UiT
THE ARCTIC UNIVERSITY OF NORWAY

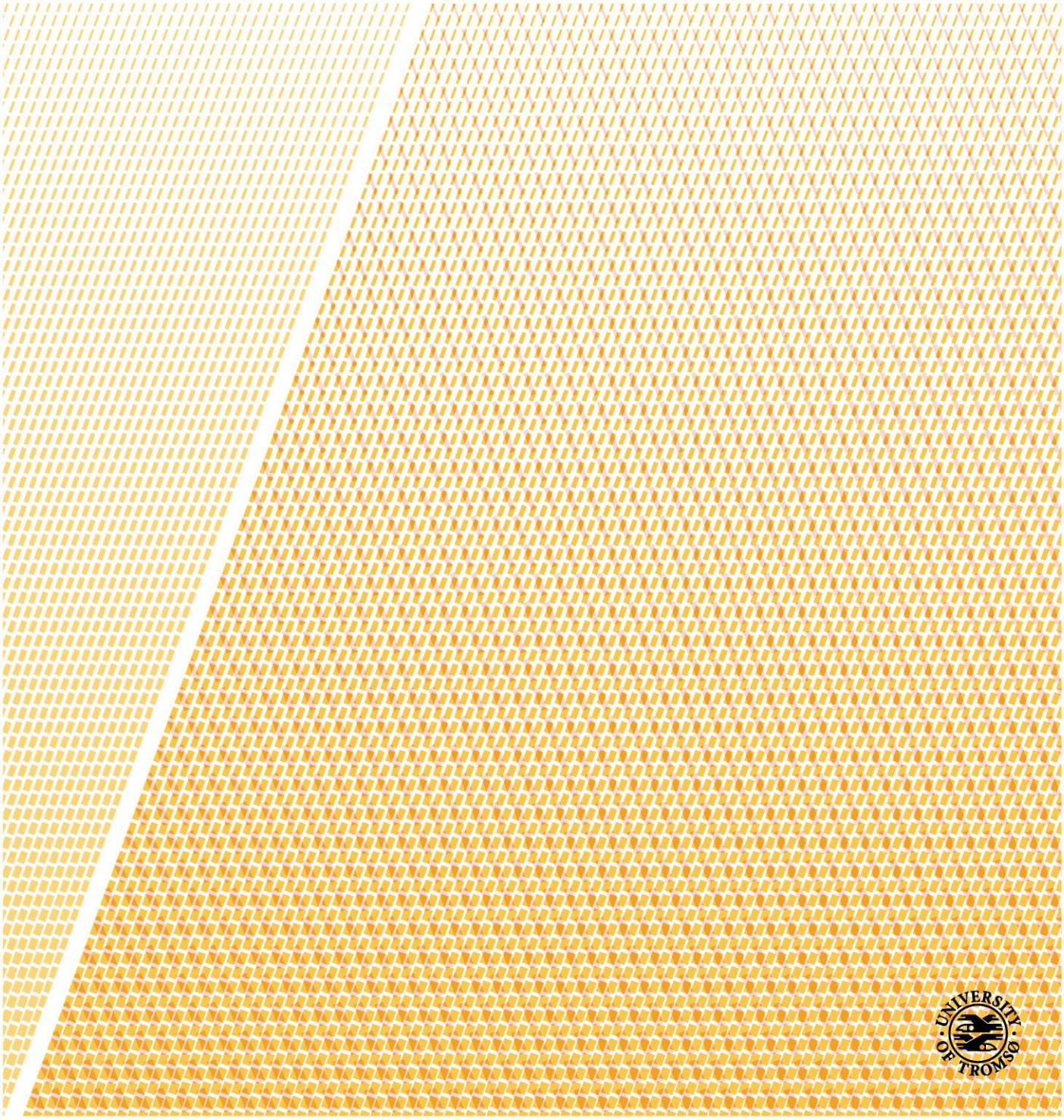
Faculty of Health Sciences
Department of Clinical Medicine

Mortality, substance use disorder and cardiovascular health care in persons with severe mental illness

—

Ina H. Heiberg

A dissertation for the degree of Philosophiae Doctor – June 2019



Acknowledgements

For many years, I thought that doing a PhD was synonymous with frustration and regret. Instead I found myself situated with a dream team of wise, knowledgeable, encouraging and genuinely kind-hearted supervisors. In particular I would like to thank my main supervisor, Anne Høye, who invited me into a, for me, new and exciting area of research, shared her clinical knowledge and vast network, and provided me with excellent academic support, guidance and encouragement throughout this project. Thank you, Anne, for all this, and for taking the hard work of acquiring permissions, funding and data.

My warmest thanks also to my co-supervisor, Bjarne K. Jacobsen, for always having the time, preventing many of my mistakes, and generously sharing your high class know-how on methods and writing, as well as good stories and quotes! The warmest thanks also go to my other co-supervisor, Ragnar Nesvåg. Your firm, thorough and excellent academic supervision has been invaluable for my work on this thesis. Together, the three of you have made my doctoral period a pleasure!

I was also lucky to have first-class co-authors in the former Psyk-Link group at the Norwegian Institute of Public Health. Jørgen G. Bramness, Øyvind Næss, Eivind Ystrøm, Christina M. Hultman and Ted Reichborn-Kjennerud all shared their extensive expert knowledge in medicine, epidemiology and writing, and gave constructive and inspiring comments and advice. Furthermore, I would like to express my greatest thanks to Gro R. Berntsen, Trine Magnus and Barthold Vonen as former and current leaders of SKDE for giving me the opportunity, support and facilities to conduct this work. I also would like to thank all my dedicated and interesting colleagues at SKDE for providing a stimulating and fun work environment. A special thanks to Lise Balteskard, who gave me basic insights into the world of medicine and medical coding, and also contributed with discussions, co-authorship and support. Thanks also to Frank, Bård, Heidi, Janice, Marianne and Vibeke for helping me with practicalities and advice along the way.

This Ph.D. project was funded by unrestricted grants from by The Northern Norway Regional Health Authority, which also kindly extended the scholarship period when problems with

erroneous data deliveries delayed the progress. Epinor has offered excellent statistical courses and a great summer school experience, and deserves an applause.

I am also grateful for the critical feedback I received from external referees, which advice and constructive criticism greatly improved my work. I also would like to thank the members of my doctoral thesis committee. I really appreciate that you are willing to spend time reading my work!

Finally, I want to thank my friends for not giving up on me, and my extended family for always being there for me. A special thanks to my sister Guri for discussions, advice and shared PhD courses along the way. Very warm thanks also to my beloved children Birk, Brage, Brynjar and Bjørk for love, fun and distractions, and Eirik for all that and everything else. Voluntary proofreading this thesis must be the ultimate declaration of love?

CONTENTS

List of Tables

List of Figures

Summary

In the Nordic countries, people with severe mental illness die 15-20 years younger than others. Substance use and higher level of undiagnosed/untreated somatic diseases contribute to this disparity. We aimed to investigate; (i) mortality among people with schizophrenia and/or substance use disorder, with emphasis on the impact of a dual diagnosis; whether people with schizophrenia or bipolar disorder had (ii) higher odds of not being diagnosed with cardiovascular disease prior to cardiovascular death, and; (iii) equal prevalence of diagnostic testing and treatment of cardiovascular disease prior to cardiovascular death, compared to people without such disorders who died due to cardiovascular disease.

We used nationwide registries to calculate standardized mortality ratios in a 7-year open cohort study including 125,744 residents of Norway aged 20-79 with schizophrenia and/or substance use disorders diagnosed in specialized care (i). We applied multivariate logistic (ii) and log-binomial regression (iii) to study undiagnosed cardiovascular disease and uptake of cardiovascular health care services prior to cardiovascular death among approximately 72,400 residents aged 18 and above with and without schizophrenia or bipolar disorder diagnosed in primary or specialized health care in Norway.

We found a four-fold (schizophrenia only) to seven-fold (substance use disorder with or without schizophrenia) increased mortality compared to the general population, with the highest excess mortality observed for poisoning, suicides and respiratory diseases. The excess mortality implicated that five out of six persons with schizophrenia and/or substance use disorder died prematurely. Despite many health care contacts, people with schizophrenia and women with bipolar disorder were more likely to die from undiagnosed cardiovascular disease. People with schizophrenia or bipolar disorder also had lower prevalence of specialized cardiovascular examinations and invasive treatment prior to cardiovascular death, compared to individuals without such disorders. We found, however, no difference in uptake of invasive treatment in those diagnosed with cardiovascular disease prior to death.

The large and persistent mortality gap between people with severe mental illness and the general population highlights the need of securing proper access to specialized somatic care, and a more effective prevention of deaths from unnatural causes in this group. Our findings suggest that underdiagnosis and underutilization of specialized cardiovascular examinations are among the main obstacles to achieve more equal access to cardiovascular health care among those with severe mental illness.

Sammendrag

I Norden dør personer med alvorlige psykiske lidelser 15-20 år yngre enn andre. Ruslidelser og udiagnostisert/ubehandlet somatisk sykdom bidrar til denne ulikheten. Formålet i denne studien var å undersøke; (i) dødelighet blant personer med schizofreni og/eller ruslidelse, med særlig vekt på betydningen av en dobbeltdiagnose; (ii) om personer med schizofreni eller bipolar lidelse hadde høyere odds for ikke å bli diagnostisert med kardiovaskulær sykdom før kardiovaskulær død, og (iii) om personer med schizofreni eller bipolar lidelse hadde samme forekomst av diagnostisk testing og invasiv behandling av kardiovaskulær sykdom før kardiovaskulær død sammenlignet med personer uten slike lidelser.

Vi brukte landsdekkende registre til å beregne standardiserte mortalitetsratioer i en 7-årig åpen kohortstudie, som inkluderte 125 744 innbyggere i alderen 20-79 år med schizofreni og/eller ruslidelse diagnostisert i norsk spesialisthelsetjeneste. Vi benyttet multivariat logistisk (ii) og log-binomisk regresjon (iii) for å studere udiagnostisert kardiovaskulær sykdom og bruk av hjerte-/karrelaterte helsetjenester forut for kardiovaskulær død blant circa 72 400 innbyggere i alderen 18 og over med og uten schizofreni eller bipolar lidelse diagnostisert i primær- eller spesialisthelsetjenesten i Norge.

Dødeligheten var firedoblet blant personer med schizofreni (uten samtidig ruslidelse) og syv ganger høyere blant personer med ruslidelser (med eller uten schizofreni) sammenlignet med den generelle befolkningen, med særlig høy risiko knyttet til forgiftninger, selvmord og respirasjonssykdommer. Overdødeligheten innebar at fem av seks personer med schizofreni og/eller ruslidelse døde prematurt. Vi fant også at personer med schizofreni og kvinner med bipolar lidelse hadde høyere odds for å dø av udiagnostisert kardiovaskulær sykdom. Personer med schizofreni eller bipolar lidelse hadde også lavere forekomst av spesialiserte kardiovaskulære undersøkelser og invasiv kardiovaskulær behandling sammenlignet med personer uten slike lidelser. Vi fant ingen forskjell i tilgang til invasiv behandling blant de som ble diagnostisert med kardiovaskulær sykdom før de døde.

Det store gapet i forventet levealder mellom personer med alvorlige psykiske lidelser og den generelle befolkningen understreker behovet for bedret tilgang til spesialisert somatisk diagnostikk og behandling, og en mer effektiv forebygging av unaturlige dødsfall i denne gruppen. Våre funn tyder på at underdiagnostikk og underutnyttelse av spesialisert diagnostikk er viktige hindre for å oppnå likere tilgang til kardiovaskulær behandling for personer med alvorlige psykiske lidelser.

List of papers

This thesis is based on the following papers, which are hereafter referred to as paper I, paper II and paper III:

I Heiberg, I. H., Jacobsen, B. K., Nesvåg, R., Bramness, J. G., Reichborn-Kjennerud, T., Næss, Ø., Ystrom, E., Hultman, C. M. and Høye, A., *Total and cause-specific standardized mortality ratios in patients with schizophrenia and/or substance use disorder*. PLoS One, 2018. **13**(8): p. e0202028.

II Heiberg, I. H., Jacobsen, B. K., Balteskard, L., Bramness, J. G., Næss, Ø., Ystrom, E., Reichborn-Kjennerud, T., Hultman, C. M., Nesvåg, R. and Høye, A., *Undiagnosed cardiovascular disease prior to cardiovascular death in individuals with severe mental illness.* Acta Psychiatr Scand, 2019. **139**(6): p. 558-571.

III Heiberg, I.H., Nesvåg, R., Balteskard, L., Bramness, J. G., Hultman, C. M., Næss, Ø., Reichborn-Kjennerud, T., Ystrom, E., Jacobsen, B. K., Høye, A., *Diagnostic tests and treatment procedures prior to cardiovascular death in individuals with severe mental illness* (submitted).

Abbrevations

AUD	Alcohol use disorder
BD	Bipolar disorder
CABG	Coronary artery bypass graft
CDR	The Cause of Death Registry
CHF	Congestive heart failure
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CUD	Cannabis use disorder
CVD	Cardiovascular disease
DAG	Directed acyclic graph
DUD	Drug use disorder
ECG	Electrocardiography
FEP	First episode psychosis
GP	General practitioner
HbA1c	Glycated hemoglobin
HR	Hazard ratio
ICD-10	The International Statistical Classification of Diseases and Related Health Problems, 10th revision
ICPC-2	The International Classification of Primary Care, 2nd version
IHD	Ischemic heart disease
KUHR	The Norwegian Directorate of Health's system for control and payment of health reimbursements in primary care [Kontroll og utbetaling av helserefusjoner]
MI	Myocardial infarction
NCMP	Norwegian Classification of Medical Procedures
NCRP	Norwegian Classification of Radiological Procedures
NCSP	NOMESKO Classification of Surgical Procedures
NPR	The Norwegian Patient Registry
NSTEMI	Non ST elevation myocardial infarction
OR	Odds ratio
OUD	Opioid use disorder
PCI	Percutaneous coronary intervention
RR	Relative risk
SCZ	Schizophrenia/schizophrenia spectrum disorder
SD	Standard deviation
SES	Socioeconomic status
SMI	Severe mental illness
SMR	Standardized mortality ratio
STEMI	ST elevation myocardial infarction
SUD	Substance use disorder

1 Introduction

In the Nordic countries, people with severe mental illness (SMI) die 15-20 years younger [1, 2], and people with substance use disorder (SUD) 24-28 years younger [1, 3] than people without such conditions. Although the risk of death from external causes of death such as suicides, poisoning and accidents is highly increased in people with SMI, most life years lost is due to premature deaths from potentially modifiable somatic causes such as cardiovascular disease (CVD) [4]. The Norwegian health minister recently referred to this gap in life expectancy as "*one of the biggest and ugliest differences we have in our country*" [5]. As a possible explanation for this inequity, the minister argued that ".. *often* [] *somatic diseases and lifestyle challenges are not seen or captured*". Besides pinpointing a major social injustice and public health challenge, these statements also provide a good summary of the topics of this thesis, which aims were to investigate mortality among patients with SCZ and/or SUD in nationwide Norwegian data, especially the effect of concomitant SUD among those with schizophrenia (SCZ)), and to examine the impact of SMI on underdiagnosis and under-treatment of CVD prior to cardiovascular death (see section 1.7, page 43 for detailed aims). All these topics seem to be understudied.

Further motivation for this thesis was that there had not been published nationwide studies of mortality among persons with SCZ in Norway since the 1970s [6]. Also, accumulating evidence suggested both increasing rates of concurrent SUD among persons with SMI [7], and a possible rising mortality gap between persons with and without SMI [8-18].

The WHO's multilevel model of risk for excess mortality in persons with SMI, reproduced in Table 1, summarizes the many factors likely involved in the pathway leading to excess mortality among people with SMI, and offers as such a central framework for the current thesis. Paper I-III examined a few of these potential explanations for excess mortality at the individual and provider level (in red letters in Table 1), specifically the effect of SUD (paper I), and health care seeking and provision (paper II and III) among persons with SMI.

Disease- and patients-specific characteristics are of great importance in understanding health care seeking and provision, as well as increased mortality. A brief description of the four patient groups included in this study (i.e. SCZ, bipolar disorder (BD), SUD and CVD) is therefore presented in the next sections.

Table 1 - The World Health Organization's multilevel model of risk for excess mortality in persons with severe mental illness

INDIVIDUAL FACTORS	HEALTH SYSTEMS	SOCIAL DETERMINANTS OF HEALTH
Disorder-specific • Severity of disorder • Family history • Symptoms/pathophysiology • Early age of onset • Recency of diagnosis • Stigma Behavior-specific • Tobacco use • Poor diet • Inadequate physical activity • Sexual and other risk behaviors • Substance use (alcohol and drugs) • Low motivation (e.g., treatment seeking, adherence)	Leadership • Absence of relevant policies and guidelines Financing • Low investment in quality care Information • Limited health information systems Service delivery • Verticalization and fragmentation of health services • Lack of care coordination and management • Limited access to services Human resources • Poor quality service provision • Negative beliefs/attitudes of workforce • Poor communication Medications • Antipsychotic medications (no treatment, polypharmacy, higher than recommended dosages)	Public policies • Discriminating policies • Low financial protection and limited coverage in health packages Socio-economic position • Unemployment • Homelessness • Low health literacy Culture and societal values • Stigma and discrimination in society • Negative perceptions about persons with SMI Environmental vulnerabilities • Infections, malnutrition • Access to means of suicide • Impoverished or unsafe neighborhoods Social support • Limited family, social and community resources

Source: https://www.who.int/mental_health/evidence/excess_mortality_meeting_report.pdf

1.1 Severe mental illness

Mental illnesses involve abnormal changes in emotions, thinking or behavior. Mental and addictive disorders affect a significant portion of the population and were among the top leading causes of disability in 2017 [19, 20], with increasing prevalence the past decades [21]. Definitions of *severe* mental illness (SMI) differ across authors, but share a common feature in trying to capture mental disorders characterized by long duration and significant disability. Some apply a narrow definition of nonorganic psychosis (i.e. SCZ or BD), some include SCZ, BD and moderate to severe depression (e.g. The World Health Organization (WHO)), some also include diagnoses such as organic mental disorder, severe anxiety disorders, severe eating disorders and severe panic disorder, while others apply criteria such as severity, duration and dysfunction [22]. We defined SMI in a narrow sense of the term, i.e. as any diagnosis of either narrow SCZ (code F20 in the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) or code P72 in the International Classification of Primary Care 2nd Edition (ICPC-2)) or BD (ICD-10 codes F30-F31/ICPC-2 code P73).

1.1.1 Schizophrenia spectrum disorder

SCZ involves fundamental and characteristic changes of perception, cognition, emotion and behavior, affecting cognitive abilities [23], psychosocial functioning, work ability and every-day life. Common symptoms include hallucinations and delusions, agitation, disturbed behavior (so called positive symptoms), social withdrawal, affect flattening, lack of motivation, attention deficit and stereotyped behavior (so called negative symptoms). While positive symptoms usually vary over time, negative symptoms often persist in all stages of the disease. SCZ was ranked as the 11th most disabling condition globally in 2013 [20].

The term schizophrenia *spectrum* disorder reflects that SCZ, rather than one distinct unitary disorder, is a group of related disorders that share some symptoms and underlying causal mechanisms. For the sake of simplicity, we have used the abbreviation SCZ both to describe schizophrenia spectrum disorders (ICD-10 codes F20-F29, paper I), and narrow schizophrenia (ICD-10 code F20/ICPC-2 code P72, paper II and III).

1.1.1.1 Risk factors for SCZ

SCZ is believed to result from an interplay between genes [24, 25] and a range of environmental and behavioral factors. Many genes are probably involved, with each gene only contributing small effects to the overall susceptibility. Estimates of heritability varies from 31% [26] to nearly 80% [27]. The non-genetic risk factors with the highest quality evidence, reporting medium effect sizes, are advanced paternal age, obstetric and perinatal complications, and cannabis use [28-30]. Other environmental risk factors for SCZ, with small effect sizes, include childhood adversities [31], living in urbanized communities [32] and a personal or family history of migration [33, 34].

1.1.1.2 Incidence and prevalence

SCZ-spectrum is a relatively rare condition, with a median incidence of 15-18 per 100,000 person-year [35-37], and a median lifetime prevalence of 0.4-0.7% [37-39], with varying incidence across places and population groups [37]. In Norway, the one-year prevalence of SCZ in specialized treatment is estimated to be 0.17% [40], and the five-year prevalence in persons aged 24 to 63 years estimated to be 0.34% [41].

Onset of disease, defined as the first psychotic episode, typically occurs in late adolescence or young adulthood [35]. About one in four receive the diagnosis after age 40 [42]. Incidence rates are higher in men up to age 39, and higher in women from 50 years and above [35]. Meta-analyses report a slightly higher lifetime morbidity risk in men, compared to women [35, 43].

1.1.1.3 Treatment of SCZ

Most people with SCZ receive pharmacological treatment with second-generation antipsychotic agents, which offer symptom relief but no cure. Treatment efforts therefore focus on early diagnosis, rapid treatment of acute psychiatric episodes, reintegration into society and prevention of new acute psychiatric events and complications [44]. The national guidelines for the treatment of psychosis in Norway recommend antipsychotic medication as the first-line treatment both in acute psychosis and in the prevention of relapse. About 20-30% of patients do not have a positive treatment response using newer antipsychotic drugs in adequate doses, and many also discontinue their antipsychotic medication due to side effects [45].

Supplementary psychosocial interventions can help ameliorate symptoms, improve functioning and patient satisfaction, and prevent relapse [44]. In a recent review, assertive community treatment, cognitive behavioral therapy, family interventions, psycho-education, social skills training, supported employment, and early interventions for first episode psychosis, were all found to improve various functional outcomes compared to usual care [46]. Hospitalization, sometimes involuntary, may also be required in situations involving risk of harm to oneself or others.

1.1.1.4 Prognosis

The clinical course of SCZ is heterogeneous, but for most patients the disease is chronic with periodic exacerbations and hospitalizations. Estimates of recurrence varies considerably, depending on time span studied and definitions used. A recent review found that most patients (57%) had a chronic course and that 39% had episodic relapses [47]. Another review found that approximately 1 in 7 could be expected to recover over 10 years [48], while a review of outcome in the long run (follow-up period 5-20 years), found symptomatic remission in 16% of never-treated patients and 38% in patients treated with antipsychotics [49].

Early diagnosis, intensive treatment of the first psychotic episode, as well as access to continued psychosocial treatment and support in the following years are associated with better outcomes [49]. Men tend to have more negative symptoms and a more severe disease course than women [50], and people with early onset of the disease often have worse functioning and more cognitive impairment than those with a later onset [51]. A concurrent diagnosis of SUD is associated with particular poor prognosis (see section 1.3.1, page 22). Many persons with SCZ also have additional mental health disorders such as depressive disorder [52], personality disorder [53], anxiety disorder [54, 55] or dementia [56], and also substantial physical comorbidity (see section 1.3, page 22).

1.1.2 Bipolar disorder

BD describes a group of affective disorders characterized by episodes of depression and abnormal mood elevation (mania or hypomania), separated by periods of normal mood. Manic episodes are typically associated with elevated or irritable mood, overactivity, grandiose self-esteem and decreased need for sleep. The clinical manifestations differ, from severe forms of mania or depression, accompanied by psychosis (bipolar I), via mild

hypomania or mild depression, but no manic episodes (bipolar II), to cyclothymic disorder (hypomanic and depressive symptoms that do not meet the criteria for depressive episodes). Rapid cycling is a particularly disabling form of BD, characterized by four or more episodes within a year [57]. Since a diagnosis of BD requires a manic or hypomanic episode and there is no objective biomarker, many patients with BD are initially diagnosed with severe depression. The average delay in diagnosis is reported to be 8-10 years after the onset of symptoms, with a longer delay in women [58].Women have a higher frequency of depression, a later onset, more seasonal variations in mood disturbance, and increased susceptibility to relapse, and are more often diagnosed with BD II disorder than men [59].

Persons with BD are generally less impaired, cognitively, clinically and socially than persons with SCZ. Still, BD is a severe illness due to its early onset, chronicity and high suicide rates, and was ranked among the 20 most disabling conditions globally in 2013 [60].

1.1.2.1 Risk factors for BD

As for SCZ, the causes of BD are multifactorial, including both genetic, psychosocial and environmental contributors. Susceptibility to BD is most likely influenced by many genetic risk factors with individually small effects [61]. Heritability is estimated to be around 70% [62], and life time risk for BD in first-degree relatives is estimated to be 5–10%, seven times higher than the general population [63]. Family studies and genome-wide studies show strong evidence for shared genetic risk factors for BD and SCZ [64, 65], with a considerable crossover between the two disorders. Numerous environmental risk factors have been identified as potential risk factors for BD, but the effect sizes are often small and most are not specific to BD but associated with SMI in general. Among these, early life stressors, cannabis abuse, certain infectious diseases and inflammation, seem to be supported by the strongest evidence [66-69].

1.1.2.2 Incidence and prevalence

Like SCZ, BD is a relatively rare disease, with an incidence of 28 per 100,000 per person-years [70] and a lifetime prevalence of 1-2% [60, 71, 72], with marked variation between geographic areas [72], but no differences according to sex [57]. Lifetime worldwide prevalence is slightly higher for BD I, compared to BD II [72]. Five-year prevalence of treated BD in persons 24-63 years old is estimated to be 0.58% in Norway [41]. In a

Norwegian study, 75% of incident BD cases were diagnosed in late adolescence or young adulthood, with 23 years as the mean age of onset [73].

1.1.2.3 Treatment of BD

Treatment of BD usually include a combination of pharmacotherapy and psychotherapy. Due to high risk of suicide and relapse [74], a prolonged prophylactic pharmacological treatment is often initiated, typically with a mood stabilizer (lithium or an anticonvulsant) as the first choice. Antipsychotics, antidepressants and electrostimulation are also used in the management of psychotic symptoms and depression. Non-adherence to medication is common in BD [75], partly due to side effects such as weight gain and cognitive consequences.

1.1.2.4 Prognosis

For most people with BD, a chronic course is the rule, characterized by periods of partial or full recovery between recurrent episodes of relapse [74]. Prospective studies investigating the long-term symptomatic status of treated BD over a mean 13 year follow-up, found that persons with BD were symptomatically ill approximately half the time, with depression as the dominating symptom in both BD I and II [76, 77]. Early recognition and intervention may improve prognosis, as the symptoms in earlier stages often are less severe and more responsive to treatment [78]. Early onset, rapid cycling, psychotic features and longer duration of affective episodes are associated with worse outcomes [57]. Depression and persistent cognitive impairment are also strongly correlated with functional impairment [79]. A high degree of somatic (see section 1.3.2, page 23) and psychiatric comorbidity [80] is often observed in patients with BD, and also very high (8%-19%) suicide rates [81].

1.1.3 Substance use disorder

SUD describes harmful or hazardous use of alcohol or other psychoactive substances, typically with an impact on mental and physical health, ability to work, participation in society, financial security and interpersonal relationships. In ICD-10, a diagnosis of SUD is justified if three or more of the following criteria are met within one year: (i) a strong desire to take the substance, (ii) impaired capacity to control the substance consumption, (iii) abstinence symptoms when intake of substances is reduced, (iv) increased tolerance to the effect of the substance, (v) preoccupations with substance use, other activities are reduced

because of substance use, and (vi) despite harmful consequences the substance use continues. Both harmful use and dependence syndrome are included in this definition. The substances may be legal (e.g. alcohol and tobacco), illegal (e.g. heroin, amphetamine, cocaine and cannabis) or licensed for medical purposes (e.g. sedatives).

1.1.3.1 Risk factors for SUD

Like SCZ and BD, a complex interplay between genetic [82, 83] and psychosocial factors [84] is involved in the development of SUD. Also, the availability of substances, as well as how addictive the drug is, is important in the development of SUD. Environmental factors unique to the individual play an significant role in exposure and initial use of substances, while genetic factors have a major influence on the progression of substance use to dependence [85]. Male sex [86], young age [86], having other mental problems, a family history of SUD [87, 88], as well as adverse family conditions [84], are all known risk factors for SUD. Early adolescent substance use substantially increases the risk of lifelong SUD [88, 89].

1.1.3.2 Incidence and prevalence

SUD is one of the most prevalent mental disorders in Norway. Globally, SUDs account for 11% of total health burden [90]. In high-income countries such as Norway, alcohol use disorder and illegal drug use disorders contribute equally to the burden of disease [91].

