
</tbody>
</table>

**Table 3.4.2. Cardiovascular disease (covariate in Paper III)**

<table>
<thead>
<tr>
<th></th>
<th>ICD-8</th>
<th>ICD-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular diseases</td>
<td>390-458</td>
<td>I00-I99</td>
</tr>
</tbody>
</table>
### Table 3.4.3. Charlson Comorbidity Index (covariate in Paper II-III)

<table>
<thead>
<tr>
<th>Information on diseases included in the Charlson Comorbidity Index obtained from the Danish National Patient Register (Paper III)</th>
<th>ICD-8</th>
<th>ICD-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>410</td>
<td>I21-I23</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>427.09, 427.10, 427.11, 427.19, 428.99, 782.49</td>
<td>I50, I11.0, I13.0, I13.2</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>440-445</td>
<td>I70-I74, I77</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>430-438</td>
<td>I60-I69, G45, G46</td>
</tr>
<tr>
<td>Dementia</td>
<td>290.09-290.19, 293.09</td>
<td>F00-F03, F05.1, G30</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>490-493, 515-518</td>
<td>J40-J47, J60-J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>712, 716, 734, 446, 135.99</td>
<td>M05, M06, M08, M09,M30-M36, D86</td>
</tr>
<tr>
<td>Ulcer disease</td>
<td>530.91, 530.98, 531-534,</td>
<td>K22.1, K25-K28</td>
</tr>
<tr>
<td>Mild liver disease</td>
<td>571, 573.01, 573.04</td>
<td>B18, K70.0-K70.3, K70.9, K71, K73, K74, K76.0</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>249.00, 249.06, 249.07, 249.09, 250.00, 250.06, 250.07, 250.09</td>
<td>E10.0, E10.1, E10.9, E11.0, E11.1, E11.9</td>
</tr>
<tr>
<td>Hemiplegia</td>
<td>344</td>
<td>G81, G82</td>
</tr>
<tr>
<td>Moderate/severe renal Disease</td>
<td>403,404,580-583, 584, 590.09, 593.19, 753.10-753.19, 792</td>
<td>I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61</td>
</tr>
<tr>
<td>Diabetes mellitus with chronic complications</td>
<td>249.01-249.05, 249.08, 250.01-250.05, 250.08</td>
<td>E10.2-E10.8, E11.2-E11.8</td>
</tr>
<tr>
<td>Condition</td>
<td>Code</td>
<td>ICD-10 Codes</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>Any tumor</td>
<td>140-194</td>
<td>C00-C75</td>
</tr>
<tr>
<td>Leukemia</td>
<td>204-207</td>
<td>C91-C95</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>200-203, 275.59</td>
<td>C81-C85, C88, C90, C96</td>
</tr>
<tr>
<td>Moderate/severe liver Disease</td>
<td>070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00-456.09</td>
<td>B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85</td>
</tr>
<tr>
<td>Metastatic solid tumor</td>
<td>195-199</td>
<td>C76-C80</td>
</tr>
<tr>
<td>AIDS</td>
<td>079.83</td>
<td>B21-B24</td>
</tr>
</tbody>
</table>
Table 3.4.4. Substance abuse (covariate in Paper II-IV)

Information on substance abuse obtained from the Danish National Patient Register and the Danish Psychiatric Central Research Register

<table>
<thead>
<tr>
<th>Drug-related abuse</th>
<th>ICD-8</th>
<th>ICD-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>304.09, 304.19</td>
<td>F11.0–F11.9</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>304.59</td>
<td>F12.0–F12.9</td>
</tr>
<tr>
<td>Sedatives/hypnotics</td>
<td>304.29, 304.39</td>
<td>F13.0–F13.9</td>
</tr>
<tr>
<td>Cocaine</td>
<td>304.49</td>
<td>F14.0–F14.9</td>
</tr>
<tr>
<td>Other stimulants</td>
<td>304.69</td>
<td>F15.0–F15.9</td>
</tr>
<tr>
<td>Hallucinogens</td>
<td>304.79</td>
<td>F16.0–F16.9</td>
</tr>
<tr>
<td>Other and multiple drugs</td>
<td>304.89, 304.99</td>
<td>F18.0–F19.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alcohol-related abuse</th>
<th>ICD-8</th>
<th>ICD-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol psychosis and abuse syndrome</td>
<td>291.09–291.99, 303.09–303.99</td>
<td>F10.0–F10.9</td>
</tr>
<tr>
<td>Cirrhosis and steatosis of the liver</td>
<td>571.09, 571.10, 571.19</td>
<td>K70.0–K70.9</td>
</tr>
<tr>
<td>Esophageal varices</td>
<td>456.00, 456.01, 456.09</td>
<td>I85.0–I85.9</td>
</tr>
</tbody>
</table>
Table 3.4.5. Risk factors for dementia (covariates in Paper IV)

<table>
<thead>
<tr>
<th>Information on comorbidity (i.e. other risk factors for dementia) obtained from the Danish National Patient Register, the Danish National Diabetes Register and the Danish Psychiatric Central Register</th>
<th>ICD-8</th>
<th>ICD-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic heart disease</td>
<td>410–414</td>
<td>I20–I25</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>427.09-427.11, 427.19, 428.99, 782.49</td>
<td>I50, I11.0, I13.0, I13.2</td>
</tr>
<tr>
<td>Atrial fibrillation or flutter</td>
<td>427.93, 427.94</td>
<td>I48</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>440, 441, 442, 443, 444, 445</td>
<td>I70-I74, I77</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>430-438</td>
<td>I60-I69, G45, G46</td>
</tr>
<tr>
<td>Diabetes</td>
<td>See above</td>
<td></td>
</tr>
<tr>
<td>Substance abuse</td>
<td>See above</td>
<td></td>
</tr>
</tbody>
</table>
CHAPTER 4:

RESULTS IN SUMMARY
This chapter offers a brief summary of the results from each paper in the thesis. A more detailed description of the results is presented in Chapters 5-8.

**Paper I**

The cohort comprised 4,734,703 persons of whom 37,389 persons had SMI (9,540 deaths), 248,176 had diabetes (56,858 deaths) and 4,284 persons had SMI and diabetes (1,083 deaths).

Compared to persons without the two disorders, the all-cause mortality was three-to-four-fold higher for persons with SMI and diabetes (MRR, men: 4.14, 95% CI: 3.81-4.51; MRR, women: 3.13, 95% CI: 2.88-3.40), almost two-fold higher for persons with diabetes only (MRR, men: 1.75, 95% CI: 1.72-1.77; MRR, women: 1.56, 95% CI: 1.54-1.58) and two-to-three-fold higher for persons with SMI only (MRR, men: 3.06, 95% CI: 2.97-3.15; MRR, women: 2.26, 95% CI: 2.20-2.32). The mortality due to natural causes of death was also three-to-four-fold higher for persons with SMI and diabetes compared to those without the two disorders.

For persons with both disorders, the AP of natural deaths due to interaction between SMI and diabetes was around 14%, whereas the AP of natural deaths due to diabetes was around 33%, corresponding to 338 out of 1,013 natural deaths, which could be attributed to diabetes.

The mortality for all causes of death was higher for persons with SMI, persons with diabetes and persons with SMI and diabetes than for persons without the two disorders. For persons with both diseases, the cause-specific MRRs were lowest for malignant neoplasms (MRR, men: 2.08, 95% CI: 1.69-2.56; MRR, women: 1.98, 95% CI: 1.64-2.39) and highest for unnatural causes of death (MRR, men: 7.89, 95% CI: 5.51-11.29; MRR, women: 12.31, 95% CI: 6.80-22.28).

The absolute risk of dying within seven years of the diabetes diagnosis for persons with SMI and diabetes was between 15.0% and 63.8% depending on age, compared to between 5.2% and 53.6% for persons with diabetes only in the same age categories.
Paper II

The cohort comprised 105,448 women with incident breast cancer, hereof 1,106 women with SMI. A total of 648 (58.6%) women with SMI and 41,771 (40.0%) women without SMI died within ten years after the diagnosis of breast cancer.

Women with SMI had a 60% higher risk of death within ten years after a breast cancer diagnosis (MRR: 1.60, 95% CI: 1.48-1.73) than women without SMI. The association was basically unaffected by adjusting for tumor stage of breast cancer, medical comorbidities, and substance abuse. The MRR was higher for women with schizophrenia (MRR: 1.73, 95% CI 1.57-1.90) than for women with bipolar affective disorder (MRR: 1.39, 95% CI 1.22-1.59).

The ten-year all-cause MRR tended to increase by increasing calendar period, but decrease with increasing stage of breast cancer and increasing comorbidities. The ten-year all-cause MRRs, evaluated as a function of calendar time, tended to increase over time for women with a localized or regional breast cancer stage, although not statistically significantly. Within ten years after a breast cancer diagnosis, 347 (58.0%) deaths among women with SMI and 25,731 (66.3%) deaths among women without SMI were classified as breast cancer-specific deaths, which corresponded to a MRR of 1.38 (95% CI: 1.24-1.54) for women with SMI compared to those without. The conditional MRRs for the association between SMI and the all-cause mortality did not differ substantially when evaluated for different time periods after a breast cancer diagnosis.

Paper III

The cohort comprised 806,835 persons hospitalized for an infection, of whom 11,343 had SMI (7,388 with schizophrenia and 3,955 with bipolar affective disorder). Persons with as well as without SMI had a markedly increased mortality after hospitalization for an infection. A total of 59,735 persons died within 30 days after admission for infection, of whom 1,052 had SMI.

The all-cause mortality within 30 days after admission for any infection was 52% higher for persons with SMI than for persons without SMI (MRR: 1.52, 95% CI: 1.43–1.61). The mortality was lower for persons with bipolar affective disorder (MRR: 1.27, 95% CI: 1.15–1.40) than for persons with schizophrenia (MRR: 1.71,
95% CI: 1.58–1.85). Within the 30 days after admission, the mortality tended to be higher for the period after discharge compared to the period before discharge, although the mortality was similar for different time periods within the 30-day period. The mortality tended to remain higher for persons with SMI than for those without for up to 12 months after hospitalization for an infection (at 12 months, MRR: 1.31, 95% CI: 1.03–1.66). The MRRs for persons with SMI compared with those without decreased by increasing age, comorbid diabetes, comorbid CVD, increasing number of comorbidities (i.e., increasing CCI score), and comorbid substance abuse. The all-cause MRR after any infection did not change substantially when adjusting for comorbidity and substance abuse.

The MRRs were higher after all types of infections causing the hospitalization and ranged from 1.27 (95% CI: 1.15–1.39) for sepsis to 2.61 (95% CI: 1.69–4.02) for central nervous system (CNS) infections.

In total, 247 (25.7%) deaths among persons with SMI and 9,565 (17.9%) deaths among persons without SMI were classified as infectious-related deaths within 30 days after an admission for an infection. This corresponded to a MRR of 2.61 (95% CI: 2.30–2.96) for death due to infection for persons with SMI compared to those without.

The absolute risk of dying within 30 days after a hospitalization for infection for persons with SMI was between 2.3% and 16.8%, depending on age, compared to between 0.6% and 14.2% for persons without SMI in the same age categories.

**Paper IV**

The cohort comprised 2,845,440 persons, of whom 20,683 had schizophrenia. A total of 136,012 persons developed dementia during up to 18 years of follow-up, including 944 individuals with a history of schizophrenia.

The risk of all-cause dementia was more than two-fold higher in persons with schizophrenia compared to those without (IRR: 2.13, 95% CI: 2.00–2.27). Adjusting this estimate for civil status and subsequently for medical comorbidities did not change the estimate much, whereas the adjustment for substance abuse attenuated the association somewhat. The risk of dementia associated with schizophrenia was stable when evaluated in subgroups
characterized by demographics and comorbidities, although the IRR was higher among men, persons under age 65, those living with a partner, those without cerebrovascular disease and those without substance abuse. The IRR estimate did not differ after restricting the dementia definition to the 129,546 diagnoses recorded in the DNPR and the DPCR, but was marginally higher after restricting the dementia definition to the 63,323 diagnoses from the DPCR. The risk of dementia was lower for early versus late-onset schizophrenia evaluated among persons younger than 65 years and among persons older than 65 years.

For persons with dementia, 22.4% of persons with schizophrenia and 6.3% of persons without schizophrenia had their dementia diagnosis before the age of 65 years. By the age of 65 years, the absolute risk of dementia was 1.8% for persons with schizophrenia compared to 0.6% for persons without schizophrenia, whereas the corresponding risks by the age of 80 years were 7.4% and 5.8%, respectively.
CHAPTER 9:

DISCUSSION OF METHODS
DESIGN AND QUALITY OF DATA

This thesis includes four observational cohort studies. A major strength of these papers lies in the nature of the design of register-based cohort studies. Register data collection is prospective in nature; thus the measurement of the exposure cannot be influenced by the outcome.\(^8^8\) The prospective follow-up design, the long duration of observation periods, and the large sizes of the register-based cohorts make these studies particularly useful in studying rare outcomes, such as mortality\(^8^9\) or an outcome, such as dementia, which in addition requires sufficient duration of observation time for the majority of the cohort to display a clinically significant risk of dementia.\(^3\) Our overall aim for these four epidemiologic studies is to obtain accurate estimates for the associations between exposures and outcomes, which are generalizable to the target population (i.e., the population for which the study results provide a basis for potential intervention).\(^8^9\) Validity and precision are both components of accuracy.\(^8^8\) By precision, we refer to estimates with little random error.\(^8^8\) The accurate linkage of recorded information by use of the personal identification number,\(^7^1\) the large number of persons in our cohort, and the large number of outcomes allowed for statistically precise estimates with narrow CIs in our four studies. By validity, we refer to the absence of systematic errors or biases, and this corresponds to the accurate measurement of the effects apart from random variation.\(^8^8\) The validity of a study is separated into internal validity (i.e., biases and confounding) and external validity (i.e., generalizability), and the internal validity is considered a prerequisite for the external validity.\(^8^8\) The complete follow-up and complete registration of the exposures (SMI, diabetes, breast cancer, and infections) as well as outcomes (all-cause death and dementia) in the registries reduced the likelihood of biases and thus yielded high internal validity in our four studies. The validity of key variables from our studies is known to be high, i.e. the positive predictive value (PPV) for a diagnosis of schizophrenia is 87%,\(^9^0\) the PPV for a diagnosis of diabetes is 90%,\(^8^0\) the correctness for a diagnosis of breast cancer is 99%,\(^9^1\) the PPV for a diagnosis of infection is 95%,\(^4^2\) the PPV for all-cause dementia is 86%,\(^9^2\) and the completeness of all-cause death is close to 100%.\(^7^1\) By generalizability, we refer to the validity of inference for the
source population (i.e., the population under study). In nationwide population-based studies like ours, the results are likely to be highly generalizable.