The incidence of SUD is highest in men and the youngest [92], with adolescence as the key period for development of SUD [85]. Estimates of SUD incidence and prevalence are somewhat uncertain, as the majority of individuals with SUD receive no treatment for their disorder, and reliable statistics for illegal use are difficult to achieve. A review of European studies found the prevalence of SUD to be more than 4% within the last year [93]. In Norway, the 1-year incidence of harmful use or dependence on alcohol estimated to be about 8% for men and 3% for women, based on surveys in the mid-90s [86, 94]. Cannabis is the most widely used illegal drug in Norway. In 2018, about 5 percent of Norwegians aged 16-64 reported using cannabis in the last 12 months [95], while approximately 20% stated that they had used cannabis one or more times during their lives [96]. The use of illicit drugs is concentrated among young adults and is highest among men, with high-risk drug use mainly related to injection of amphetamine and opioids [97]. It is estimated that around 9,000 people

inject illegal drugs in Norway. This number has stabilized since 2012, following a decline in 2008-12. Surveys show that the use of illicit drugs in Norway is somewhat lower than in most other European countries, with the exception of amphetamine. The consequence of illegal drug use in Norway are nevertheless serious, due to high rates of fatal overdoses [98].

1.1.3.3 Treatment of SUD

The multidimensional nature of SUD is reflected in diversified approaches to target the many treatment needs in this group. Treatment of SUD includes assessment, detoxification, stabilization, short- and long-term residential treatments and medication assisted treatment. The Norwegian national guidelines emphasize a client-oriented approach, early intervention, diversification of services and reintegration. This includes various psychological interventions (e.g. cognitive behavioral therapy, motivational interview and mindfulness), social interventions (e.g. involvement of family and network, issues related to adequate housing, predictable economy and job training), and medical interventions (e.g. substitution therapy for opioids and medication for severe alcohol dependence) [99]. Often long-term interdisciplinary interventions are needed to addresses the psychiatric, medical, legal and social implications of addiction.

In 2016, approximately 18,000 Norwegians were treated in specialized SUD treatment facilities, most of whom were outpatients [97]. The largest group had opioid dependency as their primary diagnosis, followed by those who received treatment for cannabis use disorder and poly-drug use. A meta-analysis of psychosocial treatments for illicit drugs showed moderate effect sizes, with the most efficacious interventions for cannabis use disorder and the least efficacious interventions for poly-substance use. Overall, one third achieved clinically significant abstinence, compared to 13% among controls [100]. Younger samples had larger treatment effect sizes, but higher drop-out rates [100].

1.1.3.4 Prognosis

SUD has a heterogeneous, but often chronic course with varying intensity over time, and a tendency to relapse after remission [101]. A meta-analysis of 21 studies published between 2000 and 2015 suggested that 35-54% of individuals with SUDs achieved remission during a mean follow-up period of 17 years [102].

SUD is associated with a significant increased risk of physical [103] and mental [104] health problems (see also section 1.3.1), and is also associated with poverty, social exclusion and criminal behavior.

1.2 Cardiovascular disease

CVD is an umbrella term for diseases involving the heart (cardiac disease), the blood vessels (vascular disease) or both. Globally CVD is the leading cause of loss of disability-adjusted life years and accounts for nearly one third of all deaths [105]. Atherosclerosis (a build-up of fatty deposits in the arteries) is involved in many of these diseases, leading to impaired circulation and lack of oxygen supply to the heart muscle and surrounding tissue. Ischemic heart disease (IHD, congestive heart failure, cardiac arrhythmias, cerebrovascular disease and peripheral vascular disease are among the most common CVDs, and are briefly described below.

- Ischemic heart disease (IHD), also called coronary heart disease, is a condition with insufficient supply of blood and oxygen to the heart and surrounding tissue, due to narrowing (stenosis) of the arteries. This increases the burden on the heart and can cause angina (chest pain caused by restricted blood flow to the heart muscle), myocardial infarction (MI, where the blood flow to the heart muscle is suddenly blocked) or heart failure (see below). MI subgroups include STEMI (with electrocardiography (ECG) changes) and NSTEMI (without ECG changes), of which STEMI is the most acute and life threatening. NSTEMI amounts to approximately 70% off all heart attacks in Norway [106].
- Congestive heart failure is a condition where the heart's pumping function is impaired. There are many causes of heart failure, with MI or prolonged stress due to hypertension as the most common causes.
- Cardiac arrhythmias describes conditions with irregular heartbeats or heart rhythm. Atrial fibrillation is the most common type, characterized by irregularly and faster than normal heart beats.
- Cerebrovascular disease results from an impeded blood supply to the brain. A stroke may result either from a blockage (brain infarction or ischemic stroke), or a rupture of a blood vessel (hemorrhagic stroke).

- Peripheral vascular disease are diseases caused by atherosclerosis that affect non-cardiac and non-intracranial arteries.

Acutely life-threatening CVDs include MI, stroke and ruptured aneurysm. In Norway, annual cardiovascular mortality has decreased from 772 to 230 per 100,000 men, and from 450 to 161 per 100,000 women during the past three decades [107]. The decreased mortality is assumed to result from advancement in CVD treatment, decreased out-of-hospital sudden deaths, as well as an overall improvement in lifestyle factors, particularly cholesterol levels, smoking prevalence and blood pressure levels [108, 109]. Nevertheless, CVD mortality is still a leading cause of death in Norway, responsible for about 25% of total mortality in men and women in 2017.

1.2.1 Risk factors for CVD

Very many factors (> 270) have been suggested implicated in the development of CVD [110], including both demographic, behavioral, metabolic, psychosocial and environmental factors. Male sex and older age are demographic risk factors, while behavioral risk factors include smoking, physical inactivity, excessive alcohol consumption and unhealthy diet (i.e. diets that are high in fat combined with carbohydrates). Metabolic risk factors include hypertension, diabetes, raised blood cholesterol (hyperlipidemia), overweight and abdominal obesity. Other known risk factors are low socioeconomic status, stress and genetic predisposition/family history of CVD. Of all these risk factors, hypertension, diabetes, dyslipidemia, smoking, obesity and a sedentary lifestyle, as well as stress, older age, male gender, and a family history of CHD seem to be most important [108, 111].

1.2.2 Prevention of CVD

Some of the risk factors for CVD, such as age, male sex, ethnicity, low birth weight or genetic predisposition/family history of CVD, are given, but many important risk factors are modifiable by lifestyle change or medical treatment. WHO estimates that 80% of premature CVD is preventable [112], through healthy eating, exercise, avoidance of tobacco and limited alcohol intake, and treatment of hypertension, dyslipidemia and diabetes. Smoking cessation is the single most cost-effective intervention in CVD prevention [113]. Drug therapy (such as aspirin, beta blocker, diuretic and statin) may lead to a 75% reduction in MI among those at

high risk of having one [112]. Clinical trials have shown that statins reduce the risk of CVD events by 25% and all-cause mortality by 14% [114].

1.2.3 Diagnostic tests and treatment of CVD

1.2.3.1 CVD-related diagnostic tests

We included ECG, echocardiography, heart catheterization (e.g. coronary angiography), vascular ultrasound and cardio-metabolic blood tests in the measurement of CVD-related diagnostic tests in our study. A brief description of these procedures is given in Table 2.

Table 2 - CVD-related diagnostic test included in the current study

Procedure	Description
ECG	Electrical signals are recorded to detect irregularities in heart rhythm and structure, such as arrhythmias, heart muscle changes caused by inflammation (myocarditis), oxygen deficiency due to atherosclerosis, or clot formation in coronary arteries (angina pectoris, MI).
Echocardiography	Ultrasound waves and their different reflections ("echo") from the various parts of the heart are used to show and analyze detailed images of the heart's structure and function.
Heart catheterization	An invasive procedure where a thin, flexible plastic tube (catheter) is passed into an artery or vein, and forwarded to the heart under X-ray disclosure. This allows measurement of blood pressure and oxygen content in the vessels. The most common heart catheterization procedure is coronary angiography, where an X-ray is taken using injected contrast agents to visualize the coronary arteries in order to detect atherosclerosis.
Vascular ultrasound	Sound waves are used to evaluate the body's circulatory system and help identify blockages in the arteries and veins, and detect blood clots (such as deep venous thrombosis) in the major extremity veins.
Cardiometabolic blood tests	Measurement of total cholesterol, blood glucose and glycated hemoglobin (HbA1c).

CT or MR technics may also be used to detect significant arterial disease, but data on these procedures were not available in the current study.

1.2.3.2 Invasive cardiovascular treatment

We included common procedures for invasive treatment of MI or angina pectoris, arrhythmia and peripheral vascular disease in our study. The included procedures are briefly described in Table 3.

Table 3 - Procedures for invasive treatment of MI or angina pectoris, arrhythmia and peripheral vascular disease

Type of treatment	Procedure	Description
Treatment of MI/ angina pectoris	Percutaneous coronary intervention (PCI)	A non-surgical procedure used to open coronary arteries that are narrowed or blocked by atherosclerotic plaque. A small tube (stent) is usually implanted to prevent the artery from narrowing again.
	Coronary artery bypass graft (CABG)	A surgical technique used to improve blood flow to the coronary arteries by using normal arteries from the chest wall and veins from the legs to bypass blocked arteries, often performed with the help of a heart-lung machine. The procedure provides more effective symptom relief than medical management and is superior to PCI in multi-vessel coronary disease.
Arrhythmia treatment	Pacemakers or implantable cardioverter defibrillators	Devices that sends electrical impulses to the heart muscle to keep up a suitable heart rate and rhythm.
	Ablation	A non-surgical procedure where high-frequency radio waves are used to destroy a small area of heart tissue that is causing rapid and irregular heartbeats.
Treatment of peripheral vascular disease		Surgical treatments of conditions in arterial, venous and lymphatic systems, excluding intracranial and coronary arteries. Main procedures include carotid artery surgery, aneurysm surgery and thrombectomy.

1.3 Comorbidity in individuals with severe mental illness

1.3.1 Schizophrenia and concurrent substance use disorder

Comorbid SUD in people with SCZ is highly prevalent [41, 115-119]. A recent meta-analysis of 123 studies including nearly 166,000 subjects in in- or out-patient settings found a prevalence of any SUD of 42% among patients with SCZ or first episode psychosis [120]. Illicit drugs (28%), cannabis (26%) and alcohol (24%) were present in every fourth individual with SCZ or first episode psychosis. Comorbid SUD was more frequent in men (48%) than in women (22%), and associated with an earlier age of onset of SCZ [120]. A previous review found cannabis use disorder to be especially common in younger patients and in first episode psychosis [118]. A registry-based study from Norway examining the prevalence of SUD in patients aged 24-63 with SCZ treated in specialized health care, reported a 5-year prevalence of 25% for any SUD, 5% for alcohol use disorder, 7% for cannabis use, 8% for stimulants and 15% for poly-substance use[41]. The prevalence reported in the Norwegian study are, with the exception of stimulants, well below the estimates reported in recent meta-analyses [117, 118, 120].

Comorbid SMI is likewise significantly overrepresented in individuals with SUD [115]. Two recent meta-analysis found a doubled risk of psychosis among cannabis users [121, 122], with other studies suggesting also an increasing prevalence [7, 123]. Persons with illicit drug disorders have especially high rates of comorbid mental disorders [124], and are 3-4 times more likely to be diagnosed with major depression or anxiety disorder [104] compared to controls. Persons with alcohol use disorder are also at increased risk of major depression and any anxiety disorder [104], and almost half meet criteria for at least one other mental disorder [125].

Having a concurrent diagnosis of SCZ and SUD is associated with a variety of detrimental outcomes, such as increased symptom severity [126-128], poorer functional outcomes of SCZ [129-133], non-adherence with treatment [75, 134-136], increased somatic [137-139] and psychiatric comorbidity [140, 141], increased risk of victimization [142, 143], violent behavior [144-147], and suicides [148-150].

1.3.2 Severe mental illness and physical health

People with SMI have an increased risk of a wide range of medical conditions, but are especially burdened by CVD, metabolic syndrome, diabetes, cancer, pulmonary conditions and infections [151-153]. Between 50% and 90% of persons with SMI have at least one chronic physical illness, and these typically develop at a younger age [154]. Recent literature reviewing risk of CVD, diabetes and cardio-metabolic conditions in persons with SMI is outlined below, and findings regarding risk of other medical diseases briefly summarized at the end of the section.

1.3.2.1 Risk of CVD in persons with SMI

Persons with SMI are at particular high risk of CVD [153]. A large meta-analysis of 92 studies including 3.2 million individuals with SMI found that one out of ten individuals with SMI (i.e. SCZ, BD or major depression) had at least one comorbid CVD at a mean age of 50 [155]. Table 4 shows risk estimates for CVD in individuals with SMI reported in recent meta-analytic studies [155-161]. In the largest meta-analysis to date [155], persons with SMI had a 78% higher risk of developing CVD and a 53% higher risk of having a CVD, compared to controls. Individuals with SCZ or BD had a 95% and 57% increased risk of CVD, respectively.

Prospective studies included in the meta-analysis referred to above showed a 54% and 59% increased risk of IHD in individuals with SMI and SCZ, respectively, but no increased risk in individuals with BD [155]. Increased risk of IHD has also been documented in users of antipsychotic medications [160, 161]. Estimates of risk of cerebrovascular disease or stroke showed a 64% increased risk in individuals with SMI, and an approximately 50-74% increased risk in individuals with SCZ [155, 158, 159] or BD [157, 159]. The risk of congestive heart failure was reported to be doubled in individuals with SMI [155], and 88% increased in individuals with SCZ [158], while hypertension was found to be increased in BD, but not SCZ [156].

Table 4 - Risk of CVD in individuals with severe mental illness reported in meta-analytic studies with healthy controls.

Author (year)	No. of studies	Patients	Controls	Disease	SMI patent group	RR (95% CI)	OR (95% CI)
Correll 2017 [155]	65/38	3,211,768	113,383,368	CVD	SMI pooled	1.78 (1.60-1.98)	1.53 (1.27-1.83)
	14/13				SCZ	1.95 (1.41-2.70)	
	10/12				BD	1.57 (1.28-1.93)	
	18/5			IHD	SMI pooled	1.54 (1.30-1.82)	1.51 (1.47-1.55)
	5				SCZ	1.59 (1.08-2.35)	
	4				BD	1.16 (0.76-1.78)	
	11/6			Cerebro	SMI pooled	1.64 (1.26-2.14)	1.42 (1.21-1.66)
	5				SCZ	1.57 (1.09-2.25)	
	4				BD	1.60 (0.99-2.57)	
	2/4			CHF	SMI pooled	2.10 (1.64-2.70)	1.28 (0.99-1.65)
Prieto 2014 [157]	5	27,092	13,088,819	MI	BD	1.09 (0.96-1.24)	
	5			Stroke	BD	1.74 (1.29-2.35)	
Ayerbe 2018 [156]	5	NA	NA	Hypertension	SCZ	0.94 (0.75-1.14)	
					BD	1.27 (1.15-1.40)	
Fan 2013 [158]	13		422,698	CVD	SCZ	1.53 (1.27-1.86)	
	NA			IHD	SCZ	1.20 (0.93-1.53)	
	NA			Stroke	SCZ	1.71 (1.19–2.46)	
	NA			CHF	SCZ	1.81 (1.42–2.29)	
Li 2014 [159]	6	NA	NA	Stroke	SCZ	1.50 (1.25-1.80)	

Abbrevations: BD, bipolar disorder; Cerebro, cerebrovascular disease; CHF, congestive heart disease; CI, confidence interval; CVD, cardiovascular disease; IHD, ischemic heart disease; MI, myocardial infarction; NA, not available; OR, odds ratio; RR, relative risk; SCZ, schizophrenia; SMI, severe mental illness

Excess CVD risk in people with SMI has been explained partly by an increased prevalence of traditional cardiovascular risk factors (such as smoking, physical inactivity, unhealthy diet

and SUD), and which may emerge shortly after diagnosis, and at a young age [162, 163]. Smoking is particularly important, with rates up to 5.3 times higher than in the general population [164]. In a recent study from Norway, 47% of SCZ individuals and 43% of BD individuals reported daily smoking [165], compared to 12% in the general Norwegian population [95]. Genetic studies have also found overlapping genes associated with both SCZ and CVD risk factors, implying shared pathological mechanisms between SCZ and CVD [25].

1.3.2.2 Risk of metabolic syndrome and diabetes in individuals with SMI

Metabolic syndrome (MetS) describes a clustering of metabolic factors (i.e. central obesity, hypertension, dyslipidemia and glucose intolerance) which are highly predictive of CVD [2]. MetS is associated with a five times higher risk of developing diabetes [166] and a doubled risk of CVD, MI and stroke [167]. Meta-analyses report that one in three people with SCZ [168], and nearly two out of five persons with BD [169], meet the criteria for MetS.

Table 5 shows estimated relative risk for MetS and diabetes in individuals with SMI reported in recent meta-analytic studies. These studies show that persons with SMI had a 58% increased risk of MetS, and a 33-58% increased risk of its components, except for hypertension [170]. Meta-analyses and large cohort studies have reported a prevalence of type 2 diabetes of about 10% among individuals with SMI [151, 171-173], which is twice the estimated prevalence in Norway [174]. The prevalence was only about 3%, however, in anti-psychotic drug-naïve individuals with SMI [172]. The risk of diabetes was 70-153% increased risk in people with SMI compared to controls, with the highest increased risk when rigorous criteria for diabetes was applied [171]. Individuals with SCZ and BD seem to have similar risk of diabetes, despite higher education, better social functioning, less severe psychiatric symptoms and lower use of antipsychotic medication in individuals with BD.

The increased risk of MetS is partly due to side effects of antipsychotic medication. Both newer and older antipsychotics are associated with metabolic side effects that can lead to weight gain, glucose intolerance and dyslipidemia [170]. These adverse metabolic effects occur shortly after first-time exposure to antipsychotic medication [175]. Antipsychotic medication may also cause alterations of cardiac function, blood pressure and heart rate [176].

Mood stabilizers and antidepressants are also associated with metabolic side effects [176], but these side effects are considered less severe than for antipsychotic medication.

Table 5 - Risk of metabolic syndrome (MetS) and diabetes in individuals with severe mental illness reported in meta-analytic studies with healthy controls.

Author (year)	No. of studies	Patients	Controls	Disease	SMI patent group	RR (95% CI)
Vancamp	30	6,610		MetS	SMI	1.58 (1.35-1.86)
fort 2015	18			Abdominal obesity	SMI	1.43 (1.23-1.66)
	19			Low HDL cholesterol	SMI	1.33 (1.15-1.54)
	19			Hypertriglyceridemia	SMI	1.49 (1.28-1.73)
	20			Hyperglycaemia	SMI	1.51 (1.24-1.84)
	12			Hypertension	SMI	1.12 (0.99-1.28)
Osborn	12	2,333/6,249	261,228/2,169,371	Hypertension	SMI	1.11 (0.91-1.35)
2008	26	9,612	3,449,677	Diabetes	SMI	1.70 (1.21-2.37)
	NA	NA	NA	Diabetes	SCZ	1.87 (1.68-2.09)
Vancamp	13	438,245	5,622,664	Diabetes II	SMI	1.85 (1.45-2.37)
fort 2016	22			Diabetes II	SCZ	2.04 (1.69-2.49)
	17			Diabetes II	BD	1.89 (1.29-2.77)
Stubbs	25	145,718	4,343,407	Diabetes II	SCZ	1.82 (1.56–2.13)
2015	8			Diabetes II (recognized criteria)	SCZ	2.53 (1.68–3.80)
	13			Diabetes II (medical records)	SCZ	1.65 (1.34–2.03)

Abbrevations: BD, bipolar disorder; CI, confidence interval; HDL, high-density lipoprotein; MetS, metabolic syndrome; NA, not available; RR, relativ risk; SCZ, schizophrenia; SMI, severe mental illness

1.3.2.3 Risk of other physical diseases in individuals with SCZ or BD

Meta-analytic studies also document that individuals with SCZ or BD are at increased risk of respiratory diseases [177, 178], obstructive sleep apnea [179], hepatitis C [180, 181], poor oral health [178, 182], fractures [183, 184] and dementia [56, 185] compared to controls. Individuals with SCZ also have higher risk of breast cancer [186-188], infectious diseases (e.g. HIV and hepatitis B), osteoporosis [189, 190], as well as altered pain sensitivity, sexual dysfunction and obstetric complications [189] compared to controls. Individuals with BD also have higher risk of asthma [191] and irritable bowel syndrome [192] compared to controls.

1.4 Mortality in individuals with SMI and/or SUD

People with SMI have a life expectancy that is decades shorter than others. A recent meta-analysis documented a 15 years reduced life expectancy among persons with SCZ, compared to the general population [2, 193], and a large Nordic study including more than 270,000 patients with recent onset SMI found a reduced life expectancy of 20 and 15 years in men and women with SMI, respectively, compared to the general population [1]. In the latter study, life expectancy was reduced by 21-24 years for those with SUD, 16-20 years for those with SCZ and 16-17 years for those with affective disorders.

While life expectancy in developed countries has increased by nearly a decade in the general population since the 1970s [17], most studies suggest that people with SMI have benefited less from this development. Recent reviews and meta-analyses [8, 17, 194] report a rising mortality gap between those with and without SCZ. Studies from Northern Norway [10] and Denmark also report a rising mortality gap in patients with SCZ compared to the general population [13, 195], whereas Finnish studies have reported a flattening out of the mortality gap [196, 197] or a declining trend [198] between those with and without SMI.

1.4.1 Mortality in individuals with schizophrenia spectrum disorder

A worldwide systematic review in 2007, including approximately 22,000 deaths, found that persons with SCZ had a 2.6 times increased mortality risk compared to the general population [8]. Another worldwide meta-analysis published eight years later found similar results for psychosis [199], while a worldwide review from 2018 including more than 1.7 million community-dwelling participants, found that people with psychosis had a 3.1 increased mortality compared to the general population [17]. Cohort studies from the Nordic countries have reported standardized mortality ratios (SMRs, see section 2.6.1, page 51 for a definition) for SCZ in comparable ranges. Nationwide all-cause SMRs reported since 2000 in studies from Denmark, Sweden or Finland [1, 195, 200-204] are shown in Table 6, together with all-cause SMRs reported in hospital-based samples from Norway [10, 12].

Table 6 - Standardized Mortality Ratios (SMRs) in individuals with schizophrenia reported in Nordic countries since 2000.

Author, year	Country	Setting	No. of patients	Period	Age group	Definition SCZ	SMR all	SMR men	SMR women
Honkonen et al 2008 [204]	Finland	Hospital-based; in- and outpatients	3,837	1993-2005	18–64	SCZ (F20–F29)	3.9	3	6.1
Kiviniemi et al 2010 [203]	Finland	Nationwide; inpatients and individuals with disability pension due to SCZ	7,591	1995-2001	NA	Incident SCZ (F20, F25)	4.5	4.5	4.3
Nome et al 2012 [12]	Norway	Hospital-based; inpatient	4,474	1985-2003	18+	Incident psychiatric admission		2.9	2.2
Høye et al 2011 [10]	Norway	Hospital-based; inpatient	1,111	1980-1992 1993-2006	NA	SCZ (F20-F21, F25)		3.5 3.6	2.6 4.6
Wahlbeck et al 2011 [201]	Denmark Finland Sweden	Nationwide; inpatients	NA	1987-2006	15+	Mental disorder (F00–F69)		3.0 2.3 2.9	2.5 1.9 2.0
Nordentoft et al 2013 [1]	Denmark Finland Sweden	Nationwide; inpatients	270,770	2000-2006	NA	Incident SCZ (F20–F29)		3.3 2.9 3.3	2.9 2.4 2.8
Laursen et al 2012 [200]	Denmark Finland Sweden	Nationwide; inpatients	66,088	2000-2007	15+	Incident SCZ (F20)		3.0 3.3 2.9	2.7 3.9 2.9
Castagnini 2013 [202]	Denmark	Nationwide; in- and outpatients	233	1995-2008	15-64	Incident SCZ (F20)	4.6		
Lomholt et al 2019 [195]	Denmark	Nationwide; in- and outpatients	38,500	1995-2014	< 65	SCZ (F20–F29)	4.6		

Abbrevations: No, Number; SCZ, schizophrenia; SMR, Standardized mortality ratio; NA, not available;

In these Nordic studies, estimates of all-cause SMR for men with SCZ range from 2.3 [201] to 4.5 [203], while all-cause SMR for women with SCZ range from 1.9 [201] to 4.6 [10]. In Norway and Denmark, the highest SMRs were reported in the most recent studies [10, 195], whereas SMRs in recent Swedish and Finnish studies seem stable or possibly declining compared to those found in previous studies.

The majority of deaths in individuals with SCZ are caused by somatic diseases, especially CVD, cancer and respiratory diseases [14, 205, 206], and somatic diseases contribute more to

the shorter life expectancy in SCZ than deaths from external causes of death such as accidents, suicides or homicides [4]. A recent study from the UK estimated that natural causes of death accounted for nearly 80% of lost life-years among persons with SMI [207]. Studies from the Nordic countries show that excess mortality from natural causes of death is 2-to 3-fold increased in individuals with SCZ, compared to the general population [1, 202-204, 208]. Studies from Europe and the US show that excess mortality from CVD is of the same magnitude [205, 208], and possibly increasing [8, 11, 15, 197].

SMRs from unnatural causes of death are substantially elevated in persons with SCZ, and range from approximately 5 to 8 in the Nordic countries [202, 203, 208], with higher SMRs in women [208]. SMRs for suicide are 11- to 15-fold increased in individuals with SCZ in Nordic studies [202-204]. A recent Finnish study reported that SMRs for suicidal deaths decreased from 11 in 1984 to less than seven in 2014 [197].

1.4.2 Mortality in people with substance use disorder

A meta-review found that SUD, together with anorexia nervosa, had the highest risk of premature death of all SMIs [209]. In meta-analyses addressing specific SUDs, excess mortality risk ranged from a four-fold increased mortality risk among persons with alcohol use disorder [209, 210] to a 15-fold increased mortality risk among opioid users [211] and persons who inject drugs [209, 212]. Studies from Nordic countries also show high SMRs among those with SUD, with varying estimate sizes according to inclusion criteria, patient group and length of follow up. A recent 19-year follow up study of mortality among 291 Norwegians receiving specialized treatment for poly-SUD or alcohol use disorder only, found SMRs of 3.8 among those with any SUD, 3.4 among those with alcohol use disorder-only and 5.2 among those with poly-SUDs [213]. Much higher SMRs were reported in a 13-year follow up study of 172 injecting drug users in Norway [214], reporting an all-cause SMR of 39 in women and 21 in men, and in a previous study of mortality among hospitalized opioid addicts in Norway, reporting a SMR of more than 13 in the years 1995-1999 [215].

A Danish study reported SMRs of 4.9 for cannabis use, 6.4 for cocaine use, 6.0 for amphetamine use, 9.1 for heroin use, and 7.7 for other opioids [216], and a Swedish study reported an all-cause SMR of 5.9 among 561 illicit substance abusers followed up to 37 years [217]. Another Swedish study with 30-year follow up of 1,163 SUD inpatients in Sweden

found a SMR of 12.7 in men and 10.3 in women, with the highest mortality risk in opiates users (SMR 16.7) and persons with alcohol use disorder (SMR 13.1), followed by stimulants, cannabis and "other SUD", all with SMRs around 10 [218]. While natural causes of death accounted for about 70% of deaths among patients with alcohol use disorder in a recent meta-analysis, substance related deaths and unnatural causes of death are often reported as the most common cause of death among those with illicit SUD [213, 215, 217].

1.4.3 Mortality in people with SMI and comorbid SUD

Although comorbidity between SMI and SUD is very common, relatively few studies have focused on the impact of SMI and comorbid SUD on premature mortality [130, 217, 219]. Existing studies on this topic are heterogeneous, both in terms of patient groups and settings that are studied, and with regard to results. Estimates of all-cause mortality among patients with SMI and/or SUD identified in studies published after year 2000 are shown in Table 7 .

Of these studies, most [12, 130, 220-226], but not all [151], reported an increased risk of mortality in the dually diagnosed, compared to SCZ-only/SMI-only. Estimates of excess mortality risk in those with SMI and comorbid SUD ranged from about 50% increased risk to a 2- to 3-fold increased risk, compared to those with only SCZ/SMI. In the two studies that reported sex-specific results, the increased risk in the dually diagnosed was somewhat more pronounced in men than in women [12, 222].

There are few studies investigating cause-specific mortality risk in the dually diagnosed, with partly conflicting results. Mortality from natural causes of death was found to be both similar [151, 224] and increased [226] in those with both SMI and SUD, compared to those with SMI only. Likewise, risk of cardiovascular death was reported to be both similar [151] and increased [226] in patients with SCZ and comorbid SUD, compared to those with SCZ only. Also, diverging gender-specific results has been reported for unnatural causes of death [151, 222, 226, 227].

Table 7 - Summary of studies comparing all-cause mortality in persons with SMI and/or SUD.

Author, year	Setting	Patient category	Period	Patient groups	Results SMI-only	Results SMI+SUD	Results SUD-only
Maynard 2004 USA [220]	State-wide	Inpatients	1996–2001	Mental illness +/- SUD	Ref	HR **1.44**	
Rosen 2008 USA [221]	Hospital	Middle-aged male veterans	1998	Mental illness +/- SUD	Ref	OR **1.55**	
Schmidt 2011 Denmark [130]	Hospital	Inpatients	1993-2008	SCZ+/- SUD	Ref	HR **1.74**	
Nome 2012 Norway [12]	Hospital	Inpatients	1985-2003	SMI+/- SUD	SMR 2.6 (m) SMR 2.1 (w)	SMR **6.6** (m) SMR **5.0** (w)	
Björkenstam 2012 Sweden [222]	Nationwide	In- and outpatients	2006-2007	Mental illness +/- SUD	RR 4.2 (m) RR 3.6 (w)	RR **12.5** (m) RR **10.8** (w)	RR 6.1 (m) RR 7.9 (w)
Crump 2013 Sweden [151]	Nationwide	In- and outpatients	2003–2007	SCZ+/- SUD	HR 2.4 (m) HR 2.8 (w)	HR 2.2 (m)	HR 2.7 (w)
Hjorthøj 2015 Denmark [223]	Nationwide	In- and outpatients	1990-2012	SCZ+/- SUD	SMR 3.6	SMR **8.5**	
Reininghaus 2015 UK [224]	Hospital	In- and outpatients	2003-2012	FEP+/- SUD	Ref	RR **2.3**	
Aagaard 2016 Denmark [225]	Hospital	Psychiatric emergency room patients	2005–2007	SCZ+/- SUD	SMR 5.0	SMR **18.0**	
Lumme 2016 Finland [226]	Nationwide	Inpatients	2008-2010	SMI+/-SUD	Ref	RR ≈**1.8** (m) RR ≈**2.1** (w)	
Sørensen 2005 Denmark [228]	Hospital	In- and outpatients	1984-199	OUD+/- SMI		HR 1.8	Ref
Mattison 2011 Sweden [229]	Community -based	Study participants	1947-1997	AUD+/- SCZ		HR 1.0	Ref
Arendt Denmark 2011 [216]	Nationwide	Patients in specialized SUD treatment	1996-2006	DUD+/- SCZ		SMR 7.9	SMR 7.0
Koola 2012 USA [219]	State-wide	Inpatients	2003-2007	SCZ+/-CUD SCZ+/-AUD	HR 0.5 HR 0.8	Ref	
Bogdanowicz 2015 UK [141]	Hospital	In- and outpatients	2008-2012	OUD+/- SCZ		HR 0.7	Ref
Manrique-Garcia 2016 Sweden [230]	Nationwide	Military conscripts	1969-2011	CUD+/- SCZ Ever use Heavy use		 HR 1.2 HR **1.8**	 HR 0.9 HR **1.2**
Steingrímsson 2016 Iceland [231]	Nationwide	Inpatients	1983-2007	SUD+/- SCZ		HR 1.1 (m) HR 0.9 (w)	Ref

Abbrevations: AUD, alcohol use disorder; CUD, cannabis use disorder; DUD, drug use disorder; FEP, first episode psychosis; HR, hazard ratio; m, men; OR, odds ratio; OUD, opioid use disorder, Ref, reference category in the statistical model; RR, relativ risk; SCZ, scgizophrenia; SMI, severe mental illness; SMR, standardized mortality ratio; SUD, substance use disorder; w,women. **Bold** figures: significant at p-value 0.05.

Identified studies comparing all-cause mortality in persons with SUD and comorbid SCZ/SMI are heterogenous both with regard to settings, patients included, type of SUD studied and results. All-cause mortality is reported to be both higher [222, 226, 232], similar [231] and lower [217, 233], among those with any SUD and concurrent SMI, compared to those with SUD-only.

Studies report similar mortality risk in patients with alcohol use disorder with and without concurrent SCZ [219, 229] and similar mortality risk in persons with drug use disorder with and without concurrent SMI [141, 216, 228]. Studies of mortality in people with cannabis use disorder and concurrent SMI report both decreased [219], similar [230] and increased mortality risk, compared to those with cannabis use disorder only [230].

1.5 Uptake of cardiovascular health care in people with SMI

The organization and funding of health care services is of great importance when studying access to health care services, particularly for vulnerable populations. This section therefore starts with a brief overview of the Norwegian health care system. We also define key concepts such as inequity and quality of care, before summarizing some of the literature regarding uptake of cardiovascular health care in people with SMI.

1.5.1 The organization of health care services in Norway

The health care services in Norway is mainly publicly funded, with free admission to hospital and a maximum annual cost of 2,370 NOK in 2016 (approximately €293) for outpatient treatment (e.g. general practitioner (GP) visits, psychologist visits, x-ray examinations, patient travel costs and prescription medicines with preapproved reimbursement). The responsibility for primary care services is assigned to the approximately 420 municipalities, while four Regional Health Authorities are responsible for the provision of specialist health services to all inhabitants in their respective regions. Publicly funded private specialist health services, including in- and outpatient facilities, private practitioners, laboratory and radiology services, accounted for 12% of public health expenditures in the period 2010-2014 [234]. These private providers performed a significant proportion of services within SUD treatment, rehabilitation and planned orthopedic surgery. Most private health care providers are funded mainly through agreements on service provision on behalf of municipalities or Regional Health Authorities, and the services are done on the same terms for the patient as if they were provided directly

by the public health service. GPs are usually organized as private enterprises. About 2/3 of the funding comes from activity-based funding (fee-for-service), while the remaining is capitation paid by the municipalities. Approximately 14% of total health expenditures are financed by deductibles. The use of privately financed private health care services is unknown, but is assumed to constitute a small part of the total health services.

To promote continuity of care for patients with chronic disorders, all Norwegians who want it has a named accountable GP (currently 99% [235]). The GP is responsible for general medical services for all persons on their list, including acute care during daytime. GPs are in contact with a large proportion of patients with SMI, and prescribe almost 70% of all antipsychotic drugs [236]. GPs also acts as gatekeepers for referrals to the publicly funded specialized health services. A mentally ill patient may be referred to one of approximately 75 District Psychiatric Centers, which offers specialized mental health in- and outpatient services. The more severely ill may be admitted to emergency wards at psychiatric hospitals, while persons with SUD may be referred to outpatient treatment or admission at a SUD treatment facility. Pre-hospital services (i.e. ambulance service including helicopters with physician staff) is part of the specialist health service, and often initiate treatment on the way to hospital.

1.5.2 Definitions of health inequity and quality of care

Studies of inequality in health outcomes or health care use are based on a premise of avoidable injustice [237], as well as a perception that it is a social responsibility to try to remedy this. As differences in health outcomes resulting from free personal choice or chance alone would not be considered unjust per se, the notion of inequity in health or health care relates to circumstances largely beyond the individual's control, such as differences in access to, or quality of, health care services. Variation in health service provision also requires that there is a certain amount of physician's discretion with regard to whether a specific procedure is indicated or not in a particular patient [238].

While inequality is suggested used as a descriptive term for variations in health outcomes or health care uptake, inequity has a normative interpretation [239]. Equity in health care has been defined as "*equal access to available care for equal need, equal utilization for equal need, equal quality of care for all*" [237]. Imbedded in this definition is the concept that that

persons that are alike in relevant aspects, should be treated in alike fashion (horizontal equity), and that persons who are unlike in relevant aspects should be treated differently (vertical equity). Loosely stated, this implies that equitable health care requires equally accessible health care services of similar quality to all in equal need, and greater provision to those who demonstrate greater need.

Quality of care is, however, an elusive concept, partly because of its multidimensional character and context-dependency, and partly because quality never can be better than the knowledge we have about the relationship between treatment and effect. Quality of health care has been defined as: ".. *the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge»* [240]. Following Donabedian [241], quality of health care can be assessed on the basis of three different domains: structure, process and outcome. Structure measures deal with the context and attributes in, and with which, care is provided (e.g. resources, organization, reward systems, staff, facilities and equipment), process measures deal with the services provided, as well as the interaction between patients and providers, while outcomes refer to overall effects on patients' and populations' health. Process-based measures can be operationalized using readily available administrative data, and provide actionable information as to where performance falls short and quality improvements should be targeted.

In addition to these dimensions, the attainment of timely and appropriate healthcare (access), and patients' experiences and shared decision making are important quality domains.

1.5.3 Undiagnosed CVD among persons with SMI

The excess mortality due to somatic diseases in SMI patients may be caused by poorer access to somatic health care. Crump et al reported that the proportion of individuals who died from IHD undiagnosed one month prior to an IHD death was higher in individuals with SCZ than in others who died from IHD [151], but not significantly different between individuals with or without BD [152]. Importantly, when restricting the analysis to people who were previously diagnosed with IHD, SCZ was only modestly associated with higher IHD mortality, which indicates that premature cardiovascular deaths in individuals with SMI may be prevented if CVDs are identified and treated [242-244].

With the exception of the studies by Crump et al [151, 152], underdiagnosis of CVD in patients with SMI seems to be little documented, especially in relation to premature mortality. Exceptions include a recent Danish study, where patients with SCZ and a history of psychiatric admissions had 45% reduced odds of being diagnosed with CVD at least 30 days prior to cardiovascular death [245]. Also, in a study of US veterans, patients with SCZ had twice the risk of unforeseen death compared to patients without SCZ, with CVD as the most common cause [246].

More often, underdiagnosis of CVD has been indirectly indicated, for example in studies showing lower levels of screening and monitoring of risk factors for CVD [156, 247, 248], and studies showing lower use of CVD-related health services [249, 250]. Further indirect evidence is offered in a survey of mental health service users, in which 39% reported not having discussed CVD risk factors with health care professionals the previous year [251].

Also, large population based cohort studies have reported lower or similar rates of recorded CVDs such as atrial fibrillation, hypertension and IH) in individuals with SMI, compared to others [151, 252-255], in spite of increased risk of CVD. Lower prescriptions rates for cardiovascular medication in individuals with SMI compared to others have also been reported [255-259], possibly implying underdiagnosis and undertreatment of CVD in these individuals.

1.5.4 Inequalities in health care provision for patients with SMI

1.5.4.1 Screening/monitoring of cardio-metabolic risk factors in individuals with SMI

Current guidelines for management of psychosis recommend regular assessments of smoking, diet, physical activity, weight, waist circumference, blood pressure, fasting blood glucose, HbA1c and fasting lipids [260]. Still, meta-analyses report inferior preventive care of CVD in individuals with SMI regarding metabolic monitoring [247, 248], blood pressure monitoring [247] and hypertension treatment [156]. These meta-analyses mainly included studies from the US, where universal health care is lacking. Case studies from countries with universal health care also document low levels of screening for diabetes and other metabolic abnormalities [261-265], and studies from the UK and Italy found that a minority of patients in primary care using antipsychotic medication were screened for MetS in accordance with best practice recommendations [261, 262].

Table 8 summarizes identified comparative European studies investigating the uptake of screening/monitoring of cardiovascular risk factors in primary care settings among those with and without SMI. The majority of these studies are from the UK [266-271], and many of them investigated quality of care among patients with SMI and acknowledged somatic disease, particularly diabetes [266, 270, 272, 273]. Most studies reported similar or higher uptake of screening/monitoring of cardiovascular risk factors in patients with SMI, compared to controls. Among these studies is a Norwegian one reporting higher levels of diagnostic testing/monitoring of diabetes and CVD in younger persons with SCZ and acknowledged diabetes or CVD, compared to diabetes only or CVD only [272]. Similar findings are reported also from other countries [266, 271, 273]. While few studies found differences in diabetes care, several indicate challenges with regard to cholesterol measurements [267-269] and blood pressure measurements [268, 271] among subjects with SMI.

Table 8 - Summary of results in studies investigating uptake of screening/monitoring of cardiovascular risk factors in primary care in comparative studies from countries with universal health care.

Author, year and site	Study period	Patient groups	No. of SMI patients	Age	Results	
Roberts [268] 2007, UK	1998-2000	Asthma +/- SCZ Gen pop +/- SCZ	195	18+	Patients with SCZ were half as likely as asthma controls to have blood pressure and cholesterol levels recorded, and also less likely than general population controls to have either blood pressure or cholesterol recorded.	↓
Whyte [266] 2007, UK	2002-2005	SCZ/BD + diabetes	1,043	17+	The presence of SMI did not reduce the quality of diabetes care received , and patients with SMI were more likely to have good glucose control.	→↑
Hippisley-Cox [267] 2007, UK	2003-2005	SCZ/BD + IHD	701	25+	The majority of CVD care indicators were achieved equally for patients with and without SMI, but identification and treatment of raised cholesterol was suboptimal among patients with SCZ	→↓
Osborn [269] 2011, UK	2000-2007	SMI	18,696	18+	Prior to 2004, all people with SMI were significantly less likely to receive measurements of blood pressure, glucose, cholesterol and body mass index. By 2007 people with SMI under 60 were equally likely receive BMI and cholesterol measurements, while people with SMI aged 60 and above remained less likely to be screened.	→↓
Hardy [270] 2013, UK	2009-2010	Diabetes +/- SMI	386	NA	Twenty-one % of patients with SMI received a full CVD screen compared with the 96% of those with diabetes. Patients with SMI received fewer than two (from four) screening interventions and less than one (from three) components of lifestyle advice.	↓
Hetlevik [272] 2015, Norway	2009	Diabetes +/- SCZ CVD +/- SCZ	10,112	25–60	Diagnostic tests (e.g. HbA1c, ECG) were equally or more frequent used among patients with SCZ and comorbid diabetes/CVD than among similar patients without SCZ.	↑
Woodhead [271] 2016, UK	2012-2013	Primary care patients +/- SMI	4,056	16+	For most quality indicators, there were no difference between patients with and without SMI. Among patients with hypertension, SMI status was associated with greater recording of BMI and HbA1c. Patients with SMI with CHD were less likely to have a BP record, whereas those with stroke/TIA were less likely to have a record of BP.	→↓↑
Rathmann [273] 2016, Germany	2009-2013	Diabetes +/- SCZ	1,321	NA	There is no evidence that type2 diabetes patients with SCZ have worse diabetes control than those without SCZ in general practices.	→
Gal [274] 2016, Israel	2016	CVD +/- SCZ	8,208	40+	Individuals with SCZ were less likely to meet similar indexes of care as their counterparts regarding cholesterol tests, stress tests and visits to specialists	↓
Gal [275] 2017, Israel	2017	No SMI versus SCZ/BD, Diabetes +/- SCZ/BD	19,258	40+	Persons with SCZ had slightly lower measures of cholesterol and stress tests, whereas persons with BD had similar or higher health care use compared to controls. No disparities were noted in the health services provided to diabetes patients with and without SMI.	↓
Ritchie [276] 2017, Canada	2013-2015	No SMI versus psychosis	106	18+	Screening rates for cardiovascular risk factors were similar in patients with and without SMI.	→

Abbrevations: BD, bipolar disorder; BMI, Body mass index; CVD, cardiovascular disease; ECG, electrocardiography; IHD, ischemic heart disease; NA, not available; SCZ, schizophrenia; SMI, severe mental illness

→↓↑: Indicates similiar, lower and higher uptake, respectively, of CVD-related procedures among patients with SMI compared to controls.

Table 9 gives a summary of identified comparative studies investigating uptake of specialized cardiovascular examinations in countries with universal health care. We were not able to identify many studies on this topic, and the majority of these studies only investigated uptake of cardiac catheterizations, including coronary angiography [274, 277-279], or access to cardiologists [280, 281]. Both cardiac catheterizations and access to cardiologists were found to be reduced in persons with SMI in these studies, compared to controls. A small Danish study found increased use of exercise-ECG in patients with SCZ and incident MI [279], compared to patients without SCZ.

Table 9 - Summary of results in comparative studies investigating uptake of specialized cardiovascular examinations in countries with universal health care.

First Author, year and site	Study period	Patient groups	No. of SMI patients	Age	Results	
Kisely [277] 2009, Canada	1995-2001	IHD +/- psychosis	1,285	15+	Patients with psychosis and comorbid IHD were less likely to receive cardiac catheterization.	↓
Bresee [280] 2012 Canada	1995-2006	SCZ identified in primary or specialized care	28,755	20+	Individuals with SCZ and established coronary artery disease were less likely to have seen a cardiologist (OR 0.76; 95% CI 0.72-0.80), but more likely to se an internist (OR 1.64; 95% CI 1.51-1.79)	↓
Kurdyak [281] 2012 Canada	2002-2006	Acute MI +/- SCZ	1,087	20-104	Individuals with SCZ and incident acute MI were less likely to see a cardiologist within 30 days of discharge (OR 0.53, 95% CI 0.43–0.65).	↓
Wu [278] 2013 Taiwan	1996-2007	SCZ/BD versus no SMI	834	18+	Patients with SCZ and acute MI had 62-67% lower odds, and patients with BD and acute MI 59-64% lower odds, of receiving cardiac catheterizations, compared to patients without SCZ or BD.	↓
Gal [274] 2016, Israel		SCZ versus matched controls		40+	Service users with SCZ had lower rates of cardiac catheterization compared with matched controls.	↓
Attar [279] 2017 Denmark	1995-2015	SCZ versus psychiatric healthy control	47	NA	Patients with SCZ and incident MI received lower levels of coronary angiography than controls (91.1% among SCZ individuals and 97.9% among controls), but this difference was statistically insignificant. Individuals with SCZ received higher levels of exercise-ECG (8.9% among SCZ and 1.1% among controls, p: 0.04).	→↑

Abbrevations: BD, bipolar disorder; BMI, Body mass index; CVD, cardiovascular disease; IHD, ischemic heart disease; MI, myocardial infarction; NA, not available; SCZ, schizophrenia; SMI, severe mental illness
→↓↑: Indicates similiar, lower and higher uptake, respectively, of CVD-related procedures among patients with SMI

1.5.4.2 Uptake of cardiovascular treatment in individuals with SMI

Meta-analyses have reported lower levels of cardiovascular prescriptions in persons with SMI [250]. A large Danish cohort study also found lower prescription of cardioprotective medications among individuals with SCZ than in the general population, particularly lipid lowering and antihypertensive medication [257]. A recent Danish study found lower prescribing of cardioprotective medications following MI among patients with SCZ, contributing to higher post-MI mortality among those with SCZ [259]. A recent UK study, however, found higher rates of statin prescriptions to younger individuals with SMI, but lower rates of statin initiation for older individuals with SCZ, both relative to individuals without SMI [282].

Many previous studies have focused on uptake of invasive treatment after incident MI among patients with SMI, and meta-analyses, mainly based on studies from the US, have reported lower likelihood of invasive coronary treatment such as PCI and CABG among patients with SMI compared to patients without SMI [249]. Lower receipt of invasive treatment of CVD have also been reported in comparative studies from countries with universal health care. A summary of identified studies on this topic is shown in Table 10. All of the identified studies investigated uptake of revascularizations in patients with IHD and comorbid SMI. Most [11, 274, 278, 280, 281, 283], but not all [279, 284], reported lower uptake of revascularization in those with SCZ, compared to those without SCZ. Patients with BD were found to have similar [11, 284] or lower [278] uptake of revascularizations, and patients with mood disorder higher, similar or lower uptake depending on age, with decreasing likelihood with increasing age [283].

Invasive cardiovascular treatment other than revascularization among those with SMI seems to be little studied. Studies from Canada [277], the US [285] and Israel [274] have, however, reported that ischemic stroke patients with comorbid psychiatric disease had lower likelihood of intravenous thrombolysis [285] and cerebrovascular arteriography [277], but similar likelihood of carotid endarterectomy [277]. Lower likelihood of pacemaker implantation in patients with CVD and comorbid SCZ has also been reported [274].

Table 10 - Summary of results in studies investigating uptake of invasive treatment for CVD in comparative studies from countries with universal health care.

First Author, year and site	Study period	Definition SMI	No. of SMI patients	Age	Results	
Kisely [277] 2009, Canada	1995-2001	IHD +/- psychosis	1,285	15+	Patients with psychosis and comorbid IHD were less likely to receive revascularization. Patients with psychosis and comorbid stroke were less likely to receive cerebrovascular arteriography, but were equally likely to receive carotid endarterectomy	→
Laursen [286] 2009, Denmark	1994-2006	SMI versus no SMI	4,997	15+	The fraction undergoing invasive procedures within 5 years was reduced among patients with SMI and incident IHD as compared with the non-psychiatric general population (7.04% vs 12.27%, respectively).	↓
Laursen [11] 2011, Denmark	1994-2006	SCZ/BD versus no SMI	1,854	15+	The entire period saw a lower hospitalization rate and fewer invasive cardiac procedures (i.e. CABG and PTCA) among persons with schizophrenia than among the general population.	↓
Manderbacka [283] 2012 Finland	1998-2009	SCZ/affective disorder versus no SMI	67,659 50,135	40+	Patients with SCZ had lower likelihood of receiving revascularizations in all age groups. Persons with mood disorders aged 40-59 years had increased likelihood of receiving revascularizations, while persons with mood disorders aged 70-99 years had lower likelihood of receiving revascularizations.	↓↑
Kurdyak [281] 2012 Canada	2002-2006	SCZ versus no SMI	1,087	20-104	Individuals with SCZ and incident acute MI were less likely to receive specialist care and cardiac procedures.	↓
Bresee [280] 2012 Canada	1995-2006.	SCZ versus no SMI	28,755	20+	Individuals with SCZ and coronary artery disease were less likely to undergo coronary revascularization.	↓
Wu [278] 2013 Taiwan	1996-2007	SCZ/BD versus no SMI	834	18+	Patients with SCZ and BD were half as likely to receive revascularization procedures after acute MI	↓
Bodén [284] 2014 Sweden	1997-2010	SCZ/BD versus no SMI	983	15+	The use of different acute treatment modalities for STEMI/LBBB was similar for patients with and without SMI over different time periods and across age strata	→
Gal [274] 2016, Israel	2000-2009	SCZ versus matched controls	2,277	40+	Lower rates of CABG and pacemaker implantation were recorded among service users with SCZ compared with matched controls	↓
Attar [279] 2017 Denmark	1995-2015	SCZ versus psychiatric healthy controls	47	NA	Patients with and without SCZ received similar levels of PCI (83% of SCZ patients, compared to 76% of controls) and CABG (2.4% of SCZ individuals, compared to 8.8% of controls).	→

Abbrevations: BD, bipolar disorder; CABG, coronary artery bypass graft; IHD, ischemic heart disease; MI, myocardial infarction; NA, not available; PCI, percutaneous coronary intervention; SCZ, schizophrenia; SMI, severe mental illness
→↓↑: Indicates similiar, lower and higher uptake, respectively, of invasive cardiovascular treatment among patients with SMI, compared to controls.

1.6 Gaps in the current knowledge base

Relatively few studies have investigated mortality in individuals with SMI and comorbid SUD (cf. section 1.4.3, age 30), despite the high comorbidity between SMI and SUD. The identified studies also show contradictory findings. Studies assessing the impact of comorbid SUD in individuals with SCZ or SMI have found both increased [12, 130, 220-226] and decreased [219] all-cause mortality, similar [130] and increased [227, 287] suicide mortality, and increased [226] and similar [151, 254] cardiovascular mortality compared to SCZ individuals without SUD. Studies of SUD individuals report both higher [229, 231], similar [141, 216, 228, 231, 288, 289], and lower [217] mortality in individuals also diagnosed with a psychotic disorder, compared to individuals with SUD-only, depending on type of SUD and gender [231]. Of the identified studies on this topic, only four studies [130, 220, 221, 223] had mortality in the dually diagnosed as the main topic, while other studies examined the topic in secondary or subgroup analyses. Only a few studies with complete national coverage have investigated all-cause [151, 222, 223, 226, 231], cause-specific [222, 226] or sex-specific [222] mortality in patients with SCZ and/or SUD. Neither of these reported results for different age groups.

There is also a scarcity of comparative studies investigating undiagnosed CVD in persons with and without SMI, particularly in older persons and those in a severe phase of CVD (i.e. close to cardiovascular death), cf. section 1.5 (page 32). Two previous nationwide studies have reported on the proportion of unrecognized CVD among people with SMI who died of CVD, but only in unadjusted sub-analyses [151, 152]. Previous studies [151, 152, 246] on this topic did not differentiate between sexes, although sex is associated with severity of both SMI [50, 290, 291], CVD [292] and health care utilization [293, 294]. As premature death from CVD mainly is due to modifiable causes, premature cardiovascular deaths in individuals with SMI may be prevented if CVDs are timely identified and treated. It is thus important to investigate to what extent individuals with SMI are in contact with and treated in primary or specialized somatic health care prior to cardiovascular death.

In line with this, a recent meta-analysis noted that it is unclear at what stage along the clinical pathway persons with SMI lose access to CVD prevention and care [295]. Previous studies on uptake of prevention and treatment of CVD have mainly been conducted in the UK or the USA, where either financial incentives (UK) or lack of universal health care (US) may

hamper the generalizability of findings to other settings. With the exception of post-MI treatment, there is also a scarcity of studies on uptake of specialized examinations and treatment for CVD among persons with SMI (see section 1.5.4, page 35). While many previous studies have focused on prevention and treatment of CVD in relatively young persons with SMI, likely to be in an early and probably less severe phase of CVD [268, 270, 272, 296], less is known about whether the lower uptake of CVD-related diagnostic tests and cardiovascular treatment persists in the more severe phase of CVD, i.e. in the period prior to cardiovascular death. As far as we know, no previous studies on this topic have investigated uptake of diagnostic tests and invasive treatment of CVD for individuals with SCS or BD across health care sectors. Studies that can help answer the question of where along the pathway of care disparities in cardiovascular care arise are thus needed.

1.7 Aims of the thesis

The overall aim of this thesis was to investigate mortality among patients with SCZ and/or SUD in nationwide Norwegian data, and to explore the impact of SMI on detection and treatment of CVD. The specific aims of the thesis were:

1. To investigate SMRs for all-cause mortality in patients with SCZ, SCZ-only, SUD-only and comorbid SCZ and SUD, diagnosed in Norwegian psychiatric or somatic specialist health care (paper I)
2. To describe how much of the excess mortality that could be attributed to a concurrent diagnosis of SCZ and SUD (paper I)
3. To investigate age-, sex-, and cause-specific SMRs in patients with SCZ-only, SUD-only or SCZ+SUD (paper I)
4. To examine if individuals with and without SCZ or BD had equal likelihood of not being diagnosed with CVD prior to cardiovascular death, compared to those without SCZ or BD who died from CVD (paper II)
5. To describe characteristics of individuals with SCZ or BD undiagnosed with CVD prior to CVD death (paper II)
6. To examine whether SCZ and BD were associated with lower prevalence of diagnostic testing and invasive treatment of CVD prior to cardiovascular death, compared to patients without SCZ or BD who died from CVD (paper III)
7. To investigate in which setting (i.e. primary or specialist health care) any disparities in access to cardiovascular care among patients with SCZ or BD arise (paper III)

2 Materials and methods

2.1 Data sources

We utilized national diagnostic data and information on health care utilization from the Norwegian Patient Registry (NPR) [297] and the Norwegian Directorate of Health's system for control and payment of health reimbursements in primary care (the KUHR database) [298], and mortality data from the Norwegian Cause of Death Registry (CDR) [299]. Accurate linkage across data sources was obtained using the unique and encrypted 11-digit personal ID number included in all registries.

Annual number of deaths in gender-stratified five-year age groups for the Norwegian population were obtained from the Norwegian Institute of Public Health [300], and annual population figures in the age groups 20-79 in the years 2009-2015 were obtained from Statistics Norway [301].