It is vital for the methodological discussion of these four cohort studies to go into detail about the features affecting internal validity, i.e., biases. Most violations of internal validity can be separated into selection bias, information bias and confounding, of which only the latter can be dealt with in statistical analyses. Also, issues concerning the generalizability of the results for the studies need to be addressed.
Discussion of methods

INTERNAL VALIDITY

Selection bias

Selection bias is defined as a systematic error which stems from procedures used to select study subjects and from factors that influence study participation. This bias arises when the relation between exposure and outcome is different for study participants and non-participants. Our studies had complete inclusion of all persons in Denmark (Paper I and IV) and complete inclusion of all incident hospitalization for infections and diagnoses of breast cancer (Paper II and III). In addition, we had complete follow-up, which was ensured by the CRS as described previously. These aspects eliminated basically all selection bias in our four studies.

Information bias

Information bias in a study may arise when information collected about study participants is erroneous. Misclassification of the exposure, the outcome, or the confounding factors can cause such errors. Misclassification can be differential of non-differential: Non-differential misclassification is a misclassification unrelated to other study variables, whereas differential misclassification differs according to the value of other study variables. Non-differential misclassification of dichotomous variables biases an association toward unity, whereas differential misclassification biases the association in an unpredictable manner. In Papers I-III, cause-specific mortality was explored to ensure comparability to previous literature. However, this outcome measure is subject to information biases owing to low quality of information on causes of death and cause-of-death-attribution-bias (see Chapter 1, Life-expectancy gap in persons with SMI). In Paper I, in which all causes of death were under study, a differential misclassification of causes of death in persons with SMI could entail an overestimation of ‘expected causes of death’ in persons with SMI, such as deaths caused by CVDs, as these chronic conditions are known to be associated with SMI. Contrarily, other causes of death might be underestimated. In Papers II and
III, in which breast-cancer-specific mortality and infection-specific mortality were under study, physicians might tend to over-report, for instance, CVD as the underlying cause of death in persons with SMI, as this is a condition commonly associated with SMI (i.e., cause-of-death attribution bias). This could, thus, give rise to differential misclassification. On the other hand, physicians might tend to over-report breast cancer and infection, respectively, as the underlying cause of death in persons just recently hospitalized for these conditions. This type of misclassification does not depend on whether a person has SMI or not and would, thus, be characterized as non-differential misclassification. In summary, these mechanisms would tend to bias the results towards the null.

In Paper I, information on diabetes could be differentially misclassified according to the exposure, SMI, as at the proportion of undiagnosed diabetes is as high as 70% among persons with SMI compared to 25% among persons without SMI. This potential bias was, however, difficult to avoid because testing all participants for diabetes in this large cohort was not feasible. Nevertheless, such potential bias would tend to underestimate any true effect of diabetes on the excess mortality in persons with SMI.

In Paper II, information on tumor stage could be subject to information bias. The validity of tumor stage classification of breast cancer in the DCR differs by severity; around 90% of localized or regional disease is correctly staged, whereas this is only the case for around 65% of breast cancers with metastasis. Thus, this could give rise to differential misclassification, if the classification of tumor stages depended on the presence of SMI. Women with SMI with newly diagnosed breast cancer might be more prone to desisting further investigation of tumor stage due to SMI-related barriers, such as paranoia and adherence difficulties. Although, this scenario seems implausible, it cannot be ruled out that this was the case, as the proportion of missing and unknown stages was slightly higher and the proportion of localized stages was slightly lower among women with SMI in our study. Therefore, the analyses including metastatic stage in Paper II should be interpreted cautiously.
In Paper IV, information bias pertaining to the dementia diagnosis was of general concern. The validity of a dementia diagnosis in persons with schizophrenia is unknown and could be subject to differential misclassification. Persons with schizophrenia often have preexisting cognitive dysfunction, behavioral problems, and negative symptoms,\textsuperscript{4,5,93} which may challenge the clinician in diagnosing the dementia, although the diagnosis of dementia has been shown to have high validity for other disorders with preexisting cognitive impairments, such as Down’s syndrome.\textsuperscript{94} However, even subtle cognitive deficits or behavioral problems in persons with schizophrenia could be mistaken for dementia by physicians with less experience within psychiatry. On the other hand, misattribution of dementia symptoms to the schizophrenia (i.e., ‘diagnostic overshadowing’\textsuperscript{95}) or the general tendency to under-diagnose physical comorbidity in persons with SMI\textsuperscript{19,20} could lead to an under-recognition of dementia in persons with schizophrenia. However, neurologists, psychiatrists and geriatricians, who make the majority of the dementia diagnoses in Denmark,\textsuperscript{96} have been shown to diagnose dementia with a PPV of 95\%.\textsuperscript{96} Furthermore, dementia suspicion in persons with preexisting psychiatric diseases, such as schizophrenia, would presumably lead to referral to a psychiatrist, and we found a slightly stronger association between schizophrenia and dementia, when the analysis was restricted to a subgroup of persons diagnosed by psychiatrists only. Still, persons with schizophrenia may experience dementia-like symptoms at an earlier age compared to persons without schizophrenia owing to preexisting cognitive impairment, which could meet a clinician criteria for dementia more readily with age. However, as the definition of dementia requires a loss of cognitive function compared to the starting point of the patient, we expected physicians, and in particular psychiatrists, to diagnose only severe cognitive impairment, beyond that which could be attributed to the psychopathological features of schizophrenia, as dementia. Nevertheless, the PPV for dementia diagnoses has been shown to be as low as 59\% among individuals under the age of 65 years,\textsuperscript{97} and the analyses for risk of dementia among younger individuals should, therefore, be interpreted with caution. On the other hand, the risk of differential misclassification of dementia diagnoses owing to incentives for adding dementia
diagnoses to persons with schizophrenia to improve their access to health care, is limited in Denmark in which access to care is free and equal.

**Confounding**

Confounding may be considered a confusion of effects, i.e., the effect of another variable is mistaken for or mixed with the actual exposure effect, leading to bias. In order for a variable to be a confounder, it must be associated with both the exposure and outcome under study, without being an intermediate variable on the pathway from exposure to outcome.

Each of the studies was limited by lack of information on potentially confounding factors, which were either unavailable or were substantially affected by missing information. In all papers, we lacked information on socioeconomic factors (e.g., low educational level) and life style factors (e.g., smoking, high body mass index (BMI), and physical inactivity). These factors are generally associated with SMI as well as with poorer prognosis after diabetes, breast cancer, and infections and with risk of dementia. In addition, general health status, severity of SMI, severity of the comorbid physical condition (i.e., diabetes, breast cancer and infections), treatment modalities for the physical condition (e.g., diabetes medication, type of surgery and adjuvant therapy for breast cancer, antibiotic treatment of infection, and treatment of dementia risk factors), health care utilization, and treatment adherence could potentially also play roles for the associations in Paper I-IV. This introduced the possibility of residual confounding. However, all of these unavailable factors could also be intermediate variables and thus represent important steps on the causal pathway for the association between SMI (with comorbid diabetes, breast cancer or infection) and mortality or between schizophrenia and dementia. In Paper II-IV, we did adjust for comorbidity and substance abuse, and these analyses did not change the results substantially. This suggested that these factors, although not confirmed as either confounders or intermediate variables, presumably did not play major roles for the associations. However, substance abuse and physical comorbidity could be under-diagnosed among persons with SMI, which might lead to an
underestimation of the excess mortality or the excess risk of dementia accounted for by these conditions.