2.1.1 The Norwegian Patient Registry

The NPR is a national administrative register covering all specialized health care in Norway, with person-identifiable data since April 2007. The registry contains all contacts in government-owned hospitals and outpatient clinics, as well as private hospitals and health clinics with governmental reimbursement. The coverage in the NPR is almost complete for the years 2008-2016, with the exception that about 15% of contacts with private somatic health clinics with governmental imbursement are missing in the period, mainly due to technical problems with reporting [302, 303], and that data for SUD treatment institutions is missing for 2008 (included in the NPR from 2009).

Diagnostic codes in the NPR are recorded according to ICD-10, with up to 20 codes per episode. Medical, surgical and radiological procedure codes are recorded according to The Norwegian Classification of Medical Procedures (NCMP), the NOMESKO Classification of Surgical Procedures (NCSP), and the Norwegian Classification of Radiological Procedures (NCRP), respectively, all allowing up to 20 procedures per episode. Radiological procedure codes are available only from 2016. Outpatient fees are recorded according to national tariff agreements, with up to 15 codes per episode.

2.1.2 The KUHR database

The KUHR database, person-identifiable from 2006, is a national administrative register containing claims data for primary care providers and private specialists with public funding, as well as laboratory claims for both primary and specialized health care. As these health care services are funded mainly on a fee-for-service basis, the completeness of reported episodes in the KUHR database is considered to be almost 100%. The data quality, including registration of the national identity number, is assumed to have improved after the introduction of electronic registration of deductibles in 2009.

In the present thesis, we had access to data on procedures provided by GPs and private specialists, and laboratory tests performed in primary and specialized health care. Diagnostic codes for GP contacts follow the ICPC-2, while diagnostic codes for private specialists with governmental reimbursement, and laboratory claims from specialized heath care, follow the ICD-10. At least one diagnosis per patient contact must be recorded to receive refunding.

2.1.3 The Cause of Death Registry

The CDR contains information regarding underlying, contributing and immediate cause of death since 1951, and also patient demographics and information on circumstances surrounding the death. All deceased residents are included, irrespective of whether they died in Norway or abroad, and since 2012 also non-residents (tourists, workers, migrants etc.) who died in Norway have been included [304].

The basis of cause of death statistics is the mandatory medical death certificate issued by the physician who certified the death. Immediate, underlying and contributing causes of death are stated in a standardized certificate, using medical terminology and common language. The key concept is the underlying cause of death, defined as the disease or injury that started the series of morbid conditions that led to death, or the external circumstances (e.g. accidents, violence) that caused death. The term “contributing cause of death” refers to other significant conditions contributing to the death, but not related to the disease or condition causing it.

In some cases (currently 2%) [304], the CDR may request supplementary information from doctors, hospitals or other institutions (such as nursing homes). In addition, the CDR receives diagnostic information from the Cancer Registry (cancer deaths) and the Medical Birth Registry (deaths during the first year of living), reports of road traffic accidents, and

notifications of autopsy findings conducted in departments of pathology or at the Forensic Institute. During the period 2008-2013, the proportion of autopsies in Norway remained stable at 7.5%, equally distributed between medical and forensic autopsies [305]. In approximately half of all cases, the underlying cause of death is determined using the Automated Classification of Medical Entities (ACME) software (since 2005) or the IRIS software (since 2011) [304, 306], which processes data according to the rules of the ICD-10. Underlying cause of death in the remaining cases are set by professional coders in the CDR (supervised by medical doctors) based on the death certificate and any supplementary information. The CDR is linked to the Norwegian Population Register to capture deaths that are only registered in the latter registry.

In Norway the coverage and completeness in the CDR is high (98%), with missing death certificates mainly for residents who died abroad [304]. In the most recent quality assessment of cause of death statistics covering the period 2005-2012, the CDR was ranked in the best group, but below the other Nordic countries [307].

2.2 Study samples

The papers included in the current thesis utilized two different linked datasets. Dataset 1 (study I) included all episodes in all in- and outpatient settings within Norwegian specialized health care for all residents in Norway with a registered diagnosis of SCZ or SUD (see definitions on page 50). In studies II and III, we utilized another dataset that included all episodes for all patients who had a CVD diagnosis recorded on the death certificate. Figure 1 and Figure 2 give an overview of data sources, selection criteria, included variables and exclusion criteria for these two data sets, respectively.

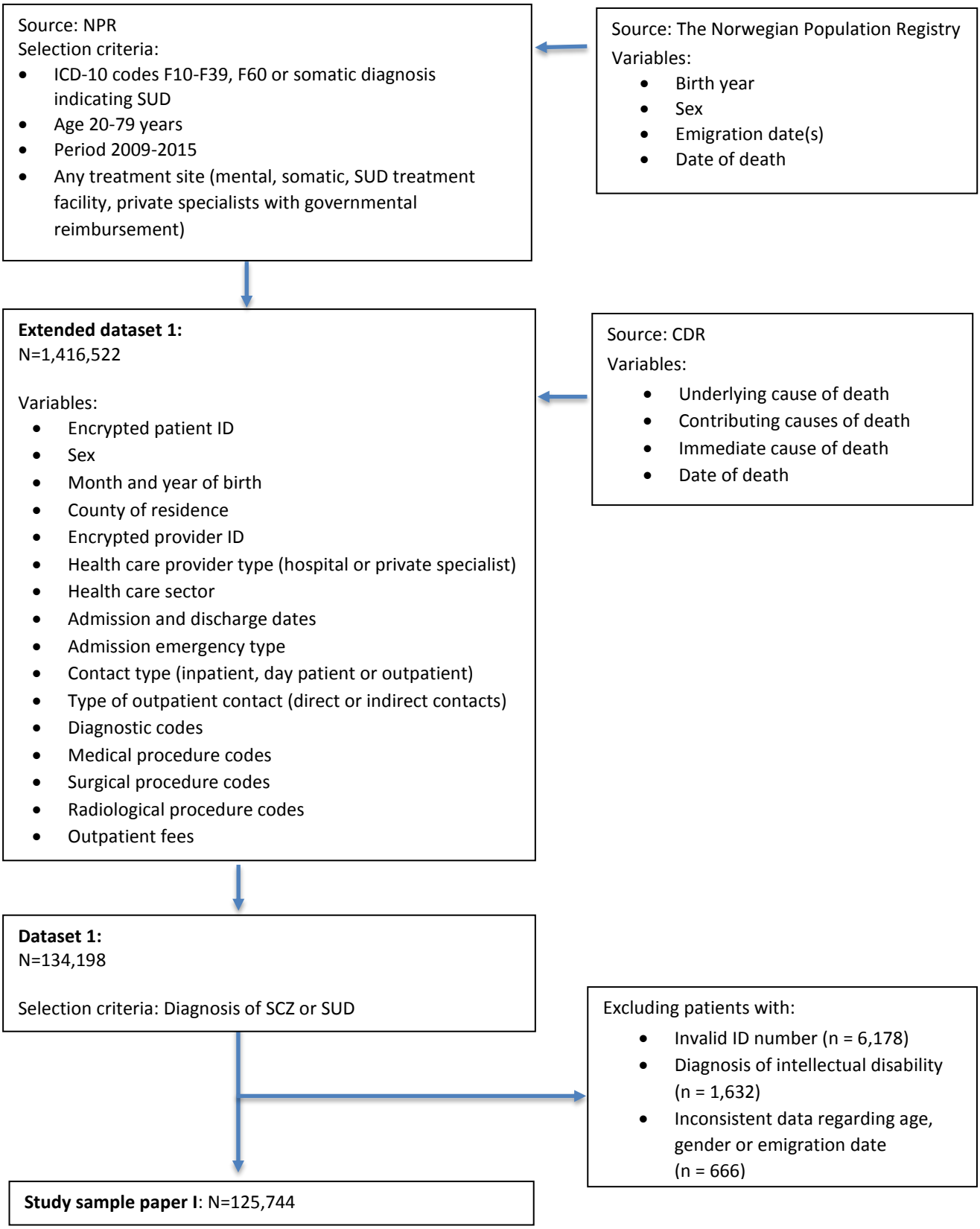


Figure 1 - Data sources, number of participants and variables in dataset 1

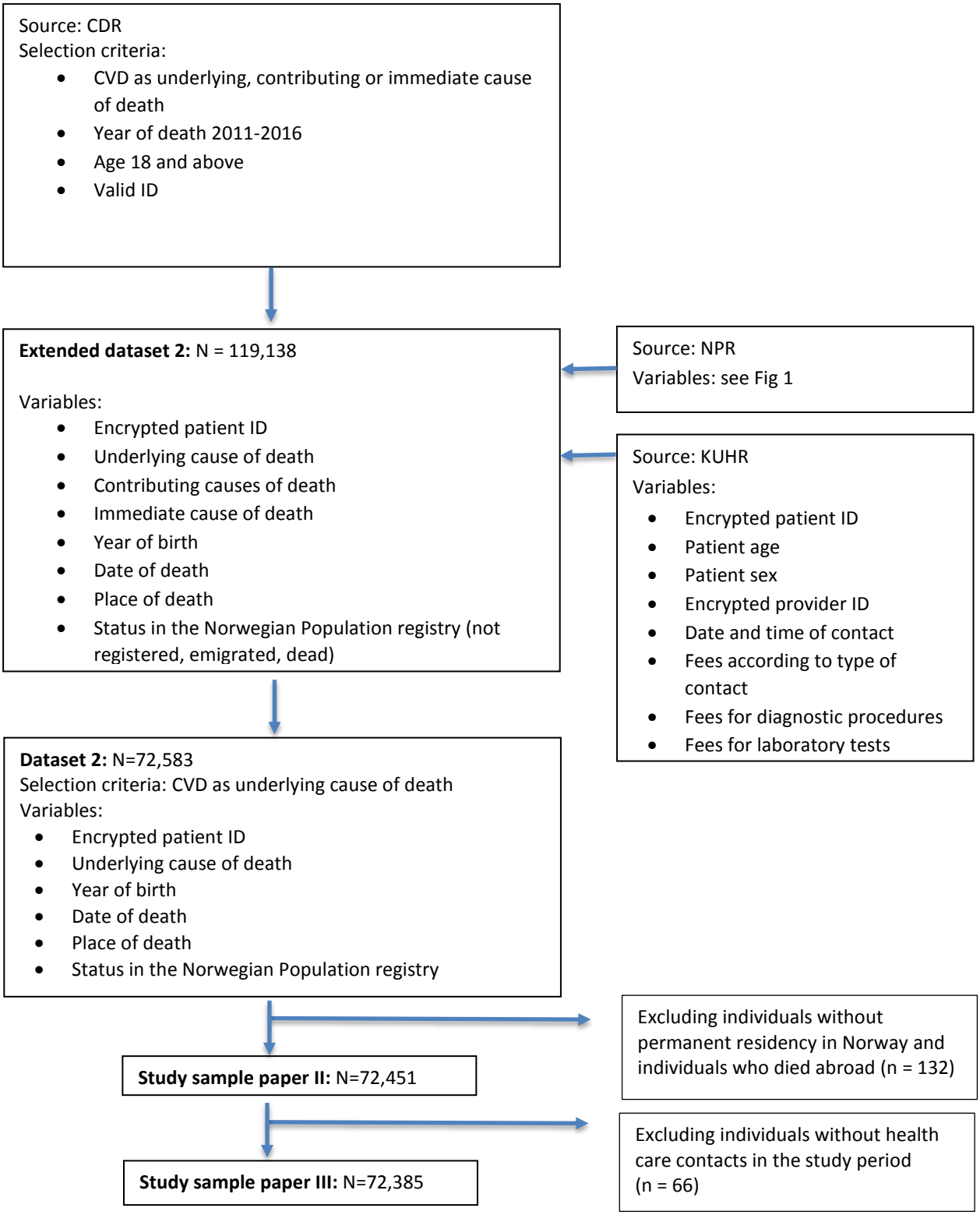


Figure 2 - Data sources, number of participants and variables in dataset 2

2.3 Study design

Classifications of epidemiological studies usually distinguish between designs according to the directionality or timing of data collection (i.e. prospective, retrospective or cross-sectional studies), and according to whether the study involve sampling on an outcome (case-control study). These classification schemes are less relevant in studies utilizing linked and complete secondary population-wide data, as in our case. Pearce et al [308] proposed an alternative classification for epidemiologic studies with dichotomous outcomes, using two criteria; (i) the type of outcome measure under study (incidence or prevalence), and (ii) whether there is sampling on the basis of the outcome. According to this classification scheme, there are only four basic study designs when the outcome is binary, namely incidence studies, incidence case-control studies, prevalence studies and prevalence case-control studies [308]. Adopting this terminology, the design in study I can be described as an incidence study, and the designs in paper II and III as prevalence studies.

Alternatively, in the more conventional terminology, the study design in paper I could be described as a population-based open historical cohort study (prospective design). A cohort is here defined as any designated group of persons who are followed or traced over a period of time. The study designs in and in paper II and III could, in the conventional terminology, be described as national cross-sectional studies.

The design in paper II and III, a follow-back of deceased persons, is not a classic epidemiological design. When we chose to do this, it was because it identifies people who all had CVD with approximately the same severity (since they died of it), allowing comparison of groups with CVD with and without SMI. It also enabled us to identify people with CVD who did not use health care services before death, which increased the generalizability.

An overview of included patient groups, methods applied, covariates and outcome measures in paper I-III is given in Table 11.

Table 11 - Overview of patient groups, methods, covariates and outcome measures in paper I-III

	Patient groups	Methods	Covariates (main model)	Outcome measure
Paper I	SCZ SCZ-only SUD-only SCZ+SUD	Stratification	Age Gender Calendar year	Standardized Mortality Ratio (SMR)
Paper II	SCZ BD No SMI	Logistic regression	Age Gender SUD Somatic comorbidity	Odds Ratio (OR)
Paper III	SCZ BD No SMI	Log-binomial regression, Poisson regression with robust error variance	Age Gender	Prevalence Ratio (PR)

2.4 Definitions of diagnostic groups

In paper I, patients were included in the SCZ group if a SCZ-spectrum diagnosis (F20-F29) was recorded in the NPR during 2009-2015. The SUD group included patients with a diagnosis of mental and behavioral disorders due to use of psychoactive substances (F10-F19, excluding tobacco (F17)), and patients with at least one somatic diagnosis strongly indicating substance abuse (ICD-10 codes E24.4, E52, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K86.0, O35.4, O35.5, Z50.2, Z50.3, Z71.4, Z71.5, Z72.1 and Z72.2). Patients identified by somatic diagnoses only constituted 4.1% of the SUD group. A total of 275 patients treated in substance use treatment facilities, with a diagnosis of SCZ, but no registered diagnosis of SUD (excluding pathological gambling (ICD-10 code F63.0)), were included in the SCZ+SUD group. In subgroup analyses, we differentiated between patients with a non-alcohol SUD (F11-F16, F18-F19, Z50.3, Z71.5 and Z72.2), and patients with alcohol use disorder only. Hard drug use disorder was deemed present if the patient was diagnosed with disorders due to use of opioids (F11), cocaine (F14), other stimulants (mostly amphetamines, F15), hallucinogens (F16), and multiple drug use and use of other psychoactive substances (F19). Volatile solvents (F18) were also included in the latter definition, although not strictly qualified for the term "hard drug use disorder".

In paper II and III, deceased individuals aged 18 years or older were included if a diagnosis of CVD (ICD-10 codes I00-I82) was recorded as underlying cause of death in the death certificate. Individuals were included in the SMI group if a diagnosis of narrow SCZ (ICD-10

code F20 or ICPC-2 code P72) or BD (ICD-10 codes F30-F31 or ICPC-2 code P73) was recorded in the NPR or the KUHR database during the years 2008-2016, or in the death certificate. Individuals diagnosed with both SCZ and BD (N=97) were included in the SCZ group only. In paper II and III, a diagnosis of CVD (recorded before death) was considered present if ICD-10-codes I00-I82 or G45, or corresponding ICPC-2 diagnoses (codes K70-K71, K74-K80, K82-K84, K86-K87 and K89-K94) were recorded in the NPR or the KUHR database in the period from inclusion (January 1, 2008) and up to one month prior to death. In paper II, diagnoses of CVD recorded only within the last month prior to death were not counted to avoid including CVDs secondary to other fatal diseases.

2.5 Outcome measures

All-cause and cause-specific mortality, which was the outcome measure in study I, is commonly used as a quality indicator at the population level [309], and as a mean to identify treatment deficiencies and disadvantaged population subgroups. Due to this, and its indisputable character, mortality has been termed "the gold standard of clinical outcome" [310].

In paper II and III we used process measures (see section 1.5.2, page 33) as study endpoints (i.e. receipt of diagnosis or certain health care services). These measures make it possible to identify deficiencies in relation to best practice, and are as such valuable from an equity and policy perspective in aiding decisions how to target and improve services.

2.6 Statistical methods

Statistical methods are broadly of two types: Stratification and regression techniques. We used a stratification method in paper I (SMR), and regression methods in paper II and III (logistic regression, log-binomial regression and Poisson regression, see descriptions below).

2.6.1 Standardized Mortality Ratio

The SMR reflects the relative mortality of the patient group compared to that of the general population and is computed as the ratio of the observed to the expected number of deaths. The expected number of deaths was calculated as the total number of person-years at risk in each sex-, age group- and calendar year band, multiplied by the corresponding age- (5-year age

groups), sex- and calendar-year specific (2009-2015) death rate in the general population. A SMR of one indicates that the study population had the same mortality as the reference population, while a SMR greater than one indicate increased mortality in the study population. Age was defined as attained age at the end of each calendar year, as we did not have access to exact birth dates. Person-years at risk contributed by persons who moved from one age band to the next during follow-up was assigned to the respective sex-, age group- and calendar year bands, using the "lexis" method [311]. The number of excess deaths was calculated as the difference between observed and expected deaths.

The study cohort in paper I was followed from the admission date of the index episode (their first consultation during 2009-2015). Patients already hospitalized before January 1, 2009 (n=2,633), were followed from this date. To account for diagnostic instability in SCZ patients, we defined an extended diagnostic spectrum covering SCZ (F20-F29), affective disorders (F30-F39), and personality disorder (F60). If a diagnosis of SCZ was ever recorded, the index episode was defined as the first episode with a diagnosis within the extended diagnostic spectrum. Follow-up ended on December 31, 2015, on the date of emigration from Norway, on December 31 in the year of the 79th birthday, or on the date of death, whichever came first.

Biased SMRs may be a major problem when the exposure is common, and the general population is used as reference [312]. In contrast to SCZ, unnatural deaths in the SUD subgroup constitute a large proportion of unnatural deaths in the general population, implicating risk of biased SMRs for unnatural causes of death in this subgroup. We consequently investigated the impact on SMRs for poisoning, suicide and all-cause mortality in patients with SUD (with and without SCZ), using an unexposed comparison group (i.e. no recorded SUD in specialized care), rather than the general population, for calculation of the expected number of deaths. This unexposed comparison group constituted the Norwegian population excluding subjects with recorded SUD in specialized health care and corresponding deaths from the relevant age-/gender group in the reference population. The mortality rates in this unexposed population was calculated and applied when computing the expected number of deaths.

Comparisons of SMRs between different populations are, strictly speaking, invalid unless all stratum-specific study populations are a constant multiple of the specific population rates (the

assumption of proportionality) [313]. The extent of this bias will be small, however, unless large departures from multiplicativity is present [314]. A simulation study that investigated the impact on SMRs when different age-adjustment standards were used, found that the resulting differences were too small to change conclusions [315]. In these simulations, the SMRs changed by 6-8% when the age distribution was changed from an extreme, but realistic, young distribution to an extreme, but realistic, old age distribution.

2.6.2 Logistic regression

Logistic regression is a commonly used, robust and efficient method to study the effect of independent variables on a binary outcome. The outcome of the logistic regression is the odds ratio (OR). The odds is defined as the probability of an event to the probability of a non-event (i.e. logit(p)=log(p/(1-p)), where p is the probability of the outcome)[316]. An OR of one means that the odds are the same in the two comparison groups, while an OR greater than one indicates that the event is more likely to occur in the first group. A 95% confidence interval (CI) is routinely reported with the OR as a measure of precision.

Logistic regression typically requires a large sample size, and is based on the following assumptions: (i) independent observations (i.e. no repeated measurements or matched data), (ii) absence of multicollinearity (little or no correlation between independent variables), (iii) no extreme values (outliers) in continuous predictors, and (iv) independent variables are linearly related to the log odds. Logistic regression does not require normally distributed residuals and homoscedasticity (i.e. constant variance), which are key assumptions in linear regression and general linear models.

2.6.3 Log-binomial regression / Poisson regression with robust error variance

In epidemiologic research, the relative risk (RR) is often the parameter of interest. Logistic regression, Cox and Poisson regression tend to provide comparable estimates of RR, leading to similar conclusions, when the outcome is rare. However, when the outcome is common (>10%), the OR substantially overestimates the RR, and also produce overly wide confidence intervals [317]. Although the use of OR is correct if interpreted appropriately, the RR interpretation often given to the OR is misleading when the outcome is common. Several authors [317-322] have thus advocated the use of log-binomial regression [318] or Poisson

regression with robust error variance [320] in cross-sectional or prospective designs with common outcomes, since the outcome measures (i.e. RR in prospective studies and prevalence ratios (PR) in cross-sectional data) in these studies are considered more interpretable and easier to communicate to non-specialists than the OR. The log-binomial regression yields more efficient estimators, while the Poisson model with robust error variance is less affected by outliers [323]. The log-binomial model is known to be less stable than the logistic model, and sometimes fail to converge [320]. When this is the case, Poisson regression with robust error variance may be applied [322]. Like logistic regression, but unlike Poisson regression, the log-binomial method always gives estimates of probabilities between 0 and 1.

Based on the arguments above (i.e. misinterpretation of ORs, and overly wide confidence intervals in logistic regression when the outcome is common) we used log-binomial regression to examine the common outcomes in paper III. For one specific endpoint (i.e. presence of diagnostic tests in primary care), the model did not converge, and Poisson regression with robust error variance was applied in this particular analysis [317].

2.7 Statistical modeling

2.7.1 Covariate selection

In observational studies, covariate selection (i.e. adjusting for potential confounders and avoiding over-adjustment) is a major concern. Confounding is defined as a distortion of the estimated effect of an exposure on an outcome due to uncontrolled common causes of both the exposure and the outcome [324, 325]. As confounding can both strengthen, attenuate and eliminate the actual relationship between the exposure and the outcome, it is essential to control for confounding in observational studies. If identified and measured, confounding can be controlled for in several ways, by restriction, matching, stratification or multivariate adjustment techniques.

In study I, which applied a stratification method, we only included age, gender and calendar-year, as there are limitations on covariates due to limitations in available nationwide data. Also, random variation may be large when the number of strata becomes very large.

In regressions methods, such as those used in paper II and III, confounding has often been identified through statistical associations, using stepwise selection methods or the change-in-estimate criterion. However, many authors have emphasized that confounder identification should be grounded on an a priori understanding of the causal relationship between the variables under study, and not on statistical associations [314, 325]. Another approach has thus been to check whether some necessary criteria for confounding are met, applying a somewhat weaker definition of confounding than the definition referred to above. In this approach, for a variable to be considered a confounder, the variable must be an independent risk factor for the outcome, must be associated (causally or non-causally) with the exposure, and must not be on the causal pathway between the exposure and the outcome [326].

Proponents of the directed acyclic graph (DAG) methodology (also called causal diagrams) argue, however, that all these approaches, under certain circumstances may increase confounding rather than decrease it, due to omission of important confounders or inappropriate adjustment for non-confounders [327, 328]. A DAG is a graphical representation of the causal relationships believed to exist between the variables of interest. A DAG helps to identify confounders (common causes) which should be adjusted for, and colliders (common consequences), which should not be adjusted for. Causal diagrams are also a useful way to clarify and communicate qualitative beliefs about the causal assumptions underlying the analysis.

In a DAG, variables are linked by arrows that represent direct causal effects (protective or causative) of one variable on another variable. As a cause must precede its effects, the graphs are always acyclic. A collider is a variable that is directly affected by at least two other variables in the same path (recognized when two or more arrows meet in the same path), where the ancestor variables may or may not themselves be correlated. Conditioning on a collider introduces bias (opens a "backdoor path" in the DAG terminology). After creating a DAG, mathematically proven rules can be applied to help decide which variables must be adjusted for in order to remove confounding and collider bias, to the extent that this is possible using the available data. Often causal pathways are not fully understood, as in the present thesis. In such cases, creating several causal diagrams under differing assumptions about causal relationships can help assessing the robustness of the estimated effects.

We selected covariates on the basis of prior research indicating that they were common causes of SMI and the different outcomes in paper II and III, with the limitations given by the available data. Selection of covariates were supported by the browser-based program DAGitty, version 2.3, which provides the minimum required data set to estimate unbiased total and direct effects [329].

Figure 3 and Figure 4 show two examples of DAGs underlying the current thesis. These figures show two alternative descriptions of the possible relationship between presence of SMI and uptake of CVD-related diagnostic tests prior to cardiovascular death (paper III). These DAGs differ in the way SUD, somatic comorbidity, early life stressors and genes are considered to act (i.e. as confounders, mediators or unrelated variables). Red nodes indicates measured confounders, while blue and grey nodes indicates measured and unmeasured variables, respectively. Green lines indicates causal pathways and red lines biased pathways. No line indicates independency.

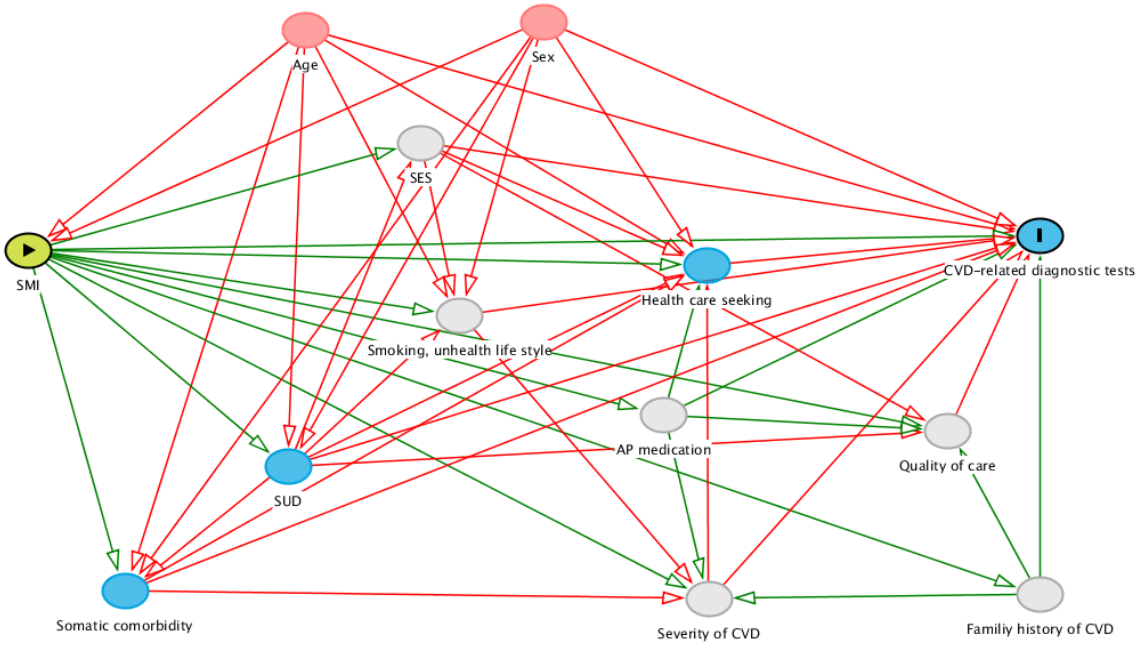


Figure 3 - Directed acyclic graph (paper III) with SUD and somatic comorbidity as mediators

The causal relationships displayed in Figure 3 are based on an assumption that SUD and somatic comorbidity, as well as socioeconomic status (SES), lies on the causal pathway

between SMI and uptake of CVD-related diagnostic tests, and also that genes and early life stressors are unrelated to the outcome. In this situation, the minimal sufficient adjustment set for estimating the total effect of SMI on uptake of CVD-related diagnostic tests is age and sex. Estimation of unbiased *direct* effects under the specified causal relationship in Figure 3 is not possible, as it would require measurement of all covariates.

Figure 4 shows an alternative description of the possible causal relationship in paper III, in which SUD [29], somatic comorbidity [69], genes [25, 330] and early life stressors [31, 33, 34, 69] are considered possible confounders. As we lack data on genes and early life stressors, unbiased estimates are impossible in this scenario.

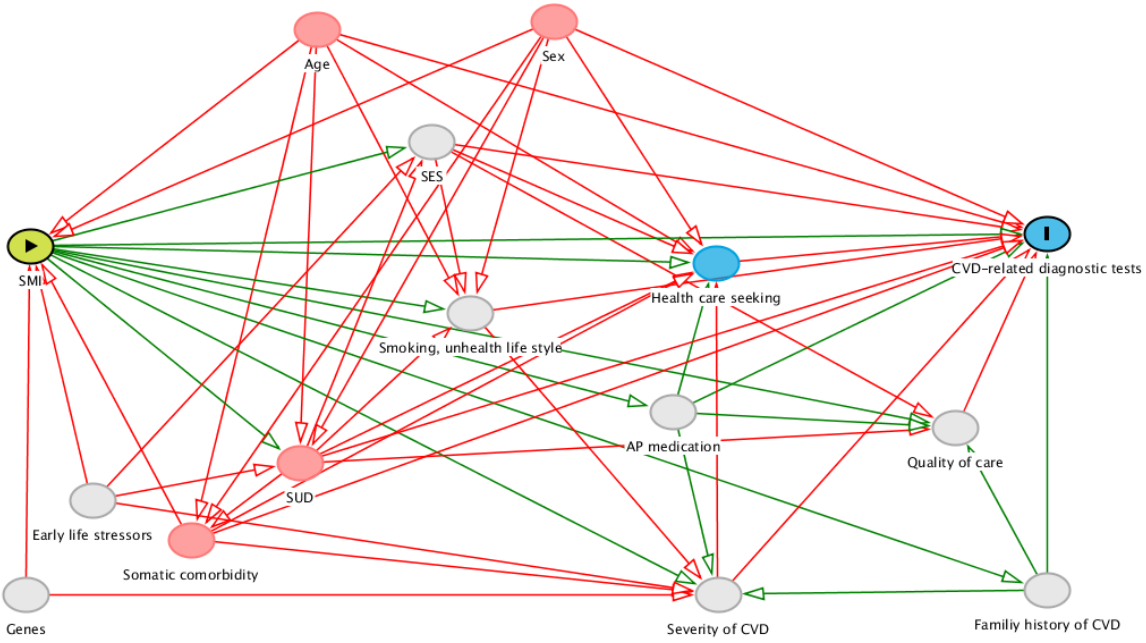


Figure 4 - Directed acyclic graph (paper III) with SUD, genes, early life stressors and somatic comorbidity as confounders.

As we did not know which of these models that best describes the true relationship between SMI and uptake of CVD-related diagnostic tests, we performed analyses according to both DAGs. However, the estimated effects differed little from one another. The same was true for models including (i) age and sex, versus (ii) age, sex, SUD and somatic comorbidity in paper II (DAGs not shown). In paper II, we selected the main model based on the overall model fit, using log likelihood tests with better fit characterized by a smaller difference between

observed and model-predicted values. In paper III, we chose the simplest model (i.e. adjustment for age and sex), as the estimates were similar, and the improvement in model fit negligible, when SUD and somatic comorbidities were included.

2.7.2 Analyses of effect modification and analytical strategy

Effect modification by sex, age and patient group was assessed by including the product of two variables in the regression analysis. In paper II, we found interaction between sex and diagnostic groups, but no linear interactions between age and diagnostic groups. We thus presented sex-stratified analyses in paper II. In paper III, we found no interaction with sex, but interaction between age above 90 year and patient group when analyzing uptake of specialized diagnostic tests and treatment. Because of the many endpoints presented in paper III, we chose not to stratify according to age, but presented results from analysis including all age groups. A sensitivity analysis excluding those aged 80 and above, gave unchanged conclusions for the main outcomes.

In paper II, we used a three-stage analytical approach showing (i) sex-specific unadjusted proportions and ORs, (ii) sex- and age-adjusted ORs, and (iii) ORs adjusted for sex, age, modified mean score on the CCI and SUD. Due to the many endpoint applied in paper III, and the negligible impact of also adjusting for SUD and somatic comorbidities, we only presented age- and sex-adjusted results in this paper.

In all three papers, we included extensive sensitivity analyses to strengthen our results and conclusions. All descriptive and statistical analyses were performed using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, N.C.).

2.8 Ethics

All patient data were fully de-identified when we received the data. In Norway, studies with de-identified information from medical health registries do not require participant consent. Legal basis and exemption from professional secrecy requirements for the use of personal health data in research were granted by the regional committee for medical and health research ethics (2014/72/REK nord). Based on privacy and confidentiality considerations, we abstained from requesting information on possible backward-identifying variables, such as date of birth and patient municipality.

3 Results

3.1 Summary of paper I

The main aim of study I was to investigate all-cause and cause-specific mortality among patients with SCZ and/or SUD in specialized health care in Norway, compared to the general population. Besides presenting nationwide estimates of mortality among those with SCZ in Norway for the first time since the 1970s, an important motivation was to investigate the impact of concurrent SUD among those with SCZ on excess mortality, and vice versa.

The study included 125,744 individuals aged 20-79 years, of which 12,318 (9.8%) died during follow-up. Comparing with the expected number of deaths based on the mortality of the general population, we found that patients in specialized health care with SCZ, SCZ-only or SUD (with or without SCZ) had a five-, four- and seven-fold increased all-cause mortality, respectively. Mortality was elevated for both genders, in all age groups and for all considered causes of death, with the highest SMRs observed for poisoning, suicides and respiratory diseases. Very high SMRs for poisoning were noted in women with SUD (with or without SCZ). The highest SMRs were found in the age group 20-39, mainly due to unnatural causes of death. The excess mortality corresponded to more than 10,000 premature deaths during a mean follow-up of four years (84% of all deaths in the cohort), implicating that five out of six patients with SCZ and/or SUD treated in specialized health care died prematurely. Four out of five deaths among those with SCZ-only, and 70% of deaths among those with SUD-only, were due to natural causes, mainly cancer and CVD (SCZ) and "other natural deaths", including mental and behavioral disorders (SUD). In patients with both SCZ and SUD, only 41% of deaths were due to natural causes. Poisoning and suicide were equally common, and caused the majority of deaths in males (56%) and nearly half of the deaths in females (46%).

About 27% of the excess deaths in patients with SCZ could be attributed to SUD (or factors associated with SUD), with the strongest effects in men and in the youngest. Presence of SCZ in patients with SUD had less effect on hypothetical numbers of death, implicating that the main reason for the high SMRs in comorbid patients was the SUD component.

Deaths due to poisoning and suicide in SUD patients in our sample constituted a large proportion of all deaths from these causes in Norway in the years 2009-2015. Using unexposed persons (i.e. individuals without a SUD diagnosis in specialized care), rather than

the complete population, to calculate expected deaths, resulted in a three-fold increase in SMR for poisoning in men and a doubled SMR for poisoning compared to the original model, showing that SMRs from unnatural causes may be substantially underestimated when using the general population as comparator.

3.2 Summary of paper II

CVD is one of the main causes of life years lost among persons with SMI, and underdiagnosed CVD may contribute to this. In paper II, we examined if individuals with and without SCZ or BD had equal likelihood of not being diagnosed with CVD prior to cardiovascular death. A secondary aim was to describe demographic characteristics, comorbidity and health care utilization in individuals with SCZ or BD and undiagnosed CVD prior to death.

The study included 72,451 Norwegian citizens aged 18 years or above who died due to CVD in the period 2011-2016. Of these, 814 were previously diagnosed with SCZ and 673 with BD. The study showed that individuals with SCZ had 66% higher odds (OR 1.66; 95% CI 1.39-1.98), women with BD 38% higher odds (OR 1.38; 95% CI 1.04-1.82), and men with BD the same odds (OR 0.88, 95% CI 0.63-1.24) to not be diagnosed with CVD prior to cardiovascular death, compared to individuals without SMI who died from CVD. The higher odds of undiagnosed CVD applied to all main causes of cardiovascular death. Women with SCZ had particularly high odds of undiagnosed CVD prior to a MI death, whereas the higher odds of undiagnosed CVD among women with BD was explained by undetected fatal cerebrovascular disease.

Individuals with SMI who died from undiagnosed CVD died approximately ten years younger than individuals with undiagnosed CVD without SMI. Almost all (98%) individuals with SMI and undiagnosed CVD had visited primary or specialized somatic health care prior to death, compared to 88% among individuals without SMI.

Compared to individuals with SMI and diagnosed CVD prior to death, individuals with SMI and undiagnosed CVD prior to death died younger, more often at home (SCZ only), less often in a nursing home, more often at places outside home and health care institutions (BD only), and more often from IHD (SCZ only). They also had fewer health care contacts in primary

care, fewer admissions and outpatient visits in specialized somatic care prior to death, and more recorded SUD than individuals with SMI and diagnosed CVD.

3.3 Summary of paper III

As a follow-up of the findings in paper II, we investigated in paper III the prevalence of diagnostic testing and invasive treatment of CVD prior to cardiovascular death among patients with SCZ or BD, compared to patients without SCZ or BD who died from CVD. A secondary aim was to investigate in which treatment setting (i.e. primary or specialist health care) any disparities in uptake of cardiovascular care did arise.

The study included 72,385 individuals who died of CVD in the years 2011-2016, who had utilized primary or specialized somatic care in the period from January 1, 2008 until death. Of those included, 814 were diagnosed with SCZ and 673 with BD. Compared to patients without SCZ or BD, patients with SCZ had similar prevalence of CVD-related diagnostic tests in primary care, but lower uptake of specialized diagnostic CVD examinations and invasive CVD treatment. The lower prevalence of CVD examinations was particularly pronounced for lengthy procedures or those that require physical contact with the patient (such as 24 hour blood pressure measurement, echocardiograms, coronary angiography and ultrasound of peripheral vessels). Patients with BD had similar prevalence of diagnostic CVD examinations in primary and specialized somatic care as patients without SMI, but lower prevalence of invasive CVD treatment. Among those with diagnosed CVD prior to cardiovascular death, prevalence of invasive cardiovascular treatment did not differ between those with and without SMI, with the exception of lower prevalence of vascular surgery in patients with BD.

Patients with SMI also had fewer contacts with a recorded CVD diagnosis both in primary and specialized somatic care, and a shorter time span from first CVD-diagnosis in the observation period until cardiovascular death.

4 Discussion of results

4.1 Main findings

1. Patients in specialized health care with SCZ, SCZ-only or SUD (with or without SCZ) had a five-, four- and seven-fold increased all-cause mortality, respectively, compared to the general population (paper I)
2. Mortality was elevated for both genders, in all age groups and for all considered causes of death, with the highest SMRs observed for poisoning, suicides and respiratory diseases. Very high SMRs for poisoning were noted in women with SUD (paper I)
3. The majority of deaths among those with SCZ-only or SUD-only were due to natural causes, while the majority of deaths among those with a dual diagnosis were due to external causes of death, particularly poisoning and suicide (paper I)
4. The excess mortality corresponded to more than 10,000 premature deaths during a mean follow-up of four years (paper I), implying that five out of six patients with SCZ or SUD died prematurely (paper I)
5. Approximately 27% of the excess deaths in patients with SCZ could be attributed to SUD (or factors associated with SUD), with the strongest effects in men and in the youngest (paper I)
6. SMRs for poisoning and suicide in patients with SMI were substantially underestimated when the general population was used as comparison. This bias was particularly severe for patients with SUD (paper I)
7. Persons with SCZ and women with BD were more likely, and men with BD equally likely, not to be diagnosed with CVD prior to cardiovascular death, compared to persons without SMI (paper II)
8. The higher odds of undiagnosed CVD among persons with SCZ applied to all main causes of cardiovascular death, and was particularly high for women with SCZ who died from MI (paper II)
9. Almost all (98%) individuals with SMI and undiagnosed CVD had visited primary or specialized somatic health care prior to death, compared to 88% among individuals without SMI (paper II)

10. Compared to individuals with SMI and diagnosed CVD prior to death, individuals with SMI and *undiagnosed* CVD prior to death died younger, more often at home (SCZ only), or outside home and health care institutions (BD only), and more often from IHD (SCZ only). They also had fewer health care contacts in primary care, fewer admissions and outpatient visits in specialized somatic care prior to death, and more recorded SUD than individuals with SMI and diagnosed CVD (paper II)
11. Patients with SCZ had similar prevalence of CVD-related diagnostic tests in primary care prior to cardiovascular death, but lower uptake of specialized diagnostic CVD examinations and invasive CVD treatment, particularly lengthy procedures or those that require physical contact with the patient (paper III)
12. Patients with BD had similar prevalence of diagnostic CVD examinations in primary and specialized somatic care as patients without SMI, but lower prevalence of invasive cardiovascular treatment (paper III)
13. Prevalence of invasive cardiovascular treatment did not differ between those with and without SMI among those diagnosed with a relevant CVD diagnosis prior to death (paper III)
14. Patients with SMI had fewer contacts with a recorded CVD diagnosis both in primary and specialized somatic care prior to cardiovascular death, and a shorter time span from first CVD-diagnosis in the observation period until cardiovascular death (paper III).

4.2 Comparison with other studies

4.2.1 Mortality among persons with SCZ

We found SMRs of 5.1 and 4.6 in men and women with SCZ (with and without SUD), which were considerably higher than the 2.6-3.1 increased mortality reported in previous meta-analyses [8, 17, 199]. Our results were also (probably) higher than the 2.3-4.5 and 1.9-4.6 increased mortality reported in men and women with SCZ in earlier Nordic studies [12, 200, 201, 204, 208, 331], with the exception of the 6-fold increased mortality reported in Finnish women with SCZ [204]. We found higher SMRs than most other Nordic studies, despite including prevalent cases and patients treated solely in outpatient settings, which, in isolation, would contribute to lower SMRs [332] (see also discussion of selection bias, page 74). Furthermore, the inclusion of SCZ-spectrum diagnoses instead of narrow SCZ, as well as the

inclusion of cases identified by secondary diagnosis only, lowered the estimates, as shown in the sensitivity analyses. Contrary to this, inclusion of older individuals suffering from somatic health problems increased the SMR in patients with SCZ in our study, also shown in the sensitivity analysis (see section 5.3.1 for a discussion of this). The relatively short follow-up (maximum 7 years), as well as the omission of patients in primary care, may also have led to a selection of more severe cases, oversampling patients with many health care episodes and patients with increased suicide risk, but this was not specific to our study. Most of the Nordic studies we refer to utilized data prior to 2009, which was the start of follow up in paper I (see Table 6, page 28). Two recent Danish studies on mortality in individuals with SCZ [195, 202], including data for the period 1995-2008 [202] and 1995-2014 [195] reported SMRs of similar magnitude as we did (i.e. SMR 4.6 in both studies). The most recent study also documented increasing SMRs every year the last two decades for both SCZ and BD [195]. One likely explanation for the high SMR found in our study is thus a rising mortality gap in SCZ patients compared to the general population, as suggested in a previous study from Northern Norway [10], studies from Denmark [13], and the meta-analysis by Saha et al [8]. Finally, the use of a single year at the start of the study period to calculate mortality rates in the general population, as done in some of these studies [1, 200, 201], may have attenuated the SMRs in these studies, since it does not take into account increased life expectancy in the general population over time.

For a discussion of cause-, age- and gender-specific mortality among persons with SCZ, see paper I.

4.2.2 Mortality among persons with SCZ and/or SUD

We found an increased all-cause and suicide mortality, and a similar cardiovascular mortality in patients with both SCZ and SUD, in accordance with some previous studies [130, 222-224, 226, 254, 333], but not in line with a study reporting decreased mortality in persons with co-occurring psychosis and cannabis use/abuse, compared to psychosis only [219]. We did not study mortality from cannabis use disorder separately, due to few deaths and suspicion of selective recording of less severe cannabis use disorder in comorbid patients (see section 5.3.2.1, page 76).

Overall, a co-occurring diagnosis of SCZ also conferred increased SMRs in SUD patients. However, when stratified according to type of SUD, we found similar SMRs for non-alcohol SUD patients with and without SCZ, in accordance with other studies [141, 216, 228, 288], and similar SMRs in patients with alcohol use disorder with and without SCZ, in contrast to a 50-year follow-up study of persons with alcohol use disorder [229]. Differences in length of follow-up may be one explanation for the latter finding. Furthermore, when stratified according to gender, we found increased SMR in comorbid men, but not in comorbid women, in accordance with a study conducted in inpatients [231]. Thus, in our study, the increased SMRs in comorbid patients, both genders combined, was explained by the high proportion of young comorbid men with a non-alcohol SUD. The eight-to-nine-fold increased SMR in patients with non-alcohol SUD with and without SCZ, is similar to [334] or higher than [216, 224] that reported elsewhere. Norway has one of the highest rates of injecting drug users among hard drug users [335], which may have contributed to this finding.

We found very high SMRs for poisoning and suicide in women with SUD, which confirms earlier findings [15, 336], and high SMRs for respiratory diseases, probably associated with increased smoking prevalence in individuals with SMI [337]. The increased mortality due to suicide in patients with SCZ was more pronounced than reported in a systematic review [8], but of similar magnitude as reported in a sample with comparable age span [227].

4.2.3 Undiagnosed CVD in persons with SMI

The 66% higher prevalence of undiagnosed CVD prior to cardiovascular death in individuals with SCZ found in our study is in accordance with, but somewhat higher than, the findings in a parallel Danish study, where individuals with SCZ had 45% reduced odds of having been diagnosed with CVD at least one month prior to cardiovascular death, compared to controls [245]. It is also in accordance with the study by Crump et al reporting a higher proportion undiagnosed IHD up to one month prior to an IHD death in individuals with SCZ, compared to individuals without SCZ [151]. Our findings also resemble a study reporting doubled risk of unforeseen death in individuals with SCZ, with CVD being the most common cause [246], and studies reporting a decreased likelihood in individuals with SCZ of being diagnosed with somatic illness in the early courses of diseases [177, 253]. Our study extends these earlier findings by documenting that the lower odds of diagnosed CVD prior to death in individuals with SCZ may be related to the low age at death. It also documents that the lower odds of

diagnosed CVD prior to death in individuals with SCZ applies to all main causes of cardiovascular death, with particular high odds of unrecognized CVD prior to death from MI in women with SCZ. Our finding of similar odds of undiagnosed CVD prior to an IHD death in individuals with BD is also in accordance with earlier findings [152], but the increased odds of undiagnosed CVD prior to a cerebrovascular death in women with BD is a novel finding. Earlier studies have found an increased incidence of vascular disease in women with BD, but not in men with BD [338, 339]. An increased risk of adverse illness course in women with BD has been reported [290], and may also contribute to this finding.

4.2.4 Uptake of CVD-related diagnostic tests and invasive cardiovascular treatment

We are not aware of other studies examining uptake of CVD-related diagnostic tests in a sample of deceased patients with and without SMI, still, our findings show similarities with other studies with adjacent topics. We found lower (SCZ) or similar (BD) prevalence of 24 hour blood pressure measurement in primary care and similar (SCZ) or higher (BD) prevalence of diabetes testing in primary care, compared to patients without SMI. A recent study from Denmark [340] comparing quality of diabetes care in diabetes patients with and without SCZ found lower rates of blood pressure measurements, but similar rates of HbA1c measurements, in individuals with SCZ, in line with our findings. A study from the UK examining screening for cardio-metabolic risk factors in individuals with SMI found lower rates of blood pressure measurements, but also lower rates of HbA1c measurement in individuals with SMI, compared to diabetes controls [341]. A Canadian study of preventive CVD care in an interprofessional primary care practice with mandate to care for persons with barriers to health care, however, reported similar levels of blood pressure measurement and higher levels of diabetes screening in patients with SMI, compared to age- and sex-matched controls [276], indicating that tailor-made treatment for this group may improve uptake. We are not aware of studies comparing receipt of ECG in primary care in patients with or without SMI, but previous studies have documented suboptimal cardiac function monitoring (such as ECG) in SMI patients [342-347]. Our finding of lower levels of CVD-related health care use in patients with SMI is in accordance with other studies investigating both primary and specialized somatic care [348], and studies reporting reduced likelihood of seeing a specialist among patients with SCZ [280, 286, 342-348].

We found a decreased prevalence of coronary angiography prior to cardiovascular death in patients with SCZ and BD, compared to patients without SMI, in accordance with earlier studies in patients with SCZ [249, 278, 349], BD [278], or mental illness in general [249, 350-353], particularly in older age groups [349, 350]. Our findings are also compatible with a study reporting lower likelihood of preventive interventions during somatic hospitalization among patients with SMI [354]. Little is known about receipt of echocardiography and ultrasound of peripheral vessels in patients with and without SMI, but patients with mental illness have been reported to have lower likelihood of left ventricular ejection fraction assessment, in which echocardiography is a common examination method [355].

We found lower prevalence of invasive cardiovascular procedures in patients with SMI, in accordance with previous studies of receipt of cardiovascular surgery in patients with and without SMI [274, 356]. We found lower prevalence of revascularization in patients with SCZ who died from CVD, but similar uptake of revascularization in patients with and without SMI who were diagnosed with IHD prior to death. The latter finding is in contrast to earlier findings in various populations [249, 280, 281, 283, 286, 357], but consistent with a recent Danish study showing no difference in post-MI treatment in patients with and without SCZ who had undergone coronary angiography, and studies showing similar likelihood of revascularization in patients with IHD and BD [357] or mood disorders [283]. The finding of similar prevalence of revascularization in those diagnosed with IHD is also compatible with a study in the general Norwegian population demonstrating that lower revascularization rates among patients with low education were explained by differences in receipt of coronary angiography [358].

With the exception of revascularization, receipt of invasive cardiovascular treatment in persons with SMI appears to be little described in the literature [359]. However, an Israeli study found a 50% reduced likelihood of cardiac pacemaker implantation in patients with SCZ [274] and a US study a reduced likelihood of receiving major surgery, including vascular surgery, among persons with SMI, particularly in those with SCZ [356]. These findings are in line with ours in the sample of those who died from CVD.

4.2.5 Why are persons with severe mental illness dying so young?

Persons with SMI are at very high risk of death from external causes of death, such as suicides, poisoning and victimization [142, 143]. Still, natural causes account for most life years lost among those with SMI [4]. Persons with SMI thus mainly die of the same causes as others, particularly from CVD and cancer, but die younger. Such deaths may be prevented or postponed if identified and managed. A UK cohort study of inpatient with SCZ or BD, found that potentially avoidable deaths comprised 60% of all deaths in the cohort. Bringing mortality from avoidable causes and suicide down to general population levels would reduce excess mortality in persons with SMI by about 50%, but would not eliminate it [360].

The excess mortality in people with SMI is most likely a result of a complex interaction between a wide range of factors, both on the individual, health system and social level [361], as emphasized in the WHO's multilevel model (Table 1, page 11). Hypertension, smoking, raised glucose, lack of physical activity, obesity and raised cholesterol are ranked as the main global mortality risk factors for premature mortality, all of which are significantly increased in people with SMI [120, 164, 362-364], with the exception of raised hypertension in SCZ (see section 1.3.2). The relative contribution of the different risk factors are not well known, but lifestyle factors such as smoking [254, 365-368], SUD [225] and physical inactivity [254, 368] are probably among the most important predictors of early mortality in the SMI population.

Active psychosis [366], and severe cognitively impairment [369] have also been identified as predictors of premature mortality. Cognitive impairment, lower health literacy, impaired self-care capacity, negative symptoms, self-stigma, depression and suspiciousness may impact the ability to recognize [370] and communicate somatic symptoms, and to seek timely somatic care [348, 371]. Psychiatric symptoms and adverse consequences related to SMI may also affect the ability to keep appointments, adhere to treatment plans [372], and make lifestyle changes [373].

Excess mortality may also be related to adverse effects of antipsychotic medication [176]. Antipsychotics are associated with increased risk of weight gain, glucose intolerance, dyslipidemia [170], increasing the risk of type II diabetes [374], which may occur shortly after first-time exposure to antipsychotic medication [175]. Users of antipsychotic medication are also at increased risk of arrhythmias, deviations in blood pressure, heart failure,

myocarditis and cardiomyopathy [375, 376], possibly leading to sudden cardiac death [377-379]. On the other side, antipsychotic has been associated with reduced risk of all-cause mortality [380, 381], implying that the risk of adverse CVD-related effects must thus be balanced against the effect of decreased overall mortality.

Lower uptake of potentially effective treatment, and lower quality of care, also contribute to excess mortality among those with SMI. A number of studies in a variety of settings have documented suboptimal screening/monitoring of CVD risk factors [156, 247, 248, 268], lower rates of cardiovascular prescriptions [250, 255-259, 271] and invasive cardiovascular treatment [11, 249, 277, 278] among those with SMI. The current literature also confirms disparities in cancer screening [382], COPD treatment [383], osteoporosis treatment [384], pre-dialysis renal care [385], and end-of-life care [386, 387] among those with SMI.

Plausible mechanisms at the provider level explaining this disparity include complexity of care, time constraints and poor communication with patient or primary care health workers [388]. Also, a tendency to focus on mental rather than somatic health, as well as misattributing of physical symptoms to mental illness may contribute [388-390]. Discomfort with or stigmatizing attitudes towards patients with SMI among health care providers have been reported [391, 392], particularly regarding SCZ [393, 394] and those with comorbid SUD [395], and may unintendedly influence medical decision-making. In a study of quality of somatic treatment among older persons with SCZ, higher adequacy of somatic treatment was associated with lower rates of depression, fewer positive symptoms and more negative symptoms [396]. In another study of providers' decision making, a history of SCZ was found to negatively affect primary care provider's expectations of treatment adherence and ability to understand educational materials [397].

Unclear responsibility with regard to physical health examination in patients with SMI [370], as well as the separation between primary and secondary health care and between somatic and psychiatric health care, probably contribute to underdiagnosis and undertreatment [398]. Navigating between psychiatric, primary and specialized somatic health care systems may constitute a particular challenge to those with SMI. Both individuals with SMI and mental health staff point to a less fragmented health care system when asked about opportunities for

improved prevention and treatment for physical problems among persons with SMI [398, 399].

Finally, as emphasized in the comprehensive WHO multilevel model, the social and environmental circumstances in which people live their lives are essential to the understanding of the excess mortality among persons with SMI. Besides severity of illness, the very high risk of unnatural death among those with SMI is probably best understood in this context. Poorer socioeconomic conditions [400], unemployment, homelessness and lack of social support, which are all more common in those with SMI, contribute to disparities in health, including excess mortality [203, 401-404] and call for a wider set of interventions than those directed at the individual or health system level alone.

4.2.6 Mechanisms explaining underdiagnosis of CVD and suboptimal cardiovascular health care use in individuals with SMI

Many of the same mechanisms proposed as explanations for excess mortality, may also explain why people with SMI are at increased risk of underdiagnosis and undertreatment of CVD. In addition, there are some specific factors related to the association between SMI and CVD that need mentioning.

We found that undiagnosed CVD was more common in the youngest. Individuals with SMI are at increased risk of dying at ages when health care providers may not usually suspect CVD. Current risk prediction algorithms for CVD have been shown to underestimate the risk of CVD in individuals with SCZ, particularly in younger men [405], and may likely lead to lower detection rates in individuals with SCZ compared to others. There is also a possibility that younger patients are prescribed higher doses of antipsychotic medicine due to more severe symptoms at an early stage in the disease course, and hence are at higher risk of adverse cardiac effects such as arrhythmias, deviations in blood pressure, heart failure, myocarditis, and sudden death [377, 378, 380, 406-408].

Previous studies have found impaired glucose tolerance and insulin resistance in patients with first episode psychosis [409], and a genetic overlap in risk factors for SMI and MetS [330, 410] and SCZ and CVD [25, 411], suggesting that individuals with SMI are more susceptible to CVD. These common risk factors may imply a more malign course of CVD in persons with SMI, with shorter time to recognize symptoms. This is supported by two large Nordic studies

examining post MI-survival, which found unexplained cardiovascular mortality among those with SCZ after thorough adjustment for demographic, clinical and behavioral factors [284, 412], implying that SCZ may be an independent risk factor for CVD mortality. Another study reported that CVD in persons with SCZ appeared to be less related to weight, compared to controls, where intrinsic metabolic differences associated with SCZ was proposed as one possible explanation [413]. Increased pain tolerance [414] and increased risk of silent CVD [415] not associated with traditional cardiovascular risk factors [416, 417], have also been reported in individuals with SCZ, likely affecting timely health care seeking and diagnosis.