In Paper I, we had no information on the metabolic syndrome (MS). Around 40% of persons with SMI meet the criteria for the MS,\textsuperscript{109} which only apply to 20% of persons without SMI.\textsuperscript{110} The MS is also strongly associated with the risk of CVD,\textsuperscript{111} and could thus be an important confounder for the association between SMI with comorbid diabetes and death.
EXTERNAL VALIDITY

Generalizability

All four studies were conducted in a country with equal and free access to health-care, and our findings may, therefore, only apply to countries with similar health-care systems. However, access to care for persons with SMI might be lower in countries in which the access to health-care depends on health insurance. Therefore, in a worldwide perspective, our results may be conservative estimates of the risk of dementia as well as the excess mortality accounted for by diabetes, breast cancer and infections in persons with SMI.

Three of the studies (Paper I, II and IV) examined highly age-related disorders. Thus, as persons with SMI die 15-20 years prematurely compared to persons without SMI, those who lived long enough to develop diabetes, breast cancer, or dementia could potentially represent a selected group of more healthy persons. Our results could thereby underestimate the ‘true excess mortality’ owing to diabetes and breast cancer as well as the ‘true risk’ of dementia in persons with SMI. This theory was also supported by the finding in Paper IV of a lower absolute risk of dementia for persons with schizophrenia after their mid-eighties compared to persons without schizophrenia in the same age, when taking into account the competing risk of death. Furthermore, this could also explain why we in Paper I found a lower risk of suicide in persons with SMI and diabetes compared to persons with SMI only, although both SMI and diabetes are associated with increased risk of suicide. However, the risk of suicide is highest within the first years after the diagnosis of SMI, which would tend to lie several years prior to a potential diagnosis of diabetes. Thus, persons with SMI, who survived until they had their diabetes diagnosed, may be a selected subgroup with a lower risk of suicide.

The studies in Paper II-III were conducted in cohorts of whom the health care contact had already been established: a cohort of women who had been diagnosed with breast cancer and a cohort of persons who had been hospitalized for an infection, respectively. Thus, these cohorts may comprise reasonably healthy persons as the most severely affected persons with SMI might not even
be diagnosed with their breast cancer or hospitalized for their infection. Therefore, our results might not apply to all persons with SMI, but may, nevertheless, represent conservative estimates of the risk of death after breast cancer or after infection among persons with SMI in general. Yet, the results in Paper II may not be pertinent to women with undiagnosed breast cancer, and the results in Paper III may not be pertinent to persons with less severe infections, who were treated in psychiatric wards, primary care, or left untreated.

Paper IV only included information on the two-thirds of dementia cases in Denmark, who were diagnosed within the secondary health care system, as hospital contacts only are recorded in the DPCR and DNPR. Consequently, dementia cases diagnosed in primary care or private psychiatric and neurologic practices were not included, unless registered with dementia at a subsequent hospitalization, or if they redeemed prescriptions for anti-dementia drugs. Our results, therefore, represented the risk of a hospital diagnosis of dementia associated with schizophrenia.
We analyzed data from these four open dynamic cohorts by taking into account the amount of time each individual spent in the population at risk and calculated incidence rates by dividing the number of new outcome events by the amount of person-time experienced by the population at risk.\textsuperscript{58} We used Poisson regression analyses for these calculations, which approximate Cox-Regression analyses, but have the advantage of handling large datasets and several time-dependent covariates.

In Paper II-IV, we adjusted for covariates which could be potential confounders. However, it cannot be excluded that all of these could be intermediate variables for our associations. Thus, the results from the adjusted analyses could represent the confounder-adjusted estimates. However, if we believe that these covariates indeed were intermediate variables, the estimate adjusted for demographics only could represent the ‘true risk estimate’, whereas the comparison to the fully adjusted estimate would allow for an interpretation of the excess risk accounted for by the intermediate variables.

In Paper II-IV, we made stratified analyses in subgroups of specific covariates in order to present potential effect modification between SMI and the covariate evaluated. Notably, the IRR estimate was lower when evaluated among subgroups with high absolute risk of the outcome. These apparently counterintuitive findings could be explained by the fact that when the absolute risk of the outcome is high in a subgroup, the additional effect of SMI was small on a relative scale. As an example, we showed that the risk of dementia associated with schizophrenia was lower when evaluated among persons with substance abuse (IRR: 1.09, 95% CI: 0.95-1.24) compared to when evaluated among persons without substance abuse (IRR: 1.96, 95% CI: 1.82-2.11). However, when we evaluate the risk of dementia in persons with schizophrenia only, in persons with substance abuse only and in persons with both disorders compared to the same reference group, i.e., those with neither of the two disorders, it becomes evident that the risk was highest in persons with SMI and comorbid substance abuse (see Table 9.1).
Table 9.1. *The Incidence rate ratios (IRRs) and corresponding CI for the risk of dementia in persons with schizophrenia, persons with substance abuse, and persons with schizophrenia and substance abuse compared to those without the two disorders.*

<table>
<thead>
<tr>
<th></th>
<th>Without Substance abuse</th>
<th>With Substance abuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without Schizophrenia</td>
<td>1 (Ref.)</td>
<td>3.30 (3.22-3.37)</td>
</tr>
<tr>
<td>With Schizophrenia</td>
<td>1.94 (1.80-2.09)</td>
<td>4.36 (3.83-4.98)</td>
</tr>
</tbody>
</table>

In Paper I, we calculated measures of interaction on an additive scale, including calculation of the synergy index, the AP due to interaction between SMI and diabetes, and the AP due to diabetes among persons with SMI and diabetes. However, not all literature agree upon using these measures as indications of biological interaction\(^{113,114}\) as such estimations assume no residual confounding from unknown or unmeasured risk factors.\(^{113}\) Thus the results regarding interaction on an additive scale should be interpreted carefully.

In Paper II, we chose to study the mortality 10 years after a diagnosis of breast cancer as this seemed appropriate when studying mortality for a cancer diagnosis with a fairly good prognosis. In Paper III, we chose to study the mortality 30 days after an admission for infection, as most deaths related to infections are likely to occur in close proximity to the acute condition.
CHAPTER 10:

DISCUSSION OF RESULTS
This thesis studies the significance of common, comorbid disorders for the excess mortality of persons with SMI using all-cause mortality as the primary outcome measure (Paper I-III). Contrarily, previous literature has focused on studying excess mortality related to specific causes of death in persons with SMI. However, studies using information on causes of death from death certificates may be limited in determining which role comorbid physical conditions play for the excess mortality of persons with SMI: First, using information from death certificates may bias the results due to low quality of information on causes of death\textsuperscript{39} and cause-of-death-attribution-bias\textsuperscript{38} (see Chapter 1, Life-expectancy gap in persons with SMI), which might be especially pronounced in persons with SMI. The quality of the information on causes of death varies, as the physician often do not have sufficient information on the circumstances preceding the death or on diseases in the deceased in order to identify the correct cause of death. In addition, autopsy, which has proven to provide accurate information on causes of death, has become increasingly rare in Denmark.\textsuperscript{115} Second, it can be a challenge to identify only one disease as the underlying cause of death, especially in persons with multimorbidity.\textsuperscript{42} Third, the use of only one underlying cause of death may tend to overestimate chronic diseases in older adults.\textsuperscript{42} Finally, these types of studies do not take into account that the comorbid disease under study, i.e., the target disease, may contribute to mortality without being classified as the cause of death.\textsuperscript{42,116} For instance, persons admitted for infection and women with breast cancer may constitute vulnerable groups with poor health status caused by the underlying diseases or by side effects of the treatments, which places these individual at risk of dying from causes other than their underlying disease.

On the other hand, all-cause mortality is an unbiased outcome measure,\textsuperscript{116} which may capture the contribution of deaths directly caused by the target disease as well as deaths caused by interactions between the target disease, poor health, and comorbidity.\textsuperscript{102} In addition, studying all-cause mortality after a diagnosis of the target disease is particularly interesting as a rough proxy for studying the effects of health care provision, health care utilization, and treatment adherence.
on mortality in persons with SMI, as the target disease has already been recognized and the health care contact established.
This cohort study showed that persons with SMI and diabetes had a three-to-four-fold higher risk of premature death compared to persons with neither SMI nor diabetes. In persons with SMI and diabetes, 14% of the excess mortality due to natural causes of deaths could be attributed to the interaction between SMI and diabetes, whereas 33% could be attributed to diabetes. The cause-specific MRRs in persons with both diseases were lowest for malignant neoplasms and highest for suicide and accidents. The absolute risk of dying within seven years of the diabetes diagnosis for persons with SMI and diabetes was between 15.0% and 63.8% depending on age, compared to between 5.2% and 53.6% for persons with diabetes only in the same age categories.

Three previous studies have evaluated the absolute risk of all-cause mortality within a 5- to 12-year period for persons with SMI and diabetes, based on between 16 and 96 deaths in the SMI and diabetes group. Two studies evaluated this outcome for persons with SMI and diabetes compared to persons with diabetes only. One of these found a slightly higher risk (23% vs 20%), whereas the other did not find a difference (21% vs. 21%). Another study evaluated this outcome for persons with SMI and diabetes compared to persons with SMI only and found risk estimates of 41% vs. 10%. Our study was the first to evaluate the all-cause mortality and cause-specific mortality for persons with SMI and diabetes compared to persons with neither of the two disorders.

An excess mortality among persons with SMI and diabetes may have several plausible explanations. The proportion of undiagnosed diabetes is much higher in persons with SMI compared to persons without SMI (70% vs 25%), which suggests that persons with SMI may have delayed detection for their diabetes. Such a potential delay may entail that persons with SMI and diabetes have more advanced disease at time of diagnosis, such as increased rates of macrovascular and microvascular complications.

Physical conditions in persons with SMI are known to be sub-optimally treated in general, and this has proved to be true for diabetes as well. It is, however, difficult to disentangle to what extent this under-treatment reflects...
low quality of medical health care (e.g., owing to physician time constraint due to competing conditions or other physician barriers), or SMI-related barriers, such as cognitive dysfunction, communication and adherence difficulties that could hamper diabetes self-care and treatment compliance.

SMI is known to be associated with substance abuse, which is also associated with poorer prognosis in persons with diabetes, presumably due to inadequate diabetes care adherence. In addition, the use of antipsychotic drugs has been associated with excess mortality in persons with SMI in some, but not all studies. However, it is unknown if the use of antipsychotic drugs affects the mortality in persons with SMI and diabetes. In our study, the MRR due to cardiac death (i.e., all cardiac-related causes of death, except for myocardial infarction) was notably increased in persons with SMI and diabetes. This association might be mediated by use of antipsychotic drugs, which has previously been associated with sudden cardiac death.
SMI AND BREAST CANCER (PAPER II)

This cohort study showed that the mortality up to ten years after a breast cancer diagnosis was 60% higher for all-cause death and 38% higher for breast-cancer-specific death for women with SMI compared to women without SMI. These associations could not be explained by tumor stage or comorbidity.

Four studies have found a 1.2- to-2.9-fold higher risk of breast-cancer-specific death in women with SMI compared to women without SMI.\textsuperscript{44,46,59,60} The inconsistency of these estimates may be explained by statistical imprecision and low sample size. In addition, one study showed that the five-year relative survival after breast cancer was 74% for women with schizophrenia and 79% for women without schizophrenia.\textsuperscript{58} Our study was the first to evaluate the all-cause mortality after a breast cancer diagnosis in women with SMI. We did, however, also evaluate the risk of a breast-cancer-specific death among our cohort and found a 1.4-fold higher risk in women with SMI compared to women without SMI, which was in keeping with previous literature.

Women with SMI may have a higher mortality after a breast cancer diagnosis owing to a number of reasons. Breast cancer in women with SMI could be subject to delayed detection due to suboptimal health-seeking behavior and health-care utilization. Women with SMI might display lower breast self-examination behavior, awareness of adverse symptoms, and screening participation.\textsuperscript{55,56} These assumptions are supported by studies showing that women with SMI and breast cancer present with more advanced stages at the time of diagnosis.\textsuperscript{55,56} We showed that women with SMI were less likely to present with a localized stage of their breast cancer. Nevertheless, adjusting for tumor stage did not change our findings, which indicated that tumor stage did not explain the high risk of all-cause death after breast cancer in women with SMI.

Furthermore, women with SMI and breast cancer could experience inequalities in the provision of health-care for breast cancer\textsuperscript{55,56} or for comorbid physical conditions.\textsuperscript{20,21,23,24} On one hand, women with SMI may have reduced likelihood of accepting appropriate care for their breast cancer.\textsuperscript{56} On the other hand, some
physicians might hesitate to initiate the appropriate treatment for breast cancer due to justifiable concern: women with SMI might lack effective coping strategies or have limited social network, which could lead to difficulties managing potential side effects of treatment at home. We found that the all-cause mortality associated with SMI was higher among women with localized breast cancer than among women with breast cancer and metastasis. However, these findings could be explained by the fact that the survival in women with breast cancer and metastasis is poor, which entailed that the additional effect of SMI on mortality on a relative scale was limited among those with metastasis. Nonetheless, the higher MRR among women with potentially curable breast cancer could be explained by suboptimal health care provision or utilization in women with SMI.

Although the combination of enhanced treatment options, early intensive treatment, and mass screening has improved the survival after a breast cancer diagnosis during the last decades, it is unknown if women with SMI have benefitted from these advances in health care provision. In our study, the excess mortality tended to increase over time for localized and regional stages of breast cancer, suggesting that women with and without SMI may not have equally profited from the improvements in treatment of early stage breast cancers. However, these differences were limited, did not attain statistical significance, and could have been caused by changes in the composition of the SMI cohort over time. Therefore, these results should be verified in other studies before any inference can be reached. Still, these findings were in keeping with some literature, which has shown a widening mortality gap over time for persons with SMI compared to persons without SMI.

Persons with SMI have higher rates of several comorbid physical conditions as well as substance abuse. Besides, persons with breast cancer and comorbidity have been shown to have poorer overall survival and lower chance of receiving surgery and adjuvant therapy (e.g., chemotherapy and radiation therapy). It remains unclear if such suboptimal treatment reflects low quality of health care, physician concern about toxicity due to comorbid conditions, poor adherence, or patient discontinuation of treatment caused by intolerable
side effects. Nonetheless, such limitations in treatment options may adversely affect the mortality in women with breast cancer and comorbidity. Furthermore, poor health status in women with breast cancer may increase the risk of death from breast cancer and from other causes. As we studied all-cause death, we did not only study the effect of breast cancer on mortality, but also the contribution of comorbidity and death from causes other than breast cancer. Nevertheless, our outcome was basically unaffected by adjusting for comorbidity. However, we used the CCI as a measure of physical comorbidity, which did not include less severe cases of physical comorbidity, and additionally, comorbidity is known to be under-recognized in persons with SMI. Therefore, the importance of comorbidity could be underestimated. Finally, our results remained unchanged when we adjusted for substance abuse, which is consistent with current literature indicating that substance abuse does not play a major role for the survival after breast cancer.
This cohort study showed that the thirty-day mortality after hospitalization for infection was 52% higher for all-cause death and 161% higher for infection-specific deaths for persons with SMI compared to persons without SMI. These associations could not be explained by comorbidity or substance abuse. The excess risk of all-cause death after infection depended on the type of infection causing the hospitalization and ranged from a 27% increased risk of death after admission for sepsis to a 161% increased risk of death after admission for infections of the CNS. Depending on age, 1.7 to 2.9 more deaths were observed within 30 days after admission for infection per 100 persons with SMI compared to 100 persons without SMI.