In spite of younger age, people with SMI have more comorbidities, including higher rates of smoking, obesity and SUD [418], higher risk for postoperative complications [419, 420] and mortality following cardiac treatment [284]. Disparities in invasive CVD treatment may thus reflect clinicians' uncertainty and judgments about treatment risks and compliance with postoperative care. Lack of consent, or lack of capacity to give informed consent, may also be an issue, as noted in a recent study investigating decisions about cardiac examination and treatment, where patients with SCZ tended to be more likely to decline both examination and treatment post MI [279].

5 Discussion of methods

Systematic errors (bias), random errors and confounding are threats to the internal validity of epidemiological studies. Random error reflects a problem of precision and can be reduced by increasing the sample size. Bias reflects flaws in study design, analyses, interpretation or dissemination of results, whereas confounding distorts the measurement of effects due to extraneous causal factors. Bias and confounding are major limitations in observational studies, and are discussed in more detail below.

5.1 Observational studies: Pros and cons

The aim of analytical epidemiological studies is to identify and evaluate causes or risk factors for diseases or health-related events. There are two main categories of such studies; interventional (i.e. randomized controlled study (RCT)) and observational studies, each with its own strengths and weaknesses. RCTs ranks highest in the evidence hierarchy due to two defining properties: (i) random allocation of the exposure (intervention), which reduces the probability of confounding, and (ii) blinding of participants and investigators, which minimizes bias caused by the placebo effect.

Due to strict eligibility criteria, RCTs often have low external validity (generalizability). An RCT may also be unethical to conduct (e.g. randomization to a harmful exposures or drugs that has known benefits but uncertain side effects). Other weaknesses include inability to study rare or long-term outcomes.

Strengths in the RCT design reflect limitations of observational research, and vice versa, and show the complementary roles of the two approaches. Observational studies are by definition studies that observe without intervening. Strengths in this approach include less restrictive eligibility criteria (reflecting real-world case mix, with higher external validity), longer follow-up, lower costs and greater timeliness. Observational studies are thus often used to study problems that are not addressable in an RCT, such as effectiveness in real world settings, long-term or rare side effects of treatment, or effects of harmful exposures or exposure that should not be modified for ethical reasons. The biggest obstacle in observation studies is confounding (which can produce unpredictable results), and systematic bias due to selection or information bias. However, a well-conducted observation study can provide an almost unconfounded estimate by matching or restriction at the design stage, or by adjusting

at the analysis stage. Other weaknesses in observational studies include access only to predefined variables, and noise associated with variations/changes in coding practices.

Despite the limitations of observation studies, many accepted medical causal relationships have been documented in such studies (e.g. the relationship between smoking and lung cancer). Also, two much cited meta-analyses comparing RCT versus high-quality observational cohort studies both reported similar estimates of effect in the two approaches [421, 422]. Ioannadis et al [423] found discrepancies in 16% of all studied topics, but only 8% of topics covered by prospective studies, while MacLehose et al [424] found small discrepancies in high-quality studies, but large discrepancies in low-quality studies, which had a tendency to report more extreme effect sizes. A well-known example of departure from such findings are studies on the relationship between postmenopausal estrogen and the risk of coronary heart disease, in which the RCT found higher, and the observational studies lower, risk of heart disease [425]. Hernan et al later showed that the discrepancy could largely be explained by differences in the distribution of time since menopause and length of follow-up [425].

5.2 Strengths

The major strength of the studies included in this thesis is the use of unselected and complete nationwide registry data of recent date, in a setting with free access to health services and no bias associated with selective self-reporting. The inclusion of outpatients and patients treated solely in somatic hospitals (paper I), as well as the inclusion of patients treated in primary care (paper II and III) enabled more generalizable risk estimates than reported in many previous studies. The unconventional study design in papers II and III enabled comparisons of people with and without SMI with assumed equal need of health care. Adding to the strengths is also the exploration of bias incorporated in estimates of SMRs when the exposure is common and the general population is used as reference. Furthermore, in all three papers, we included extensive sensitivity analyses to strengthen our results and conclusions.

Finally, the CDR is found to provide high quality data on the underlying cause of death [307], and the validity of a SMI diagnosis in hospital case registries is found good compared to diagnoses based on structured research interviews [426, 427].

5.3 Bias

Bias results from systematic errors in the design or conduct of a study, flaws in the method of selecting study participants, flaws in the procedures for gathering relevant exposure or outcome information, or in the interpretation, reporting or publication of results. Bias thus relates to the process, not the results per se, requiring careful evaluation of design, methods and procedures. Bias is broadly of two types, i.e. selection bias and misclassification bias, both are discussed more in detail in the following sections.

5.3.1 Selection bias

Selection bias is a distortion that results from the procedures used to select individuals into the study [316]. Of particular relevance for the studies included in the current thesis is the potential biases resulting from inclusion of prevalent cases (also called cross-sectional bias). In studies of long-lasting diseases (e.g. SMI or SUD) that include prevalent cases, a late look at those affected in young age will miss early fatal cases, but also mild cases and those who recovered (left truncation). Incidence-prevalence bias can be avoided by only including incident cases, but the relatively short history of the NPR and the KUHR database made this impossible. However, in paper I we had an intention of including as many as possible of the true SCZ population treated in specialized care in Norway, as well as capturing deaths from diseases that occur late in life, such as CVD and cancer. Also, studies of incident exposures may implicate right censoring (i.e. the study ends before the event has occurred) and may therefore be unable to assess the long-term effects of the exposure [428].

We lacked data for primary care in paper I, and thus presumably included only the most severely ill. We also included people with a diagnosis of SMI/SUD registered solely in somatic care, who were 10-20 years older than their counterparts diagnosed in psychiatric settings. Patients with SMI who only utilized specialized somatic care constituted 6%, 22% and 1% of patients with SCZ-only, SUD-only and SCZ+SUD, respectively, but 24%, 45% and 5% of all deaths in the subgroups. If these somatic diseases were unrelated to the mental disorder, we may have introduced bias by enriching the sample with persons at particularly high risk of mortality. A sensitivity analysis, excluding patients identified solely in somatic care, showed that the SMRs were reduced from 4.5 to 3.8 (-16%) in men with SCZ-only and from 4.3 to 3.6 (-16%) in women with SCZ-only. Similar results were found for individuals

with SUD-only (SMRs decreased from 6.4 to 5.7 (-11%) in men and from 7.4 to 6.3 (-15%) in women), while results for the dually diagnosed were less affected.

On the other hand, excess mortality in patients with SCZ or SUD is known to be highest the first years after diagnosis [1, 429, 430]. The older group identified in somatic health care only may thus be a group of healthy survivors who coped well with their mental illness, but were entering an age where the physical comorbidities associated with SMI had reached a severe stage. Whether inclusion of patients with SCZ or SMI treated solely in somatic care should be considered a question of external validity or selection bias depends on whether the somatic diseases that led to inclusion is related to, or independent of, the mental illness.

Survivor bias may also be present in the dually diagnosed (paper I), as individuals would have to live long enough to get a second diagnosis, and in study II and III, where the participants would have to live long enough to develop CVD.

5.3.2 Misclassification bias

Misclassification bias (also called information bias) results from a systematic tendency to classify an individual, a value or an attribute to an erroneous category [324], leading to different accuracy of information between comparison groups [324]. Misclassification that depends on the actual values of other variables in the analysis is labeled differential misclassification, while misclassification that does not depend on the actual values of other variables is labeled non-differential [314]. Differential misclassification introduces bias in an unpredictable direction (either overestimation or underestimation). Non-differential misclassification gives in most situations results biased towards the null-hypothesis, but can sometimes produce bias away from the null if the misclassification depends on the errors in classifying other variables, or if the exposure or disease variable has more than two levels [314]. Two potential sources of information bias in the current thesis are discussed below, namely medical surveillance bias and misclassification of diagnostic groups in administrative data.

5.3.2.1 Medical surveillance bias

Medical surveillance bias (also called detection bias) refers to the situation where known exposure to one factor leads to a closer surveillance of another feature relevant for the study, increasing the probability of detection of this other factor. In study I, a known diagnosis of SCZ may have led to closer surveillance of SUD due to the known higher risk of comorbidity. Less severe SUD, undiagnosed in those without SCZ, may thus have been diagnosed in those with SCZ. It may be that the same mechanism also apply to the BD group in paper II and III, as higher health care utilization probably leads to more diagnoses.

In observational studies, the best strategy for avoiding medical surveillance bias is to implement systematic, standardized, and periodic data collection procedures for everyone regardless of exposure status. This is, however, no option when using real world registry data.

5.3.2.2 Misclassification of diagnostic groups in administrative data

5.3.2.2.1 Misclassification of SMI in administrative data

Norwegian validity studies have found high agreement between clinical diagnoses in the NPR and research based diagnosis for SCZ [426, 427], fair agreement for schizoaffective disorder [427] and good [427] or moderate agreement for BD [431]. One Norwegian study reported a considerable underdiagnosis of BD in administrative data, mainly in currently depressed patients [431]. Good validity of SCZ diagnoses [432] and lower validity of schizoaffective disorder diagnoses [433] has also been reported in other countries.

SMI diagnoses in the KUHR database has not been validated, but Statistics Norway estimated that 0.3% of the ICPC-2 diagnoses in the KUHR database in 2015 were incorrect [434]. Also, primary care diagnoses have been found to be valid in GP registries in other countries, particularly for chronic diseases [435]. A possible misclassification, however, arise from the inclusion of affective disorder in primary care (ICPC-2 code P73) in the BD group. The ambiguity in this diagnosis may have led to an inclusion of individuals with severe depression but not BD. In order to get a rough estimate of this possible misclassification, we examined the concordance in diagnosis among those with a BD diagnosis registered in the primary care and a concurrent affective diagnosis registered in specialized health care (paper III). Of these, 21% had a different affective disorder than BD registered in the specialist health service. We found, however, similar estimates for the main endpoints when excluding BD cases with only

non-BD affective disorders recorded in specialized care (results not shown), and also similar results when excluding patients with a BD diagnosis from primary care only (paper III).

Diagnostic instability of SMI diagnoses may also be a concern in administrative data. A cohort study of patients with first episode psychosis, found that most patients (89%) diagnosed with SCZ at baseline maintained the diagnosis after ten years, while 32% of patients with first episode psychosis who initially received a non-SCZ diagnosis had a SCZ diagnosis by year 10 [436]. The problem of instability of diagnoses, together with the relatively short observation periods, may have affected the classification of diagnostic groups in the current studies, but probably most in study I, which had a higher proportion of younger patients. We tried, however, to minimalize this potential problem by defining start of follow-up based on a broader set of diagnoses in study I (see page 51).

5.3.2.2.2 Misclassification of SUD in administrative data

We found a seven-year prevalence of SUD in schizophrenic patients of 25%, which is equal to the prevalence of SUD reported in a recent Norwegian study [165], but considerably lower than reported in other studies [115, 437]. SUD diagnoses in the NPR have not been subject to formal validity checks, but a Norwegian hospital based validation study found SUD diagnoses to be fairly good, although only 31% classified with SUD by expert opinion were identified in administrative data [426]. In another Nordic study, SUD was underreporting for nearly 50% of individuals with SCZ in the Danish Psychiatric Register [438]. A possible underreporting of SUD in specialized care may have led to misclassification bias in study I, possibly overestimating SMRs both in patients with SCZ-only and in patients with both SCZ and SUD. In the study by Hjorthøj et al, however, identifying patients with SUD from hospital data only did not change results appreciably [223].

Ignoring the temporal relationship between SCZ and SUD (paper I), is another source of potential misclassification of patients with SUD. A post hoc analysis revealed, however, that a majority of comorbid patients had both diagnosed within a year.

5.3.2.2.3 Misclassification of CVD in administrative data

Recent meta-analyses investigating the validity of CVD diagnoses in administrative data, found valid diagnostic codes for MI and acute stroke [439, 440]. Heart failure diagnoses identified in administrative data also corresponded well to true cases, but one-quarter of actual

cases were not captured [441]. Previous Norwegian studies also found valid information regarding stroke [442] and intracranial hemorrhage [443] in the NPR. The validity of cardiovascular diagnoses in general [444, 445], atrial fibrillation and atrial flutter [446], intracerebral hemorrhage [447] have been found to be high in other Nordic registries, while the validity of heart failure [448] and peripheral arterial disease diagnoses has been questioned [449].

The validity of cardiovascular diagnoses in the KUHR database is unknown. Although it is possible to enter at least three diagnoses per GP contact, 85% of these encounters had only one recorded diagnosis. In paper II, there is a possibility that only the SMI diagnosis was recorded, even if CVD may have been a topic during the consultation. However, among individuals with SMI, only 17% of the primary health care encounters included a SMI diagnosis, so it seems reasonable to assume that any recognized CVD would be recorded at some point during the at least three-year long observation period. Furthermore, a sensitivity analysis with recorded CVD in specialized health care only as dependent variable (paper II) gave similar results as the main model. And, as already mentioned, diagnoses in GP registries have been found valid in other countries, particularly for chronic diseases [435].

Lack of information concerning history of CVD prior to the study period, may have led to misclassification of undiagnosed CVD in paper II due to stable, long-term and currently untreated CVDs. As individuals with SMI have higher fatality rate from CVD [18, 284, 450], stable, long-term and currently untreated CVDs may be less likely among persons with SMI compared to others. Our findings thus probably underestimate the real difference between individuals with and without SMI.

5.3.2.2.4 Validity of CVD-related procedures in administrative data

An investigation of medical coding practices in specialized health care in Norway found that the recording of medical procedures were more precise than the recording of diagnoses, but that non-surgical procedures were underreported [451]. Although this investigation was limited to pneumonia and hip replacement surgery, these findings probably have transfer value to other patient groups in Norway. The level of screening/monitoring of CVD risk factors in paper III may thus be underestimated in all patients, but probably most in patients without SMI as patients with SMI should also be monitored for adverse effects of antipsychotic medications.

5.3.2.3 Misclassification of underlying cause of death

Determining cause of death is subject to uncertainty, and the reliability of cause of death classification has long been a cause for concern [452]. Autopsy is regarded as the most accurate mean of determining the cause of death, but is infrequently undertaken in Norway. More than 90% of cases in the CDR are based on information in the death certificate, in some cases supplemented by information from other sources. Sources of error include uncertainties about the cause of death itself, illogical structure of reported causes of death, and incorrect or inadequate coding of the diagnosis. Classification and coding of underlying cause of death can be particularly challenging when several causes of death are reported and multiple sequences are possible (such as in multi-morbid patients). Another problem is the frequent use of intermediate, immediate, unspecified, or otherwise inapplicable causes of death, collectively termed "garbage codes" [453], such as heart failure, ill-defined cancer site, senility, ill-defined external causes of injuries, and septicemia.

In a meta-analysis of discrepancies between clinical diagnoses and autopsy findings, including studies conducted during 1970-2000, the authors concluded that at least one-third of death certificates were likely to be erroneous and that half of the autopsies contained findings that were not suspected prior to death [454]. Developments in diagnostic practices and procedures in the last decades, helping to ensure correct diagnoses before death, may, however, have improved mortality statistics. Only a few recent validation studies of the CDR have been conducted. A Norwegian population-based study examining 1,140 autopsies conducted in the years 1964-2005 found very good agreement between autopsy findings and mortality statistics in the CDR for both stroke and coronary heart disease [455]. Misclassified cases remained inside the circulatory system in approximately half of the cases, while the remaining cases were randomly distributed over the entire spectrum of diseases, reducing the risk of systematic errors. A Norwegian study published in 2005, investigating the impact of autopsies on death statistics, however, found substantial (17%) underreporting of cardiovascular deaths, particularly in the young and old, and in women [456]. Autopsy studies often include cases where the clinical uncertainty of underlying cause of death were particularly high, implicating that findings from such studies may not be directly transferable to other cases.

Another Norwegian study comparing mortality statistics to information in medical records of 1,001 cases in the years 2008-2009, found divergent content in 22% [457]. Underlying cause

of death differed in 18% of the cases, for 12% also with respect to ICD-10 chapter. A significant reduction of diagnoses such as sepsis, cardiac arrest, unspecified pneumonia, renal failure and fractures without specific cause was noted. Because of the balancing effect of exchanges between disease chapters, only minor changes in overall mortality statistics were observed.

The validity of cause of death in elderly patients has been questioned due to multi-morbidity and general frailty [458]. This potential error may be of less relevance in study I, which included only those aged 20 to 79. Excluding those aged 80 and above in study III gave, however, similar estimates for the main endpoints and qualitatively the same conclusions as the main models, as shown in the sensitivity analysis.

5.3.2.3.1 Are cardiovascular deaths at particular risk of misclassification?

Misclassification of cardiovascular deaths arises both from not recognizing actual death from CVD, and from labeling non-cardiovascular deaths cardiovascular. These types of errors are captured in the concepts of specificity, sensitivity and predictive value. The quality in cause of death assignments with respect to CVD is known to be worse than for cancer [459], and is characterized by sensitivity and specificity lower than 85% [460]. A meta-analysis of discrepancies between clinical diagnoses and autopsy findings reported that IHD/MI, pulmonary embolism and pneumonia often were misclassified and often were confused with each other in [454]. Another study reported that incorrect causal sequences on death certificates regarding CVD had increased in the US in recent years [461].

The literature shows inconsistent findings as to whether CVD deaths are over-reported [462] [463], underreported [459, 464-466] or reliably reported [455, 467]. Systematic reviews suggest that stroke deaths correspond to true stroke deaths [439], whereas the accuracy of MI as underlying cause of death may be suboptimal [440]. A Norwegian population based autopsy study examining the accuracy of IHD and cerebrovascular disease as causes of death found, however, a satisfactory quality in the mortality statistics in the city of Bergen [455]. In this study, the sensitivity and positive predictive value of fatal cerebrovascular disease were 0.75 and 0.86, respectively, and 0.87 and 0.85, respectively, for IHD deaths. Cohen's Kappa coefficients were 0.78 for cerebrovascular disease and 0.80 for IHD. About half of the mismatches remained inside the circulatory system, while the remaining cases were randomly distributed over the entire spectrum of diseases, reducing the risk of systematic errors.

The validity of MI as underlying cause of death was also good in Danish [467] and Finnish [468] studies. We found similar results when we included all deaths with CVD as underlying or contributing cause of death, as shown in the sensitivity analyses (studies II-III).

Table 12 shows selected CVD codes used as underlying cause of death, specified according to patient group (paper III). These codes were proposed by Lozani et al as markers of lower quality cardiovascular mortality categories [469]. Overall, we found similar (SCZ) or lower (BD) proportions of ill-defined cardiovascular causes of death among those SMI compared to those without SMI. The largest discrepancy was found for cardiac arrest, which was reported as underlying cause of death in 2.4% of persons with BD, compared to 1.4% among those without SMI.

Table 12 - Percentage of ill-defined cardiovascular causes of death in patients with and without schizophrenia (SCZ) or bipolar disorder (BD) in the years 2011-2016.

Underlying cause of death	SCZ	BD	No SMI
I50 Heart failure	11.2%	10.4%	11.6%
I51.6 Cardiovascular disease, unspecified	1.6%	1.2%	1.3%
I70.9 Generalized and unspecified atherosclerosis	0.6%	0.1%	1.1%
I46 Cardiac arrest	1.5%	2.4%	1.4%
I51.9 Heart disease, unspecified	1.0%	0.9%	0.8%
I49.0 Ventricular fibrillation and flutter	0.0%	0.0%	0.1%
I51.4 Myocarditis, unspecified	0.2%	0.3%	0.1%
I47.2 Ventricular tachycardia	0.1%	0.0%	0.0%
I51.5 Myocardial degeneration	0.1%	0.0%	0.0%
Any of the above	16.3%	15.3%	16.3%

To summarize, it seems reasonable to assume that the presence of misclassification of cardiovascular deaths is of similar magnitude among those with or without SMI/SUD (i.e. non-differential misclassification). Hence, the actually observed cause specific SMR (study I) probably underestimates the true effect. However, when comparing sub-diagnosis within the CVD chapter caution may be necessary. Here differential misclassification might be present, with an unpredictable direction of bias.

5.3.2.3.2 Are individuals with SMI or SUD at particular risk of misclassified death?

Young age of death, increased risk of sudden deaths [377, 378, 380, 406-408], more deaths outside health care institutions, poisoning, suicides and substance use may increase the likelihood of misclassified death among those with SMI or SUD. An Australian autopsy study found no definitive cause of death for 11% of deceased persons with SCZ who underwent an

autopsy, which the authors speculated could be attributed to sudden cardiac death [470]. Longer postmortem time before discovery in individuals with SCZ compared to others has also been reported [471], possibly affecting the reliability of assumed causes of death. On the other side, a Norwegian study reported that autopsies conducted after deaths that occurred outside hospitals had increased in the period 2007-2011, with CVD, external causes and alcoholism as the most common underlying cause of death [472].

Younger persons with multi-morbidity (such as patients with SMI or SUD), could be underrepresented in studies II and III due to competing causes of death [456]. We found, however, very few persons with a diagnosis of SMI or SUD recorded as underlying cause of death and CVD as contributing cause of death in these samples, and similar results when we included all deaths with CVD as underlying or contributing cause of death, as shown in the sensitivity analysis. Also, young age at death was a positive predictor of medical autopsy in another Norwegian study [455].

The use of ill-defined causes of death, the so called “garbage codes“ [453], is another source of error in mortality statistics. In paper I, ill-defined causes of death accounted for 10% of deaths in SCZ-only, 9% of deaths in SUD-only and 7% of deaths in patients with both SCZ and SUD. To investigate whether there were indications of systematic differences in the quality of mortality statistics between individuals with or without SMI, we compared the percentage of deaths assigned to selected ill-defined causes of death among patients with SMI in study I to that reported previously for the Norwegian population (Table 13). The comparison showed lower frequency of such diagnoses among those with SCZ or SUD compared to the general population, although some reservations have to be made since the information was partly from different time periods.

Table 13 - Percentage of selected ill-defined causes of death in the general population and in psychiatric sub-populations in Norway

Underlying cause of death	Gen pop (1996-2010)[a]	SCZ (2009-2015)[b]	SUD (2009-2015)[b]
I50 Heart failure	3.9	1.0	0.7
R99 Other ill-defined and unspecific causes of death	1.6	1.8	1.4
R96 Other sudden death, cause unknown	1.4	1.0	1.0
C80 Malignant neoplasm, without specification of site	1.2	0.8	0.5
R54 Senility	1.1	0.1	0.0
I51 Complications and ill-defined descriptions of heart disease	1.0	0.8	0.7
I70 Atherosclerosis	0.8	0.3	0.3
X59 Exposure to unspecified factor	0.7	0.6	0.6
N19 Unspecified kidney failure	0.6	0.5	0.2
A41 Other sepsis	0.6	1.0	1.0
Any of the above	12.9	7.8	6.4

[a] Source: http://www.fhi.no/dokumenter/8192560710.pdf

[b] Source: The Norwegian Patient Registry and The Norwegian Cause of Death Registry

Suicides and accidents also present a challenge in the classification of manner of death, which is relevant for mortality statistics regarding people with SMI or SUD. Some studies suggest that the "injury death of undetermined intent" diagnosis may reduce the reported suicide rate by up to 10% [473]. However, in a study of the validity of suicide statistics in relation to undetermined deaths, including 29 European countries, Norway scored highest on the quality indicator for suicide statistics [473]. Also, in a study examining the reliability of the national suicide statistics in the Nordic countries, 81% (Sweden), 88% (Norway) and 90% (Denmark) of deaths registered as suicide in the official mortality statistics were confirmed by expert classification [474]. Uncertainty was highest for suicides due to poisoning, but reclassification did not change the overall official suicide statistics of the three Scandinavian countries.

The presence of SUD also present a challenge in mortality statistics, and SUD related deaths may be underestimated when only underlying cause of death is counted, particularly alcohol related deaths [218]. A Swedish study found that mortality statistics missed one third of drug related deaths [475], while a study from the US found valid information regarding deaths from opioid overdoses [476].

5.4 Confounding

In section 2.7.1 (page 54) we discussed the possibility of distorted estimates due to confounding by common genetic susceptibility for SMI and CVD, early life stressors and childhood SES. Based on assumptions of similar causal relationships in study I, we believe that the estimates in study I may be confounded by the same factors, as illustrated in Figure 5.

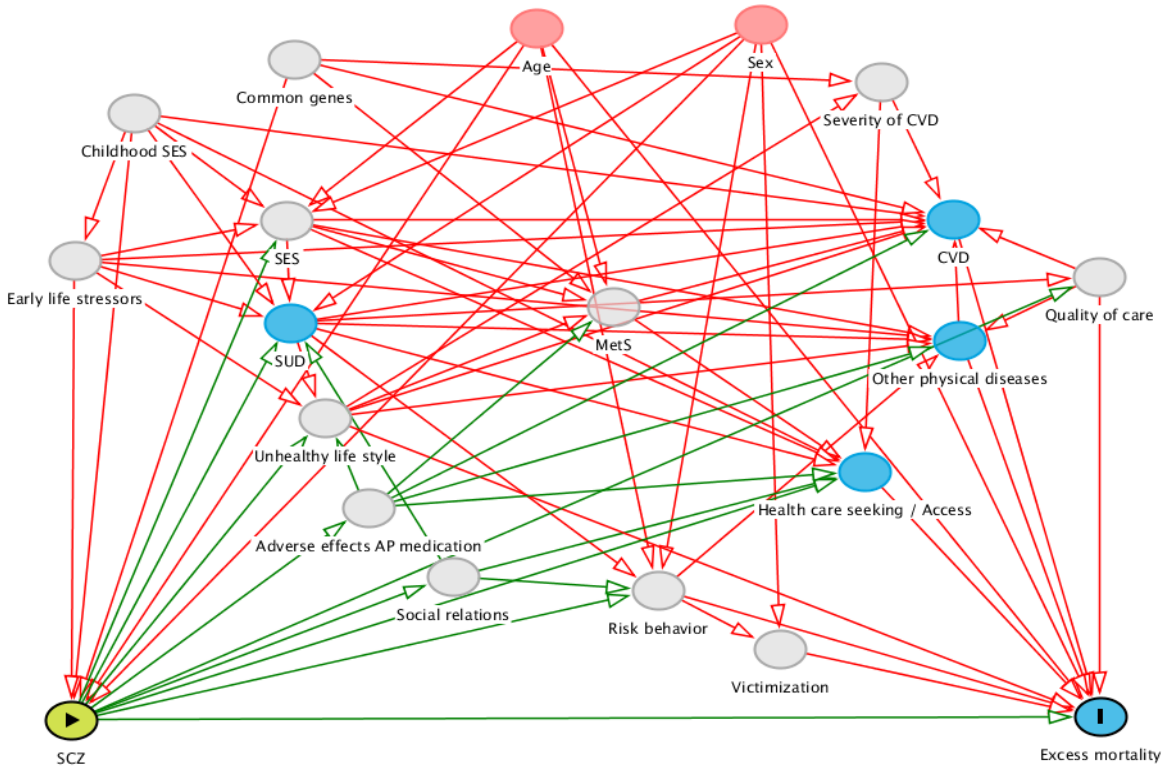


Figure 5 - Directed acyclic graph (paper I) with unmeasured confounders.

The DAG displayed in Figure 5 suggests two alternative minimal adjustment sets for estimation of the *direct* effect of SCZ on excess mortality. The minimal adjustment set requiring the smallest number of variables would include measurements of CVD, health care seeking/access, other physical diseases, quality of care, risk behavior, unhealthy life style, in addition to sex and age, as well as an unlikely assumption of no unmeasured confounding between mediator variables and the outcome in the extended model.

5.5 Other limitations

The relatively short duration of the NPR and the KUHR database is a limitation. In study I, this precluded analyses of incident cases, as well as analysis of secular trends in SMRs. In paper II and III, this may have led to misclassification of undiagnosed CVD due to stable, long-term and currently untreated CVDs.