Three studies have shown that persons with SMI compared to persons without SMI have a 3- to 7-fold higher risk of death due to pneumonia and any infection. Our study was the first to evaluate the all-cause mortality after hospitalization for infections in persons with SMI compared to persons without SMI. We did, however, also evaluate the risk of an infection-specific death among our hospitalized cohort, which was 2.6-fold higher in persons with SMI compared to persons without SMI. This result was slightly lower compared to a Nordic study, which compared persons with recent onset of psychiatric illness to persons without a psychiatric disorder and found 2- to 5-fold higher risks of an infection-related cause of death. However, these results were barely comparable, as the Nordic study included a somewhat younger cohort and additionally examined long-term outcome, whereas our study was restricted to the 30-day period after admission for infection.

Several factors may explain an excess mortality after a hospitalization for infection among persons with SMI. Persons with SMI could potentially have experienced delayed detection and treatment within the health-care system, leading to greater severity of the infections among persons with SMI. Many persons with schizophrenia have cognitive and social dysfunctions that could impede self-care and treatment compliance. Thus, persons with SMI may present with infections late in the course of disease, discharge from hospital
against medical advice, or fail to follow-up accordingly after hospitalization, all of which could lead to higher mortality. In addition, persons with SMI often experience ‘diagnostic overshadowing’ (i.e. misattribution of physical illness signs and symptoms to the mental illness), which could also lead to delayed detection of comorbidity.\(^9\) Notable, this study found a particularly high risk of 30-day mortality after admission for infections of the CNS. This could owe to delayed detection of CNS infections among persons with SMI, as clinical recognition of neurological anomalies may be challenged by pre-existing cognitive impairment, psychosis, or abnormal behavior in this group of patients.\(^4,5\)

Persons with SMI receive poorer provision of medical health care compared to persons without SMI.\(^20,21,23\) In addition, persons with SMI have an increased likelihood of being discriminated in the health care system.\(^121\) However, provision of antibiotic treatment and supportive care ought not to depend on whether a person has a history of SMI. Nonetheless, the management and treatment of infections in persons with SMI can be challenging for clinicians. Therefore, discrimination and suboptimal provision of in-hospital and follow-up care in the health-care system might play an important role for this excess mortality.\(^20,21,23,121\)

Persons with SMI have higher rates of comorbid physical conditions and substance abuse,\(^17,27\) and such comorbidities are known to be associated with poorer prognosis for persons in the general population hospitalized for infections.\(^105,122,123\) However, the risk estimate only decreased slightly after adjusting for comorbidities, suggesting that other explanations for this excess mortality exist.

SMI has been associated with increased vulnerability and familial liability for infection,\(^124\) which might lead to more serious and treatment-resistant infections,\(^124\) and thereby entail a higher risk of death after hospitalization for infections. We found that the excess mortality associated with SMI tended to remain significantly increased in the year after admission for an infection, even after adjusting for comorbidities. This indicated that persons with SMI and a previous admission for infection comprised a susceptible group with continually
high risk of premature death, independent of non-communicable comorbidities. However, we did not know if persons with SMI who had been hospitalized for an infection, in fact, were vulnerable to repeated hospitalizations for infections and subsequent premature death, because we were studying first-time hospitalizations only.
**SMI AND DEMENTIA (PAPER IV)**

This cohort study showed that the risk of dementia was more than two-fold higher in persons with schizophrenia compared to persons without schizophrenia. This risk remained 71% higher after adjusting for comorbidity and substance abuse. Before the age of 80 years, 7.4% of persons with schizophrenia and 5.8% of persons without schizophrenia developed dementia.

Four previous studies identified the total of 196 persons with schizophrenia, who developed a clinical dementia diagnosis and found relative risk estimates ranging from 2.4 to 16. It is a challenge to establish studies with sufficient follow-up time and size to allow for an adequate induction period between a diagnosis of schizophrenia and a diagnosis of dementia, as the median age of onset is 28 years for schizophrenia and 81 years for dementia. Three of the prior studies included persons with onset of schizophrenia after the age of 30 years only, entailing that the findings did not apply to the majority of persons with schizophrenia, who were diagnosed before the age of 30 years, and the fourth study was limited by a small sample size. Our study was the first to have had sufficient sample size and duration of observation time to determine the risk of dementia among persons with schizophrenia.

Numerous reasons may explain why persons with schizophrenia have high risk of developing dementia. Persons with schizophrenia have increased risk of developing several chronic conditions, which are also well-known risk factors for dementia (e.g., diabetes mellitus, IHD, CHF, AF, PVD, cerebrovascular disease, and substance abuse). The risk of dementia associated with schizophrenia decreased when we adjusted for substance abuse, which indicated that comorbid substance abuse was either an important intermediate variable or a confounder for this association. Contrarily, our results were unaffected when we adjusted for other comorbidities or for civil status. Nevertheless, the excess risk accounted for by comorbidity could be underestimated as physical comorbidity is known to be under-recognized in persons with schizophrenia. In addition, the risk estimates differed significantly when stratified for age, civil status, substance abuse, and
cerebrovascular disease, which suggested that these factors may modify the
association between schizophrenia and dementia risk.

It has been suggested that “accelerated aging” might explain part of the excess
mortality in persons with schizophrenia.\textsuperscript{35} Such hypothesis is supported by
results from a recent study, which has identified similarities between
schizophrenia and Alzheimer’s disease in patterns of macro-structural
abnormalities in magnetic resonance imaging scans of the brain.\textsuperscript{130} These
findings not only revealed a connection between the two disorders,\textsuperscript{130} but also
indicated that neurobiological as well as environmental factors could contribute
to the excess risk of dementia in persons with schizophrenia.
CHAPTER 11:

CONCLUSIONS AND IMPLICATIONS
CONCLUSIONS

Persons with SMI and diabetes had a three-to-four fold higher risk of premature death compared to persons without the two disorders, and this excess mortality could be explained by the effect of SMI, diabetes, and the interaction between the two diseases.

Women with SMI had a 60% higher risk of dying within ten years after a breast cancer diagnosis compared to women without SMI, and this excess risk could not be explained by tumor stage, comorbidity, or substance abuse.

Persons with SMI had a 52% higher risk of dying within 30 days after a hospital admission for any type of infection compared to persons without SMI, and this excess risk could not be explained by comorbidity or substance abuse.

Persons with schizophrenia had a more than two-fold higher risk of developing dementia compared to persons without schizophrenia, and this excess risk remained 71% higher even after adjusting for established risk factors of dementia, such as CVD, diabetes, and substance abuse.
Our findings indicate that the excess mortality related to diabetes, a breast cancer diagnosis, and a hospitalization for infection could partly explain why persons with SMI experience a life-expectancy gap of 15-20 years compared to persons without SMI.