The lack of information on other variables relevant to the studies is another limitation. In study I, we lacked information about SUD prescriptions, which would have enabled identification of more SUD cases. We also lacked data regarding untreated persons with SCZ/SUD and patients treated solely in primary care. Access to such data would have made the results more generalizable. In paper II, we lacked information on antipsychotic prescriptions, which made us unable to study the association between antipsychotic medication and sudden cardiac death. In paper III, we lacked complete information on procedures conducted at radiology departments (such as computed tomographic angiography and ultrasound of peripheral vessels), and information on prehospital procedures during transportation to hospital (such as ECG or thrombolysis), which reduced the precision in the measurement of performed diagnostic tests and treatment. We also lacked information on known risk factors for CVD (such as smoking), severity of CVD (such as ST-segment elevation MI and extent of coronary disease) and travel time to hospital. Equal severity of CVD could, however, be approximated by the fact that they all died from the same causes of death. Finally, we lacked information concerning cardiovascular prescriptions, which made us unable to study pharmacological prevention and treatment of CVD in paper III.

5.6 Generalizability

Study I included only patients in specialized health care, probably implying higher mortality than would be found among patients with SCZ and/or SUD in the general population. The generalizability of these findings is therefore to specialized care settings with similar health care systems and socioeconomic features.

Paper II and III included all patients who died from CVD, as well as all patients with SCZ or BD treated in any health care setting in Norway. The findings are thus assumed to be representative of individuals with severe CVD in countries with publicly funded and readily available health services for both somatic and mental disorders.

6 Conclusion

In this thesis, utilizing nationwide Norwegian data to investigate mortality among patients with SCZ and/or SUD, and the impact of SMI on detection and treatment of CVD, we demonstrated that patients with SCZ and/or SUD who receives specialized health care in Norway have a four- to seven-fold increased mortality compared to the general population. Particular high mortality was observed for poisoning, suicides and respiratory diseases. The excess mortality corresponded to more than 10,000 premature deaths during a mean of four years of follow-up, implicating that five out of six patients with SCZ and/or SUD died prematurely, and mostly from natural causes such as CVD and cancer. About 27% of the excess deaths in patients with SCZ could be attributed to SUD (or factors associated with SUD), with the strongest effects in men and in the youngest.

Despite the increased risk for CVD among those with SCZ or BD, and the fact that almost all individuals with SMI utilized primary or somatic specialist health care during the study period, we found a considerable underdiagnosis of CVD prior to cardiovascular death in individuals with SCZ. This was also the case for women with BD, but not men with BD. The higher likelihood of undiagnosed CVD applied to all main types of cardiovascular death, and was most frequent in the youngest in all diagnostic groups.

We also demonstrated lower prevalence of specialized cardiovascular examinations and invasive interventions prior to cardiovascular death in patients with SCZ and BD. Individuals with these conditions may thus not receive adequate levels of medically indicated cardiovascular treatment. We found no difference in utilization of cardio-metabolic diagnostic tests in primary care, and similar prevalence of invasive cardiovascular treatment among those with and without SMI who were diagnosed with CVD prior to cardiovascular death. These findings suggests that underdiagnosis and underutilization of specialized cardiovascular examinations, more than poor access to primary care or restraints due to contraindications or perceived noncompliance with postoperative care, are among the most important obstacles to equitable cardiovascular health care among those with SMI.

6.1 Implications

The many disease-specific, lifestyle-specific, health care-specific and socio-environmental challenges faced by persons with SMI represent huge barriers to equitable health care, and

call for complex intervention strategies addressing aspects of prevention, detection, follow-up and treatment at all levels of primary and specialist health care.

Evidence from the literature [361, 477-479], supported by the findings in our study, show that current actions and interventions have been far from able to counter the increased risks persons with SMI are exposed to. Some studies nevertheless allow some optimism. Increasing evidence demonstrates effectiveness of lifestyle and pharmacological interventions regarding weight loss and prevention of weight gain in people with SCZ [480-487], at least in the short run [485]. A systematic review found that exercise improved cardiorespiratory fitness among persons with SMI, with better outcomes observed following high intensity and high frequency interventions supervised by qualified personnel [488]. Pharmacological treatment may also reduce tobacco smoking in persons with SCZ or BD [487], and improvement of weight, blood pressure and glucose monitoring among users of antipsychotic medication was demonstrated following guideline implementation [248]. Studies have also suggested greater uptake of prevention services by people with SCZ after being given general health advice [489], and acceptability of participation in CVD risk assessment among individuals with SCZ [490]. A US study also found a positive association between better performance on process-based quality measures (e.g. psychosocial treatment, psychotherapy, continuity of care) and reduced 1- and 2- year mortality in patients with SMI and concurrent SUD [491], as well as a positive association between higher frequency of health care contacts and reduced mortality in the comorbid.

Interventions targeting health behavior (such as smoking, SUD and cardiorespiratory fitness) and metabolic risk factors (such as diabetes and hypertension) in persons with SMI are thus both necessary and possible actions to improve health outcomes. The limited evidence of long-term effectiveness of interventions addressing somatic risk factors in individual SMI and/or SUD [361, 477-479] suggests, however, that changes also at interpersonal, organizational, societal and policy levels probably are needed [478]. Such structural approaches could involve changing patterns of health service delivery, organizational models and financing systems. Screening for physical disease within psychiatric settings warrants further research. Also, physical activity as an integrated part of standard treatment of persons with SMI should be further investigated and pursued. Successful implementation in the SMI population may require personalized or tailored interventions, longer duration, more frequent contacts and trained treatment providers [492], designed in collaboration with service users.

Our studies further support and highlight the need for strengthened efforts to reduce underdiagnosis and undertreatment of somatic disease among those with SMI. A proactive, structured and tailored approach for correct diagnosis and treatment of somatic diseases is needed, underlined by the fact that these patients may have a more malignant disease course, with higher morbidity in the younger age groups and shorter time to recognize symptoms. Strengthened efforts are also needed to secure equitable access to secondary prophylactic treatment [18, 257]. There is also a need to define more accurately the responsibility for maintaining follow-up and treatment of somatic risk factors in patients with SMI. Investigations as to whether other organization models for primary, somatic and mental health services succeed better in promoting physical health among persons with SMI are also needed. Studies from the Veteran Affairs health care system [493, 494] and others [276], indicate that integrated, coordinated or collaborative health care may be beneficial in reducing inequities in health outcomes for people with SMI. Although previous studies have shown mixed results with regard to the effectiveness of financial incentives in improving quality of care [495, 496], we suggest that further investigations should be carried out to study whether the introduction of specific financial incentives for somatic health screening/monitoring in patients with SMI in primary and specialized health could help reducing underdiagnosis and undertreatment in these populations. Also, the high proportion of deaths directly linked to poisoning in SUD patients urgently calls for a more effective societal prevention of SUD-related unnatural deaths.

An approach that includes both individual focused and system focused interventions [478] is probably needed, involving both service users, primary and integrated specialist health care.

6.2 Suggestions for further work

Some unresolved issues in paper I-III could be further investigated. These include the following topics:

- We were unable to conclude whether the lower prevalence of specialized diagnostic tests in persons with SCZ and women with BD were due to lacking referrals from GPs, missed appointments, lack of patient consent, contraindications or other reasons.

Barriers to, and facilitators of, access to specialized examinations for people with SMI could be investigated in further studies.

- We observed differences with regard to health care seeking, undiagnosed CVD and health care outcomes between men and women with BD, which could be further investigated in other studies and populations.
- Few mortality studies among persons with SMI have included cases both in primary and specialized health care and in disability registries. Such studies could enhance the generalizability of findings regarding mortality in the SMI population.

In a broader perspective, further research is strongly needed that addresses possible structural changes that can be made with the specific aim to improve the health outcomes of the high-risk subgroup with SMI. The different risk profiles in younger and older persons points to the need for such efforts to be age-differentiated, with particular emphasis on the younger age groups which have the most elevated risk.

7 References

1. Nordentoft, M., et al., *Excess mortality, causes of death and life expectancy in 270,770 patients with recent onset of mental disorders in Denmark, Finland and Sweden.* PLoS One, 2013. **8**(1): p. e55176.
2. Hjorthøj, C., et al., *Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis.* Lancet Psychiatry, 2017. **4**(4): p. 295-301.
3. Westman, J., et al., *Mortality and life expectancy of people with alcohol use disorder in Denmark, Finland and Sweden.* Acta Psychiatr Scand, 2015. **131**(4): p. 297-306.
4. Laursen, T.M., *Life expectancy among persons with schizophrenia or bipolar affective disorder.* Schizophr Res, 2011. **131**(1-3): p. 101-4.
5. Høie, B. *Sykehustalen 2019 [The hospital speech 2019]*. 2019 [cited 2019 March 20 , 2019]; Available from: https://www.regjeringen.no/no/aktuelt/sykehustalen-2019/id2625399/.
6. Saugstad, L.F. and Ø. Ødegard, *Mortality in psychiatric hospitals in Norway 1950--74.* Acta Psychiatr Scand, 1979. **59**(4): p. 431-47.
7. Westermeyer, J., *Comorbid schizophrenia and substance abuse: a review of epidemiology and course.* Am J Addict, 2006. **15**(5): p. 345-55.
8. Saha, S., D. Chant, and J. McGrath, *A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time?* Arch Gen Psychiatry, 2007. **64**(10): p. 1123-31.
9. Hoang, U., R. Stewart, and M.J. Goldacre, *Mortality after hospital discharge for people with schizophrenia or bipolar disorder: retrospective study of linked English hospital episode statistics, 1999-2006.* BMJ, 2011. **343**: p. d5422.
10. Høye, A., B.K. Jacobsen, and V. Hansen, *Increasing mortality in schizophrenia: are women at particular risk? A follow-up of 1111 patients admitted during 1980-2006 in Northern Norway.* Schizophr Res, 2011. **132**(2-3): p. 228-32.
11. Laursen, T.M. and M. Nordentoft, *Heart disease treatment and mortality in schizophrenia and bipolar disorder - changes in the Danish population between 1994 and 2006.* J Psychiatr Res, 2011. **45**(1): p. 29-35.
12. Nome, S. and F. Holsten, *Changes in mortality after first psychiatric admission: a 20-year prospective longitudinal clinical study.* Nord J Psychiatry, 2012. **66**(2): p. 97-106.
13. Nielsen, R.E., et al., *Increasing mortality gap for patients diagnosed with schizophrenia over the last three decades--a Danish nationwide study from 1980 to 2010.* Schizophr Res, 2013. **146**(1-3): p. 22-7.
14. Lawrence, D., K.J. Hancock, and S. Kisely, *The gap in life expectancy from preventable physical illness in psychiatric patients in Western Australia: retrospective analysis of population based registers.* BMJ, 2013. **346**: p. f2539.
15. Ösby, U., et al., *Mortality trends in cardiovascular causes in schizophrenia, bipolar and unipolar mood disorder in Sweden 1987-2010.* Eur J Public Health, 2016. **26**(5): p. 867-871.
16. Hayes, J.F., et al., *Mortality gap for people with bipolar disorder and schizophrenia: UK-based cohort study 2000-2014.* Br J Psychiatry, 2017. **211**(3): p. 175-181.
17. Oakley, P., et al., *Increased mortality among people with schizophrenia and other non-affective psychotic disorders in the community: A systematic review and meta-analysis.* J Psychiatr Res, 2018. **102**: p. 245-253.
18. Kugathasan, P., et al., *Increased long-term mortality after myocardial infarction in patients with schizophrenia.* Schizophr Res, 2018. **199**: p. 103-108.
19. James, L.S., et al., *Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017.* Lancet, 2018. **392**(10159): p. 1789-1858.
20. Vigo, D., G. Thornicroft, and R. Atun, *Estimating the true global burden of mental illness.* Lancet Psychiatry, 2016. **3**(2): p. 171-8.

21. Rehm, J. and K.D. Shield, *Global Burden of Disease and the Impact of Mental and Addictive Disorders.* Curr Psychiatry Rep, 2019. **21**(2): p. 10.
22. Ruggeri, M., et al., *Definition and prevalence of severe and persistent mental illness.* Br J Psychiatry, 2000. **177**: p. 149-55.
23. Bortolato, B., et al., *Cognitive dysfunction in bipolar disorder and schizophrenia: a systematic review of meta-analyses.* Neuropsychiatr Dis Treat, 2015. **11**: p. 3111-25.
24. Harrison, P.J., *Recent genetic findings in schizophrenia and their therapeutic relevance.* J Psychopharmacol, 2015. **29**(2): p. 85-96.
25. Andreassen, O.A., et al., *Improved detection of common variants associated with schizophrenia by leveraging pleiotropy with cardiovascular-disease risk factors.* Am J Hum Genet, 2013. **92**(2): p. 197-209.
26. Light, G., et al., *Comparison of the heritability of schizophrenia and endophenotypes in the COGS-1 family study.* Schizophr Bull, 2014. **40**(6): p. 1404-11.
27. Hilker, R., et al., *Heritability of Schizophrenia and Schizophrenia Spectrum Based on the Nationwide Danish Twin Register.* Biol Psychiatry, 2018. **83**(6): p. 492-498.
28. Matheson, S.L., et al., *A systematic meta-review grading the evidence for non-genetic risk factors and putative antecedents of schizophrenia.* Schizophr Res, 2011. **133**(1-3): p. 133-42.
29. Marconi, A., et al., *Meta-analysis of the Association Between the Level of Cannabis Use and Risk of Psychosis.* Schizophr Bull, 2016. **42**(5): p. 1262-9.
30. Miller, B., et al., *Meta-analysis of paternal age and schizophrenia risk in male versus female offspring.* Schizophr Bull, 2011. **37**(5): p. 1039-47.
31. Rafiq, S., C. Campodonico, and F. Varese, *The relationship between childhood adversities and dissociation in severe mental illness: a meta-analytic review.* Acta Psychiatr Scand, 2018. **138**(6): p. 509-525.
32. Vassos, E., et al., *Meta-analysis of the association of urbanicity with schizophrenia.* Schizophr Bull, 2012. **38**(6): p. 1118-23.
33. Cantor-Graae, E. and J.P. Selten, *Schizophrenia and migration: a meta-analysis and review.* Am J Psychiatry, 2005. **162**(1): p. 12-24.
34. Bourque, F., E. van der Ven, and A. Malla, *A meta-analysis of the risk for psychotic disorders among first- and second-generation immigrants.* Psychol Med, 2011. **41**(5): p. 897-910.
35. van der Werf, M., et al., *Systematic review and collaborative recalculation of 133,693 incident cases of schizophrenia.* Psychol Med, 2014. **44**(1): p. 9-16.
36. Kirkbride, J.B., et al., *Incidence of schizophrenia and other psychoses in England, 1950-2009: a systematic review and meta-analyses.* PLoS One, 2012. **7**(3): p. e31660.
37. McGrath, J., et al., *Schizophrenia: a concise overview of incidence, prevalence, and mortality.* Epidemiol Rev, 2008. **30**: p. 67-76.
38. Simeone, J.C., et al., *An evaluation of variation in published estimates of schizophrenia prevalence from 1990 horizontal line 2013: a systematic literature review.* BMC Psychiatry, 2015. **15**: p. 193.
39. Moreno-Kustner, B., C. Martin, and L. Pastor, *Prevalence of psychotic disorders and its association with methodological issues. A systematic review and meta-analyses.* PLoS One, 2018. **13**(4): p. e0195687.
40. Evensen, S., et al., *Prevalence, Employment Rate, and Cost of Schizophrenia in a High-Income Welfare Society: A Population-Based Study Using Comprehensive Health and Welfare Registers.* Schizophr Bull, 2016. **42**(2): p. 476-83.
41. Nesvåg, R., et al., *Substance use disorders in schizophrenia, bipolar disorder, and depressive illness: a registry-based study.* Soc Psychiatry Psychiatr Epidemiol, 2015. **50**(8): p. 1267-76.
42. Howard, R., et al., *Late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: an international consensus. The International Late-Onset Schizophrenia Group.* Am J Psychiatry, 2000. **157**(2): p. 172-8.
43. Aleman, A., R.S. Kahn, and J.P. Selten, *Sex differences in the risk of schizophrenia: evidence from meta-analysis.* Arch Gen Psychiatry, 2003. **60**(6): p. 565-71.
44. van Os, J. and S. Kapur, *Schizophrenia.* Lancet, 2009. **374**(9690): p. 635-45.

45. Bowtell, M., et al., *Rates and predictors of relapse following discontinuation of antipsychotic medication after a first episode of psychosis.* Schizophr Res, 2018. **195**: p. 231-236.
46. McDonagh, M.S., et al., *AHRQ Comparative Effectiveness Reviews*, in *Treatments for Schizophrenia in Adults: A Systematic Review*. 2017, Agency for Healthcare Research and Quality (US): Rockville (MD).
47. Heilbronner, U., et al., *The Longitudinal Course of Schizophrenia Across the Lifespan: Clinical, Cognitive, and Neurobiological Aspects.* Harv Rev Psychiatry, 2016. **24**(2): p. 118-28.
48. Jaaskelainen, E., et al., *A systematic review and meta-analysis of recovery in schizophrenia.* Schizophr Bull, 2013. **39**(6): p. 1296-306.
49. Volavka, J. and J. Vevera, *Very long-term outcome of schizophrenia.* Int J Clin Pract, 2018: p. e13094.
50. Abel, K.M., R. Drake, and J.M. Goldstein, *Sex differences in schizophrenia.* Int Rev Psychiatry, 2010. **22**(5): p. 417-28.
51. Immonen, J., et al., *Age at onset and the outcomes of schizophrenia: A systematic review and meta-analysis.* Early Interv Psychiatry, 2017. **11**(6): p. 453-460.
52. Fusar-Poli, P., et al., *Comorbid depressive and anxiety disorders in 509 individuals with an at-risk mental state: impact on psychopathology and transition to psychosis.* Schizophr Bull, 2014. **40**(1): p. 120-31.
53. Newton-Howes, G., et al., *The prevalence of personality disorder in schizophrenia and psychotic disorders: systematic review of rates and explanatory modelling.* Psychol Med, 2008. **38**(8): p. 1075-82.
54. Achim, A.M., et al., *How prevalent are anxiety disorders in schizophrenia? A meta-analysis and critical review on a significant association.* Schizophr Bull, 2011. **37**(4): p. 811-21.
55. Swets, M., et al., *The obsessive compulsive spectrum in schizophrenia, a meta-analysis and meta-regression exploring prevalence rates.* Schizophr Res, 2014. **152**(2-3): p. 458-68.
56. Cai, L. and J. Huang, *Schizophrenia and risk of dementia: a meta-analysis study.* Neuropsychiatr Dis Treat, 2018. **14**: p. 2047-2055.
57. Muneer, A., *Treatment of the depressive phase of bipolar affective disorder: a review.* J Pak Med Assoc, 2013. **63**(6): p. 763-9.
58. Baldessarini, R.J., et al., *Effects of treatment latency on response to maintenance treatment in manic-depressive disorders.* Bipolar Disord, 2007. **9**(4): p. 386-93.
59. Arnold, L.M., *Gender differences in bipolar disorder.* Psychiatr Clin North Am, 2003. **26**(3): p. 595-620.
60. Ferrari, A.J., et al., *The prevalence and burden of bipolar disorder: findings from the Global Burden of Disease Study 2013.* Bipolar Disord, 2016. **18**(5): p. 440-50.
61. Barnett, J.H. and J.W. Smoller, *The genetics of bipolar disorder.* Neuroscience, 2009. **164**(1): p. 331-43.
62. Edvardsen, J., et al., *Heritability of bipolar spectrum disorders. Unity or heterogeneity?* J Affect Disord, 2008. **106**(3): p. 229-40.
63. Craddock, N. and I. Jones, *Genetics of bipolar disorder.* J Med Genet, 1999. **36**(8): p. 585-94.
64. Lee, S.H., et al., *Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs.* Nat Genet, 2013. **45**(9): p. 984-94.
65. Lichtenstein, P., et al., *Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study.* Lancet, 2009. **373**(9659): p. 234-9.
66. Rowland, T.A. and S. Marwaha, *Epidemiology and risk factors for bipolar disorder.* Ther Adv Psychopharmacol, 2018. **8**(9): p. 251-269.
67. Kerner, B., *Genetics of bipolar disorder.* Appl Clin Genet, 2014. **7**: p. 33-42.
68. Liu, R.T., *Early life stressors and genetic influences on the development of bipolar disorder: the roles of childhood abuse and brain-derived neurotrophic factor.* Child Abuse Negl, 2010. **34**(7): p. 516-22.

69. Bortolato, B., et al., *Systematic assessment of environmental risk factors for bipolar disorder: an umbrella review of systematic reviews and meta-analyses.* Bipolar Disord, 2017. **19**(2): p. 84-96.
70. Medici, C.R., et al., *Mortality and secular trend in the incidence of bipolar disorder.* J Affect Disord, 2015. **183**: p. 39-44.
71. Müller-Oerlinghausen, B., A. Berghöfer, and M. Bauer, *Bipolar disorder.* Lancet, 2002. **359**(9302): p. 241-7.
72. Moreira, A.L.R., et al., *Review and Meta-Analysis of Epidemiologic Studies of Adult Bipolar Disorder.* J Clin Psychiatry, 2017. **78**(9): p. e1259-e1269.
73. Larsson, S., et al., *Age at onset of bipolar disorder in a Norwegian catchment area sample.* J Affect Disord, 2010. **124**(1-2): p. 174-7.
74. Angst, J. and R. Sellaro, *Historical perspectives and natural history of bipolar disorder.* Biol Psychiatry, 2000. **48**(6): p. 445-57.
75. Garcia, S., et al., *Adherence to Antipsychotic Medication in Bipolar Disorder and Schizophrenic Patients: A Systematic Review.* J Clin Psychopharmacol, 2016. **36**(4): p. 355-71.
76. Judd, L.L., et al., *A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder.* Arch Gen Psychiatry, 2003. **60**(3): p. 261-9.
77. Judd, L.L., et al., *The long-term natural history of the weekly symptomatic status of bipolar I disorder.* Arch Gen Psychiatry, 2002. **59**(6): p. 530-7.
78. Vieta, E., et al., *Early Intervention in Bipolar Disorder.* Am J Psychiatry, 2018. **175**(5): p. 411-426.
79. Gitlin, M.J. and D.J. Miklowitz, *The difficult lives of individuals with bipolar disorder: A review of functional outcomes and their implications for treatment.* J Affect Disord, 2017. **209**: p. 147-154.
80. Plana-Ripoll, O., et al., *Exploring Comorbidity Within Mental Disorders Among a Danish National Population.* JAMA Psychiatry, 2019. **76**(3): p. 259-270.
81. Latalova, K., D. Kamaradova, and J. Prasko, *Suicide in bipolar disorder: a review.* Psychiatr Danub, 2014. **26**(2): p. 108-14.
82. Ducci, F. and D. Goldman, *The genetic basis of addictive disorders.* Psychiatr Clin North Am, 2012. **35**(2): p. 495-519.
83. Prom-Wormley, E.C., et al., *The genetic epidemiology of substance use disorder: A review.* Drug Alcohol Depend, 2017. **180**: p. 241-259.
84. Galea, S., A. Nandi, and D. Vlahov, *The social epidemiology of substance use.* Epidemiol Rev, 2004. **26**: p. 36-52.
85. Merikangas, K.R. and V.L. McClair, *Epidemiology of substance use disorders.* Hum Genet, 2012. **131**(6): p. 779-89.
86. Kringlen, E., S. Torgersen, and V. Cramer, *Mental illness in a rural area: a Norwegian psychiatric epidemiological study.* Soc Psychiatry Psychiatr Epidemiol, 2006. **41**(9): p. 713-9.
87. Deas, D., *Adolescent substance abuse and psychiatric comorbidities.* J Clin Psychiatry, 2006. **67 Suppl 7**: p. 18-23.
88. Kilpatrick, D.G., et al., *Risk factors for adolescent substance abuse and dependence: data from a national sample.* J Consult Clin Psychol, 2000. **68**(1): p. 19-30.
89. Jordan, C.J. and S.L. Andersen, *Sensitive periods of substance abuse: Early risk for the transition to dependence.* Dev Cogn Neurosci, 2017. **25**: p. 29-44.
90. Degenhardt, L., et al., *Estimating treatment coverage for people with substance use disorders: an analysis of data from the World Mental Health Surveys.* World Psychiatry, 2017. **16**(3): p. 299-307.
91. Whiteford, H.A., et al., *Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010.* Lancet, 2013. **382**(9904): p. 1575-86.

92. Whiteford, H.A., et al., *The global burden of mental, neurological and substance use disorders: an analysis from the Global Burden of Disease Study 2010.* PLoS One, 2015. **10**(2): p. e0116820.
93. Wittchen, H.U., et al., *The size and burden of mental disorders and other disorders of the brain in Europe 2010.* Eur Neuropsychopharmacol, 2011. **21**(9): p. 655-79.
94. Kringlen, E., S. Torgersen, and V. Cramer, *A Norwegian psychiatric epidemiological study.* Am J Psychiatry, 2001. **158**(7): p. 1091-8.
95. Statistisk Sentralbyrå [Statistics Norway]. *Røyk, alkohol og andre rusmidler [Tobacco, alcohol and other drugs]*. 2019 [cited 2019 April 21, 2019]; Available from: https://www.ssb.no/royk.
96. Folkehelseinstituttet [The Norwegian Institute of Public Health]. *Folkehelserapporten - Helsetilstanden i Norge 2018 [healt status in Norway 2018]*. 2019 [cited 2019 March, 25 2019]; Available from: https://www.fhi.no/nettpub/hin/.
97. European Centre for Drug Dependency and Addiction (EMCDDA). *Norway: Country drug report 2018*. 2019 [cited 2019 March 23, 2019]; Available from: http://www.emcdda.europa.eu/countries/drug-reports/2018/norway_en.
98. Simonsen, K.W., et al., *Fatal poisoning in drug addicts in the Nordic countries in 2012.* Forensic Sci Int, 2015. **248**: p. 172-80.
99. Helsedirektoratet [The Norwegian Directorate of Health], *Nasjonal faglig retningslinje for behandling og rehabilitering av rusmiddelproblemer og avhengighet [National guideline for the treatment and rehabilitation of substance abuse problems and addiction]*. 2017: Oslo.
100. Dutra, L., et al., *A meta-analytic review of psychosocial interventions for substance use disorders.* Am J Psychiatry, 2008. **165**(2): p. 179-87.
101. Maisto, S.A., et al., *Course of remission from and relapse to heavy drinking following outpatient treatment of alcohol use disorder.* Drug Alcohol Depend, 2018. **187**: p. 319-326.
102. Fleury, M.J., et al., *Remission from substance use disorders: A systematic review and meta-analysis.* Drug Alcohol Depend, 2016. **168**: p. 293-306.
103. van Amsterdam, J., et al., *Physical harm due to chronic substance use.* Regul Toxicol Pharmacol, 2013. **66**(1): p. 83-7.
104. Lai, H.M., et al., *Prevalence of comorbid substance use, anxiety and mood disorders in epidemiological surveys, 1990-2014: A systematic review and meta-analysis.* Drug Alcohol Depend, 2015. **154**: p. 1-13.
105. Naghavi M, *Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016.* Lancet, 2017. **390**(10100): p. 1151-1210.
106. Govatsmark, R.E.S., et al., *Årsrapport 2016*. 2017, Norsk hjerteinfarktregister [The Norwegian Registry of Myocardial Infarction].
107. Folkehelseinstituttet [The Norwegian Institute of Public Health]. *Norgeshelsa statistikkbank*. 2019 [cited 2019 April 24, 2019]; Available from: http://www.norgeshelsa.no/norgeshelsa/.
108. Cheng, S., et al., *Temporal trends in the population attributable risk for cardiovascular disease: the Atherosclerosis Risk in Communities Study.* Circulation, 2014. **130**(10): p. 820-8.
109. Mannsverk, J., et al., *Trends in Modifiable Risk Factors Are Associated With Declining Incidence of Hospitalized and Nonhospitalized Acute Coronary Heart Disease in a Population.* Circulation, 2016. **133**(1): p. 74-81.
110. Hopkins, P.N. and R.R. Williams, *Identification and relative weight of cardiovascular risk factors.* Cardiol Clin, 1986. **4**(1): p. 3-31.
111. De Hert, M., J. Detraux, and D. Vancampfort, *The intriguing relationship between coronary heart disease and mental disorders.* Dialogues Clin Neurosci, 2018. **20**(1): p. 31-40.
112. World Health Organization. *The challenge of cardiovascular disease - quick statistics 2019*. 2019 [cited 2019 February, 25 2019]; Available from: http://www.euro.who.int/en/health-topics/noncommunicable-diseases/cardiovascular-diseases/data-and-statistics.