Of particular interest, the design of the studies in Paper II and III possibly allowed for studying the effects of health care provision and treatment adherence on mortality in persons with SMI, as the breast cancer and the infection, respectively, had already been recognized and the health care contact established. In addition, Paper II studied the association between SMI and mortality among women with similar tumor stage of breast cancer, which also could imply studying disparities in health care provision and treatment adherence in women with SMI and breast cancer. Thus, our findings in Paper II and III suggested that inequality in health care for persons with SMI might account for, at least part of, the excess mortality.

Effective treatment options for diabetes, breast cancer, and infections are readily available: Intensive treatment of glycaemia and cardiovascular risk factors significantly reduces the risk of cardiovascular morbidity and premature death in persons with diabetes, relevant surgery and adjuvant therapies for breast cancer greatly enhance survival in breast cancer patients, and rapid initiation of appropriate antibiotic therapy is crucial for the survival in persons hospitalized for an infection. However, the health-seeking behavior and health-care-utilization in persons with SMI and comorbid physical conditions could be suboptimal. In addition, the management of diabetes requires a high degree of self-care, which may be compromised in patients with SMI. Therefore, the management and treatment of diabetes, breast cancer, and infections in persons with SMI still pose a difficult challenge for clinicians. Nevertheless, identification of higher mortality in persons with SMI and diabetes, in women with SMI after a breast cancer diagnosis and in persons with SMI after an admission for infection are all first steps to develop tailored interventions aimed at reducing the excess mortality in this group of patients.
Our results call for a collaborative care approach, which has proven effective in the treatment of depression comorbid with diabetes, and in the treatment of depression comorbid with cancers.

Further, our findings of a higher risk of dementia in persons with schizophrenia supported the hypothesis of an accelerated aging among persons with schizophrenia, as well as emphasized the need for identifying potentially modifiable factors in order to prevent dementia in persons with schizophrenia.
CHAPTER 12:

PERSPECTIVES AND FUTURE RESEARCH
The findings from our studies call for effective interventions from a coordinated and collaborating health care system to reduce the excess mortality and to prevent dementia in this high-risk population.

However, more information is warranted to determine which factors could explain the excess mortality, such as differences between persons with and without SMI in the access to or delay in diagnostics and screening, health-seeking behavior, provision of care for the physical condition (i.e., diabetes, breast cancer and infection), or adherence to treatment recommendations. In addition, more information is needed to elucidate the pathophysiology of the link between schizophrenia and dementia and to identify potentially modifiable factors, such as comorbidity or adverse health risk factors, which could explain the high risk of dementia in persons with schizophrenia.

Targeted interventions addressing the clinical challenges of managing and treating persons with SMI and comorbid diabetes, breast cancer, or infection are needed to prevent these excess deaths. Further, targeted interventions reducing dementia risk factors in persons with schizophrenia are needed to decrease the high risk of dementia. At present, clinicians should be aware of the considerably elevated mortality associated with diabetes, breast cancer, and infection as well as the elevated risk of dementia when continuously dealing with persons suffering from SMI.
CHAPTER 13:

ENGLISH SUMMARY
This PhD thesis is based on four population-based cohort studies and focuses on the significance of comorbid physical conditions on the excess mortality in persons with severe mental illness (SMI).

**Introduction**

Persons with SMI, including persons with schizophrenia and bipolar affective disorder, have a life expectancy gap of 15–20 years, most of which is explained by death due to natural causes. The underlying causal mechanisms for this excess mortality are not completely clarified, but may be associated with higher prevalence of comorbid physical diseases, poor quality of medical health care, adverse health behaviors (i.e., tobacco use, sedentary lifestyle, obesity, and unhealthy diet), antipsychotic medication, substance abuse, and suicide.

Common conditions, such as diabetes mellitus, breast cancer, and infections constitute either leading causes of death or important contributors to a reduced longevity in persons suffering from these disorders worldwide. Yet, although these conditions are known to be associated with SMI, the significance of these conditions for the excess mortality in persons with SMI remains unknown. Previous literature has focused on studying specific causes of death in persons with SMI. However, studies using information on causes of death from death certificates may be limited in determining which role comorbid physical conditions play for the excess mortality of persons with SMI.

In addition, it has been suggested that individuals with schizophrenia are subject to an “accelerated aging” that contributes to their reduced life-expectancy. This theory is rendered plausible as schizophrenia is associated with premature death due to age-related disorders, such as cancer and CVD, but also because of the existence of shared risk factors between schizophrenia and age-related disorders (e.g., low birth weight, advanced paternal age, and specific genes). Nevertheless, the literature studying the association between schizophrenia and the ultimate age-related disorder, dementia, is limited.

**Aims**

This thesis intends to shed light on the significance of common comorbid physical conditions (i.e., diabetes, breast cancer, and infection) on the excess
mortality in persons with SMI and to explore the risk of dementia in persons with schizophrenia.

Specific aims:
1) To study the long-term all-cause mortality in persons with SMI and diabetes, in persons with SMI only, and in persons with diabetes only compared to persons with neither of the two disorders.
2) To study the ten-year all-cause mortality after a breast cancer diagnosis in women with SMI compared to women without SMI.
3) To study the thirty-day all-cause mortality after a hospitalization for infection in persons with SMI compared to persons without SMI.
4) To study the long-term risk of dementia in persons with schizophrenia compared to persons without schizophrenia.

Methods
A nation-wide, population-based design was employed to the four separate papers in the thesis, using data obtained from Danish registries.

Results
1) The all-cause mortality was three-to-four-fold higher for persons with SMI and diabetes compared to persons without the two disorders. Among persons suffering from both diseases, 33% of natural deaths were attributed to diabetes, and 14% were attributed to the interaction between diabetes and SMI. The cause-specific mortality rate ratios (MRRs) ranged from a two-fold higher risk of malignant neoplasms to a 12-fold higher risk of suicide. The absolute risk of dying within seven years of the diabetes diagnosis for persons with SMI and diabetes was between 15.0% and 63.8% depending on age, compared to between 5.2% and 53.6% for persons with diabetes only in the same age categories.

2) The ten-year mortality after a breast cancer diagnosis was 60% higher for all-cause death and 38% higher for breast-cancer-specific death for women with SMI compared to women without SMI. These associations could not be explained by tumor stage, comorbidity, or substance abuse.
3) The thirty-day mortality after any infection was 52% higher for all-cause death and 161% higher for infection-specific death for persons with SMI compared to persons without SMI. These associations could not be explained by comorbidity or substance abuse. The all-cause MRRs ranged from 1.27 for persons hospitalized for sepsis to 2.61 for persons hospitalized for infections of the central nervous system. Depending on age, 1.7 to 2.9 more deaths were observed within 30 days after an infection per 100 persons with SMI compared to 100 persons without SMI.

4) The risk of dementia was more than two-fold higher in persons with schizophrenia compared to persons without schizophrenia. This risk remained 71% higher after adjusting for comorbidity and substance abuse. The absolute risk of dementia by the age of 65 years was 1.8% for persons with schizophrenia compared to 0.6% for persons without schizophrenia, whereas the corresponding absolute risks by the age of 80 years were 7.4% and 5.8%, respectively.

**Conclusions and perspectives**

Common, physical conditions, such as diabetes, breast cancer, and infections may explain some of the excess mortality in persons with SMI. In addition, persons with schizophrenia are at high risk for the ultimate age-related disorder, dementia.

As diabetes, breast cancer, and infections are common conditions with available treatments; some of these excess deaths may be potentially preventable.

Future research should identify steps on the pathway between SMI comorbid with physical conditions and death, which may account for this excess mortality, such as physician delay, patient delay, under-diagnosis, or under-treatment. In addition, future research should identify steps on the pathway between schizophrenia and dementia, which may account for this excess risk of dementia, such as comorbidity or adverse health risk factors. The identification of such potentially modifiable factors is urgently needed to design individualized and targeted interventions aimed at preventing some of the
excess deaths and reducing the inequality in outcome for persons with SMI, and additionally preventing dementia in persons with schizophrenia.
CHAPTER 14:

DANSK RESUME
Denne ph.d.-afhandling fokuserer på betydningen af komorbide fysiske lidelser for overdødeligheden blandt personer med svære psykiatriske lidelser. Afhandlingen er baseret på fire populationsbaserede kohortestudier, som hver er præsenteret i en videnskabelig artikel.

**Baggrund**

Det er velkendt, at personer med svære psykiatriske lidelser (skizofreni og bipolare affektiv lidelse) har en 15-20 år kortere forventet levetid end baggrundsbefolkningen. Hovedparten af disse dødsfald kan tilskrives naturlige årsager, men de bagvedliggende årsagssammenhænge er ikke klargjort. Meget tyder dog på, at denne overdødelighed er forbundet med en høj forekomst af samtidige fysiske lidelser, underbehandling, livsstil (f.eks. rygning, overvægt og usund kost), alkohol- og stofmisbrug, brug af antipsykotisk medicin og øget risiko for selvmord.

På verdensplan bidrager hyppige lidelser som diabetes, brystkræft og infektioner væsentligt til en kortere forventet levetid hos de personer, der rammes af dem. Selvom disse tilstande optræder hyppigere hos personer med svære psykiatriske lidelser, er det ikke undersøgt, hvad disse lidelser har af betydning for overdødeligheden i denne gruppe. Den eksisterende videnskabelige litteratur på området fokuserer primært på dødsårsagerne og er baseret på oplysninger om dødsårsager i dødsattester. Denne information kan dog ikke nødvendigvis afklare, hvilken rolle komorbide fysiske lidelser spiller for overdødeligheden hos personer med svære psykiatriske lidelser.

Formål
Denne afhandling har til formål at belyse betydningen af tre hyppigt forekommende komorbide fysiske tilstande (diabetes, brystkræft og infektion) for overdødeligheden hos personer med svære psykiatriske lidelser og at bestemme risikoen for udvikling af demens hos personer med skizofreni.

Specifikke formål:
1) At studere den totale dødelighed hos personer med svære psykiatriske lidelser og diabetes, hos personer alene med diabetes og hos personer alene med svære psykiatriske lidelser sammenlignet med personer uden disse to sygdomme.
2) At studere den totale 10-års dødelighed efter en brystkræftdiagnose hos kvinder med brystkræft og svære psykiatriske lidelser sammenlignet med kvinder med brystkræft men uden svære psykiatriske lidelser.
3) At studere den totale 30-dages dødelighed efter indlæggelse for infektion hos personer med svære psykiatriske lidelser sammenlignet med personer uden svære psykiatriske lidelser.
4) At studere risikoen for udvikling af demens hos personer med skizofreni sammenlignet med personer uden skizofreni.

Metode
Et nationalt populationsbaseret design blev anvendt i de fire separate studier, som udgør kernen i afhandlingen. Data blev udtrukket fra nationale danske sundhedsregistre.

Resultater
1) Personer med svære psykiatriske lidelser og diabetes havde en 3-4 gange større risiko for tidlig død end baggrundsbefolkningen. Af alle naturlige dødsfald kunne 33 % tilskrives diabetes, mens 14 % kunne tilskrives interaktionen mellem svær psykiatrisk sygdom og diabetes. Blandt personer med svære psykiatriske lidelser og diabetes spændte mortalitetsrateratioerne for årsagsspecifik død fra en fordoblet risiko for at dø af kræft til en 12 gange større
risiko for selvmord. I løbet af de første syv år efter en diabetesdiagnose døde 15-64 % af personerne med samtidige svære psykiatriske lidelser, mens det kun gjaldt for 5-54 % af personerne med diabetes alene i de samme alderskategorier.

2) Tiårs dødeligheden efter en brystkræftdiagnose var 60 % større for totaldød og 38 % større for dødsfald grundet brystkræft for kvinder med svære psykiatriske lidelser sammenlignet med kvinder uden svære psykiatriske lidelser. Disse associationer kunne ikke forklares med forskelle i tumorstadium, komorbiditet eller alkohol- og stofmisbrug.

3) Tredivedages dødeligheden efter indlæggelse for en infektion var 52 % større for totaldød og 161 % større for dødsfald grundet infektioner for personer med svære psykiatriske lidelser sammenlignet med personer uden svære psykiatriske lidelser. Disse associationer kunne ikke forklares med forskelle i komorbiditet eller alkohol- og stofmisbrug. Mortalitetsrateratioerne for totaldød inden for 30 dage efter hospitalsindlæggelse spændte fra en 27 % større risiko blandt personer indlagt for sepsis til en 161 % større risiko blandt personer indlagt for infektioner i centralnervesystemet. Inden for 30 dage efter indlæggelse for infektion sås 1,7-2,9 flere dødsfald (afhængig af alder) blandt 100 personer med svære psykiatriske lidelser sammenlignet med 100 personer uden.

4) Risikoen for demens var over dobbelt så stor blandt personer med skizofreni sammenlignet med personer uden skizofreni. Denne risiko var fortsat 71 % større, selv efter justering for komorbiditet og alkohol- og stofmisbrug. I alt havde 1,8 % af personerne med skizofreni i en alder af 65 år udviklet demens og blot 0,6 % af personerne uden skizofreni. De tilsvarende tal var henholdsvis 7,4 % og 5,8 % i en alder af 80 år.

Konklusion og perspektivering
Denne ph.d.-afhandling viser, at hyppige fysiske lidelser som diabetes, brystkræft og infektioner kan være vigtige medvirkende forklaringer på, hvorfor personer med svære psykiatriske lidelser generelt dør 15-20 år før baggrundsbefolkningen.

Personer med svære psykiatriske lidelser har en markant øget risiko for tidlig død ved samtidig forekomst af diabetes, en markant øget risiko for at dø inden
for 10 år efter en brystkæftediagnose og en markant øget risiko for at dø inden for 30 dage efter en hospitalsindlæggelse for infektion. Derudover har personer med skizofreni en høj risiko for at udvikle demens.

Nogle af disse dødsfald vil sandsynligvis kunne forebygges, da der findes effektive behandlingsmuligheder for diabetes, brystkæft og infektioner.

Fremtidig forskning bør fokusere på at afdække, hvilke faktorer i processen fra svære psykiatriske sygdomme med komorbide fysiske sygdomme til død, der påvirker denne overdødelighed. Det kunne for eksempel være diagnoseforsinkelser (“patient-forsinkelser” eller ”læge-forsinkelser”), underdiagnosticering eller underbehandling. Fremtidige studier bør også afdække, hvilke faktorer i processen fra skizofreni til demens, der påvirker denne risiko, såsom komorbiditet eller uhensigtsmæssig livsstil. En sådan identifikation af potentielt forebyggelige faktorer er bydende nødvendig for at kunne designe individualiserede behandlingstilbud, som er målrettet personer med svære psykiatriske lidelser, så vi fremover kan hindre disse unødige dødsfald, nedbringe den høje dødelighed og forebygge udvikling af demens hos personer med skizofreni.
The significance of comorbid physical conditions on the excess mortality of persons with severe mental illness

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The significance of comorbid physical conditions on the excess mortality of persons with severe mental illness