113. Stewart, J., G. Manmathan, and P. Wilkinson, *Primary prevention of cardiovascular disease: A review of contemporary guidance and literature.* JRSM Cardiovasc Dis, 2017. **6**: p. 2048004016687211.
114. Taylor, F.C., M. Huffman, and S. Ebrahim, *Statin therapy for primary prevention of cardiovascular disease.* Jama, 2013. **310**(22): p. 2451-2.
115. Regier, D.A., et al., *Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study.* Jama, 1990. **264**(19): p. 2511-8.
116. Hartz, S.M., et al., *Comorbidity of severe psychotic disorders with measures of substance use.* JAMA Psychiatry, 2014. **71**(3): p. 248-54.
117. Koskinen, J., et al., *Prevalence of alcohol use disorders in schizophrenia--a systematic review and meta-analysis.* Acta Psychiatr Scand, 2009. **120**(2): p. 85-96.
118. Koskinen, J., et al., *Rate of cannabis use disorders in clinical samples of patients with schizophrenia: a meta-analysis.* Schizophr Bull, 2010. **36**(6): p. 1115-30.
119. Sara, G.E., et al., *Stimulant use disorders in people with psychosis: a meta-analysis of rate and factors affecting variation.* Aust N Z J Psychiatry, 2015. **49**(2): p. 106-17.
120. Hunt, G.E., et al., *Prevalence of comorbid substance use in schizophrenia spectrum disorders in community and clinical settings, 1990-2017: Systematic review and meta-analysis.* Drug Alcohol Depend, 2018. **191**: p. 234-258.
121. Arseneault, L., et al., *Causal association between cannabis and psychosis: examination of the evidence.* Br J Psychiatry, 2004. **184**: p. 110-7.
122. Semple, D.M., A.M. McIntosh, and S.M. Lawrie, *Cannabis as a risk factor for psychosis: systematic review.* J Psychopharmacol, 2005. **19**(2): p. 187-94.
123. Kruckow, L., K. Linnet, and J. Banner, *Psychiatric disorders are overlooked in patients with drug abuse.* Dan Med J, 2016. **63**(3).
124. Jane-Llopis, E. and I. Matytsina, *Mental health and alcohol, drugs and tobacco: a review of the comorbidity between mental disorders and the use of alcohol, tobacco and illicit drugs.* Drug Alcohol Rev, 2006. **25**(6): p. 515-36.
125. Jackson, K.M., et al., *Alcohol and tobacco use disorders in a general population: short-term and long-term associations from the St. Louis epidemiological catchment area study.* Drug Alcohol Depend, 2003. **71**(3): p. 239-53.
126. Margolese, H.C., et al., *Drug and alcohol use among patients with schizophrenia and related psychoses: levels and consequences.* Schizophr Res, 2004. **67**(2-3): p. 157-66.
127. Potvin, S., P. Blanchet, and E. Stip, *Substance abuse is associated with increased extrapyramidal symptoms in schizophrenia: a meta-analysis.* Schizophr Res, 2009. **113**(2-3): p. 181-8.
128. Mauri, M.C., et al., *Substance abuse in first-episode schizophrenic patients: a retrospective study.* Clin Pract Epidemiol Ment Health, 2006. **2**: p. 4.
129. Compton, M.T., et al., *Association of pre-onset cannabis, alcohol, and tobacco use with age at onset of prodrome and age at onset of psychosis in first-episode patients.* Am J Psychiatry, 2009. **166**(11): p. 1251-7.
130. Schmidt, L.M., M. Hesse, and J. Lykke, *The impact of substance use disorders on the course of schizophrenia--a 15-year follow-up study: dual diagnosis over 15 years.* Schizophr Res, 2011. **130**(1-3): p. 228-33.
131. Dixon, L., *Dual diagnosis of substance abuse in schizophrenia: prevalence and impact on outcomes.* Schizophr Res, 1999. **35 Suppl**: p. S93-100.
132. Kavanagh, D.J., et al., *Substance misuse in patients with schizophrenia: epidemiology and management.* Drugs, 2002. **62**(5): p. 743-55.
133. Sorbara, F., et al., *Substance use and the course of early psychosis: a 2-year follow-up of first-admitted subjects.* Eur Psychiatry, 2003. **18**(3): p. 133-6.
134. Zammit, S., et al., *Effects of cannabis use on outcomes of psychotic disorders: systematic review.* Br J Psychiatry, 2008. **193**(5): p. 357-63.

135. Higashi, K., et al., *Medication adherence in schizophrenia: factors influencing adherence and consequences of nonadherence, a systematic literature review.* Ther Adv Psychopharmacol, 2013. **3**(4): p. 200-18.
136. Czobor, P., et al., *Treatment adherence in schizophrenia: a patient-level meta-analysis of combined CATIE and EUFEST studies.* Eur Neuropsychopharmacol, 2015. **25**(8): p. 1158-66.
137. Batki, S.L., et al., *Medical comorbidity in patients with schizophrenia and alcohol dependence.* Schizophr Res, 2009. **107**(2-3): p. 139-46.
138. Dickey, B., et al., *Medical morbidity, mental illness, and substance use disorders.* Psychiatr Serv, 2002. **53**(7): p. 861-7.
139. Adrian, M. and S.J. Barry, *Physical and mental health problems associated with the use of alcohol and drugs.* Subst Use Misuse, 2003. **38**(11-13): p. 1575-614.
140. Buckley, P.F., et al., *Psychiatric comorbidities and schizophrenia.* Schizophr Bull, 2009. **35**(2): p. 383-402.
141. Bogdanowicz, K.M., et al., *Double trouble: Psychiatric comorbidity and opioid addiction-all-cause and cause-specific mortality.* Drug Alcohol Depend, 2015. **148**: p. 85-92.
142. Latalova, K., D. Kamaradova, and J. Prasko, *Violent victimization of adult patients with severe mental illness: a systematic review.* Neuropsychiatr Dis Treat, 2014. **10**: p. 1925-39.
143. Maniglio, R., *Severe mental illness and criminal victimization: a systematic review.* Acta Psychiatr Scand, 2009. **119**(3): p. 180-91.
144. Fazel, S., et al., *Schizophrenia and violence: systematic review and meta-analysis.* PLoS Med, 2009. **6**(8): p. e1000120.
145. Volavka, J., *Violence in schizophrenia and bipolar disorder.* Psychiatr Danub, 2013. **25**(1): p. 24-33.
146. Witt, K., R. van Dorn, and S. Fazel, *Risk factors for violence in psychosis: systematic review and meta-regression analysis of 110 studies.* PLoS One, 2013. **8**(2): p. e55942.
147. Large, M., et al., *Systematic meta-analysis of outcomes associated with psychosis and co-morbid substance use.* Aust N Z J Psychiatry, 2014. **48**(5): p. 418-32.
148. Hawton, K., et al., *Schizophrenia and suicide: systematic review of risk factors.* Br J Psychiatry, 2005. **187**: p. 9-20.
149. Popovic, D., et al., *Risk factors for suicide in schizophrenia: systematic review and clinical recommendations.* Acta Psychiatr Scand, 2014. **130**(6): p. 418-26.
150. Suokas, J.T., et al., *Epidemiology of suicide attempts among persons with psychotic disorder in the general population.* Schizophr Res, 2010. **124**(1-3): p. 22-8.
151. Crump, C., et al., *Comorbidities and mortality in persons with schizophrenia: a Swedish national cohort study.* Am J Psychiatry, 2013. **170**(3): p. 324-33.
152. Crump, C., et al., *Comorbidities and mortality in bipolar disorder: a Swedish national cohort study.* JAMA Psychiatry, 2013. **70**(9): p. 931-9.
153. De Hert M, et al., *Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care.* World Psychiatry, 2011. **10**(1): p. 52-77.
154. Viron, M.J. and T.A. Stern, *The impact of serious mental illness on health and healthcare.* Psychosomatics, 2010. **51**(6): p. 458-65.
155. Correll, C.U., et al., *Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls.* World Psychiatry, 2017. **16**(2): p. 163-180.
156. Ayerbe, L., et al., *Hypertension risk and clinical care in patients with bipolar disorder or schizophrenia; a systematic review and meta-analysis.* J Affect Disord, 2018. **225**: p. 665-670.
157. Prieto, M.L., et al., *Risk of myocardial infarction and stroke in bipolar disorder: a systematic review and exploratory meta-analysis.* Acta Psychiatr Scand, 2014. **130**(5): p. 342-53.
158. Fan, Z., et al., *Schizophrenia and the risk of cardiovascular diseases: a meta-analysis of thirteen cohort studies.* J Psychiatr Res, 2013. **47**(11): p. 1549-56.
159. Li, M., et al., *Schizophrenia and risk of stroke: a meta-analysis of cohort studies.* Int J Cardiol, 2014. **173**(3): p. 588-90.

160. Yu, Z.H., et al., *Use of antipsychotics and risk of myocardial infarction: a systematic review and meta-analysis.* Br J Clin Pharmacol, 2016. **82**(3): p. 624-32.
161. Huang, K.L., et al., *Myocardial infarction risk and antipsychotics use revisited: a meta-analysis of 10 observational studies.* J Psychopharmacol, 2017. **31**(12): p. 1544-1555.
162. De Hert, M., et al., *Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC).* Eur Psychiatry, 2009. **24**(6): p. 412-24.
163. McEvoy, J.P., et al., *Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III.* Schizophr Res, 2005. **80**(1): p. 19-32.
164. de Leon, J. and F.J. Diaz, *A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors.* Schizophr Res, 2005. **76**(2-3): p. 135-57.
165. Rødevand, L., et al., *Cardiovascular risk remain high in schizophrenia with modest improvements in bipolar disorder during past decade.* Acta Psychiatr Scand, 2019. **139**(4): p. 348-360.
166. Kaur, J., *A comprehensive review on metabolic syndrome.* Cardiol Res Pract, 2014. **2014**: p. 943162.
167. Mottillo, S., et al., *The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis.* J Am Coll Cardiol, 2010. **56**(14): p. 1113-32.
168. Mitchell, A.J., et al., *Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders--a systematic review and meta-analysis.* Schizophr Bull, 2013. **39**(2): p. 306-18.
169. Vancampfort, D., et al., *Metabolic syndrome and metabolic abnormalities in bipolar disorder: a meta-analysis of prevalence rates and moderators.* Am J Psychiatry, 2013. **170**(3): p. 265-74.
170. Vancampfort, D., et al., *Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis.* World Psychiatry, 2015. **14**(3): p. 339-47.
171. Stubbs, B., et al., *The prevalence and predictors of type two diabetes mellitus in people with schizophrenia: a systematic review and comparative meta-analysis.* Acta Psychiatr Scand, 2015. **132**(2): p. 144-57.
172. Vancampfort, D., et al., *Diabetes mellitus in people with schizophrenia, bipolar disorder and major depressive disorder: a systematic review and large scale meta-analysis.* World Psychiatry, 2016. **15**(2): p. 166-74.
173. Roberts, E., et al., *The prevalence of diabetes mellitus and abnormal glucose metabolism in the inpatient psychiatric setting: A systematic review and meta-analysis.* Gen Hosp Psychiatry, 2017. **45**: p. 76-84.
174. Folkehelseinstituttet [The Norwegian Institute of Public Health]. *Diabetes i Norge [Diabetes in Norway]*. 2019 [cited 2019 May 19th, 2019]; Available from: https://www.fhi.no/nettpub/hin/ikke-smittsomme/diabetes/#antall-med-diabetes-i-norge.
175. Foley, D.L. and K.I. Morley, *Systematic review of early cardiometabolic outcomes of the first treated episode of psychosis.* Arch Gen Psychiatry, 2011. **68**(6): p. 609-16.
176. Correll, C.U., et al., *Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder.* World Psychiatry, 2015. **14**(2): p. 119-36.
177. Oud, M.J. and B. Meyboom-de Jong, *Somatic diseases in patients with schizophrenia in general practice: their prevalence and health care.* BMC Fam Pract, 2009. **10**: p. 32.
178. Kisely, S., et al., *A systematic review and meta-analysis of the association between poor oral health and severe mental illness.* Psychosom Med, 2015. **77**(1): p. 83-92.

179. Stubbs, B., et al., *The prevalence and predictors of obstructive sleep apnea in major depressive disorder, bipolar disorder and schizophrenia: A systematic review and meta-analysis.* J Affect Disord, 2016. **197**: p. 259-67.
180. Ayano, G., et al., *A systematic review and meta-analysis of gender difference in epidemiology of HIV, hepatitis B, and hepatitis C infections in people with severe mental illness.* Ann Gen Psychiatry, 2018. **17**: p. 16.
181. Kilbourne, A.M., et al., *Burden of general medical conditions among individuals with bipolar disorder.* Bipolar Disord, 2004. **6**(5): p. 368-73.
182. Yang, M., et al., *Poor oral health in patients with schizophrenia: A systematic review and meta-analysis.* Schizophr Res, 2018. **201**: p. 3-9.
183. Stubbs, B., et al., *Schizophrenia and the risk of fractures: a systematic review and comparative meta-analysis.* Gen Hosp Psychiatry, 2015. **37**(2): p. 126-33.
184. Chandrasekaran, V., et al., *Bipolar disorder and bone health: A systematic review.* J Affect Disord, 2019. **249**: p. 262-269.
185. Diniz, B.S., et al., *History of Bipolar Disorder and the Risk of Dementia: A Systematic Review and Meta-Analysis.* Am J Geriatr Psychiatry, 2017. **25**(4): p. 357-362.
186. Catala-Lopez, F., et al., *Inverse and direct cancer comorbidity in people with central nervous system disorders: a meta-analysis of cancer incidence in 577,013 participants of 50 observational studies.* Psychother Psychosom, 2014. **83**(2): p. 89-105.
187. Bushe, C.J., et al., *Schizophrenia and breast cancer incidence: a systematic review of clinical studies.* Schizophr Res, 2009. **114**(1-3): p. 6-16.
188. Catts, V.S., et al., *Cancer incidence in patients with schizophrenia and their first-degree relatives - a meta-analysis.* Acta Psychiatr Scand, 2008. **117**(5): p. 323-36.
189. Leucht, S., et al., *Physical illness and schizophrenia: a review of the literature.* Acta Psychiatr Scand, 2007. **116**(5): p. 317-33.
190. Stubbs, B., et al., *A meta-analysis of prevalence estimates and moderators of low bone mass in people with schizophrenia.* Acta Psychiatr Scand, 2014. **130**(6): p. 470-86.
191. Wu, M.K., et al., *Significantly Higher Prevalence Rate of Asthma and Bipolar Disorder Co-Morbidity: A Meta-Analysis and Review Under PRISMA Guidelines.* Medicine (Baltimore), 2016. **95**(13): p. e3217.
192. Tseng, P.T., et al., *A meta-analysis and systematic review of the comorbidity between irritable bowel syndrome and bipolar disorder.* Medicine (Baltimore), 2016. **95**(33): p. e4617.
193. Westman, J., et al., *Cardiovascular mortality in bipolar disorder: a population-based cohort study in Sweden.* BMJ Open, 2013. **3**(4).
194. Lee, E.E., et al., *A widening longevity gap between people with schizophrenia and general population: A literature review and call for action.* Schizophr Res, 2018. **196**: p. 9-13.
195. Lomholt, L.H., et al., *Mortality rate trends in patients diagnosed with schizophrenia or bipolar disorder: a nationwide study with 20 years of follow-up.* Int J Bipolar Disord, 2019. **7**(1): p. 6.
196. Tiihonen, J., et al., *11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study).* Lancet, 2009. **374**(9690): p. 620-7.
197. Tanskanen, A., J. Tiihonen, and H. Taipale, *Mortality in schizophrenia: 30-year nationwide follow-up study.* Acta Psychiatr Scand, 2018. **138**(6): p. 492-499.
198. Gissler, M., et al., *Patterns in mortality among people with severe mental disorders across birth cohorts: a register-based study of Denmark and Finland in 1982-2006.* BMC Public Health, 2013. **13**: p. 834.
199. Walker, E.R., R.E. McGee, and B.G. Druss, *Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis.* JAMA Psychiatry, 2015. **72**(4): p. 334-41.
200. Laursen, T.M., T. Munk-Olsen, and M. Vestergaard, *Life expectancy and cardiovascular mortality in persons with schizophrenia.* Curr Opin Psychiatry, 2012. **25**(2): p. 83-8.
201. Wahlbeck, K., et al., *Outcomes of Nordic mental health systems: life expectancy of patients with mental disorders.* Br J Psychiatry, 2011. **199**(6): p. 453-8.

202. Castagnini, A., L. Foldager, and A. Bertelsen, *Excess mortality of acute and transient psychotic disorders: comparison with bipolar affective disorder and schizophrenia.* Acta Psychiatr Scand, 2013. **128**(5): p. 370-5.
203. Kiviniemi, M., et al., *Regional differences in five-year mortality after a first episode of schizophrenia in Finland.* Psychiatr Serv, 2010. **61**(3): p. 272-9.
204. Honkonen, H., et al., *Mortality of Finnish acute psychiatric hospital patients.* Soc Psychiatry Psychiatr Epidemiol, 2008. **43**(8): p. 660-6.
205. John, A., et al., *Premature mortality among people with severe mental illness - New evidence from linked primary care data.* Schizophr Res, 2018.
206. Olfson, M., et al., *Premature Mortality Among Adults With Schizophrenia in the United States.* JAMA Psychiatry, 2015: p. 1-10.
207. Jayatilleke, N., et al., *Contributions of specific causes of death to lost life expectancy in severe mental illness.* Eur Psychiatry, 2017. **43**: p. 109-115.
208. Laursen, T.M., et al., *Life expectancy and death by diseases of the circulatory system in patients with bipolar disorder or schizophrenia in the Nordic countries.* PLoS One, 2013. **8**(6): p. e67133.
209. Chesney, E., G.M. Goodwin, and S. Fazel, *Risks of all-cause and suicide mortality in mental disorders: a meta-review.* World Psychiatry, 2014. **13**(2): p. 153-60.
210. Roerecke, M. and J. Rehm, *Alcohol use disorders and mortality: a systematic review and meta-analysis.* Addiction, 2013. **108**(9): p. 1562-78.
211. Degenhardt, L., et al., *Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies.* Addiction, 2010. **106**(1): p. 32-51.
212. Mathers, B.M., et al., *Mortality among people who inject drugs: a systematic review and meta-analysis.* Bull World Health Organ, 2013. **91**(2): p. 102-23.
213. Hjemsæter, A.J., et al., *Mortality, cause of death and risk factors in patients with alcohol use disorder alone or poly-substance use disorders: a 19-year prospective cohort study.* BMC Psychiatry, 2019. **19**(1): p. 101.
214. Gjersing, L. and A.L. Bretteville-Jensen, *Gender differences in mortality and risk factors in a 13-year cohort study of street-recruited injecting drug users.* BMC Public Health, 2014. **14**: p. 440.
215. Bjornaas, M.A., et al., *A 20-year prospective study of mortality and causes of death among hospitalized opioid addicts in Oslo.* BMC Psychiatry, 2008. **8**: p. 8.
216. Arendt, M., et al., *Mortality among individuals with cannabis, cocaine, amphetamine, MDMA, and opioid use disorders: a nationwide follow-up study of Danish substance users in treatment.* Drug Alcohol Depend, 2011. **114**(2-3): p. 134-9.
217. Nyhlén, A., et al., *Substance abuse and psychiatric co-morbidity as predictors of premature mortality in Swedish drug abusers: a prospective longitudinal study 1970-2006.* BMC Psychiatry, 2011. **11**: p. 122.
218. von Greiff, N., et al., *Mortality and Cause of Death-A 30-Year Follow-Up of Substance Misusers in Sweden.* Subst Use Misuse, 2018: p. 1-9.
219. Koola, M.M., et al., *Alcohol and cannabis use and mortality in people with schizophrenia and related psychotic disorders.* J Psychiatr Res, 2012. **46**(8): p. 987-93.
220. Maynard, C., et al., *Substance use and five-year survival in Washington State mental hospitals.* Adm Policy Ment Health, 2004. **31**(4): p. 339-45.
221. Rosen, C.S., et al., *Substance abuse-related mortality among middle-aged male VA psychiatric patients.* Psychiatr Serv, 2008. **59**(3): p. 290-6.
222. Björkenstam, E., et al., *Quality of medical care and excess mortality in psychiatric patients--a nationwide register-based study in Sweden.* BMJ Open, 2012. **2**: p. e000778.
223. Hjorthøj, C., et al., *Association between alcohol and substance use disorders and all-cause and cause-specific mortality in schizophrenia, bipolar disorder, and unipolar depression: a nationwide, prospective, register-based study.* Lancet Psychiatry, 2015. **2**(9): p. 801-8.

224. Reininghaus, U., et al., *Mortality in schizophrenia and other psychoses: a 10-year follow-up of the ÆSOP first-episode cohort.* Schizophr Bull, 2015. **41**(3): p. 664-73.
225. Aagaard, J., et al., *Clinically useful predictors for premature mortality among psychiatric patients visiting a psychiatric emergency room.* Int J Soc Psychiatry, 2016. **62**(5): p. 462-70.
226. Lumme, S., et al., *Excess Mortality in Patients with Severe Mental Disorders in 1996-2010 in Finland.* PLoS One, 2016. **11**(3): p. e0152223.
227. Limosin, F., et al., *Ten-year prospective follow-up study of the mortality by suicide in schizophrenic patients.* Schizophr Res, 2007. **94**(1-3): p. 23-8.
228. Sørensen, H.J., et al., *Drug-use pattern, comorbid psychosis and mortality in people with a history of opioid addiction.* Acta Psychiatr Scand, 2005. **111**(3): p. 244-9.
229. Mattisson, C., et al., *Mortality in alcohol use disorder in the Lundby Community Cohort--a 50 year follow-up.* Drug Alcohol Depend, 2011. **118**(2-3): p. 141-7.
230. Manrique-Garcia, E., et al., *Cannabis, Psychosis, and Mortality: A Cohort Study of 50,373 Swedish Men.* Am J Psychiatry, 2016. **173**(8): p. 790-8.
231. Steingrímsson, S., et al., *Total population-based study of the impact of substance use disorders on the overall survival of psychiatric inpatients.* Nord J Psychiatry, 2016. **70**(3): p. 161-6.
232. Oregon Department of Human Services Addiction and Mental Health Division, *Measuring premature mortality among Oregonians*. 2008, Department of Human Services Salem, Oregon.
233. Dickey, B., et al., *Externally caused deaths for adults with substance use and mental disorders.* J Behav Health Serv Res, 2004. **31**(1): p. 75-85.
234. Pedersen, A.G., *Private aktører i spesialisthelsetjenesten. Omfang og utvikling 2010-2014 [Private providers in the specialist health service. Scope and development 2010-2014]*. 2016, Helsedirektoratet [The Norwegian Directorate of Health]: Oslo.
235. Helsedirektoratet [The Norwegian Directorate of Health]. *Styringsdata for fastlegeordningen, 4. kvartal 2018 [Management data for the GP, 4th quarter 2018]*. 2019 [cited 2019 May, 28]; Available from: file:///C:/Users/ekoinh/Downloads/hovedtallsrapport%20fastlegeordningen%20landstall%202018-4.pdf.
236. Kjosavik, S.R., S. Ruths, and S. Hunskaar, *Psychotropic drug use in the Norwegian general population in 2005: data from the Norwegian Prescription Database.* Pharmacoepidemiol Drug Saf, 2009. **18**(7): p. 572-8.
237. Whitehead, M., *The concepts and principles of equity and health.* Int J Health Serv, 1992. **22**(3): p. 429-45.
238. Fisher, E.S. and J.E. Wennberg, *Health care quality, geographic variations, and the challenge of supply-sensitive care.* Perspect Biol Med, 2003. **46**(1): p. 69-79.
239. Kawachi, I., S.V. Subramanian, and N. Almeida-Filho, *A glossary for health inequalities.* J Epidemiol Community Health, 2002. **56**(9): p. 647-52.
240. Institute of Medicine (US), *Committee to Design a Strategy for Quality Review and Assurance in Medicare*, in *Medicare: A Strategy for Quality Assurance: Volume 1*, K.N. Lohr, Editor. 1990, National Academies Press (US): Washington (DC).
241. Donabedian, A., *The quality of care. How can it be assessed?* Jama, 1988. **260**(12): p. 1743-8.
242. World Health Organization, *Prevention of cardiovascular disease: guidelines for assessment and management of total cardiovascular risk*. 2007, World Health Organization,: Geneva, Switzerland.
243. Cohn, J.N., et al., *Screening for early detection of cardiovascular disease in asymptomatic individuals.* Am Heart J, 2003. **146**(4): p. 679-85.
244. Newby, D.E., et al., *Coronary CT Angiography and 5-Year Risk of Myocardial Infarction.* N Engl J Med, 2018. **379**(10): p. 924-933.
245. Brink, M., et al., *Excess medical comorbidity and mortality across the lifespan in schizophrenia.: A nationwide Danish register study.* Schizophr Res, 2019. **206**: p. 347-354.

246. Copeland, L.A., et al., *Unforeseen inpatient mortality among veterans with schizophrenia.* Med Care, 2006. **44**(2): p. 110-6.
247. Lord, O., D. Malone, and A.J. Mitchell, *Receipt of preventive medical care and medical screening for patients with mental illness: a comparative analysis.* Gen Hosp Psychiatry, 2010. **32**(5): p. 519-43.
248. Mitchell, A.J., et al., *Guideline concordant monitoring of metabolic risk in people treated with antipsychotic medication: systematic review and meta-analysis of screening practices.* Psychol Med, 2012. **42**(1): p. 125-47.
249. Mitchell, A.J. and D. Lawrence, *Revascularisation and mortality rates following acute coronary syndromes in people with severe mental illness: comparative meta-analysis.* Br J Psychiatry, 2011. **198**(6): p. 434-41.
250. Mitchell, A.J., O. Lord, and D. Malone, *Differences in the prescribing of medication for physical disorders in individuals with v. without mental illness: meta-analysis.* Br J Psychiatry, 2012. **201**(6): p. 435-43.
251. Pitman, A.L., et al., *Cardiovascular screening of people with severe mental illness in England: views of service users and providers.* Psychiatr Serv, 2011. **62**(11): p. 1338-45.
252. Gabilondo, A., et al., *Comorbidities with chronic physical conditions and gender profiles of illness in schizophrenia. Results from PREST, a new health dataset.* J Psychosom Res, 2017. **93**: p. 102-109.
253. Munk-Jørgensen, P., et al., *The schizophrenic patient in the somatic hospital.* Acta Psychiatr Scand Suppl, 2000. **102**(407): p. 96-9.
254. Kilbourne, A.M., et al., *Excess heart-disease-related mortality in a national study of patients with mental disorders: identifying modifiable risk factors.* Gen Hosp Psychiatry, 2009. **31**(6): p. 555-63.
255. Smith, D.J., et al., *Multimorbidity in bipolar disorder and undertreatment of cardiovascular disease: a cross sectional study.* BMC Med, 2013. **11**: p. 263.
256. Lahti, M., et al., *Cardiovascular morbidity, mortality and pharmacotherapy in patients with schizophrenia.* Psychol Med, 2012. **42**(11): p. 2275-85.
257. Laursen, T.M., et al., *Cardiovascular drug use and mortality in patients with schizophrenia or bipolar disorder: a Danish population-based study.* Psychol Med, 2014. **44**(8): p. 1625-37.
258. Skrede, S., et al., *Incident users of antipsychotic agents and future use of cholesterol-lowering drugs: an observational, pharmacoepidemiologic study.* J Clin Psychiatry, 2015. **76**(1): p. e111-6.
259. Kugathasan, P., et al., *Association of Secondary Preventive Cardiovascular Treatment After Myocardial Infarction With Mortality Among Patients With Schizophrenia.* JAMA Psychiatry, 2018. **75**(12): p. 1234-1240.
260. Kuipers, E., et al., *Management of psychosis and schizophrenia in adults: summary of updated NICE guidance.* BMJ, 2014. **348**: p. g1173.
261. Barnes, T.R., et al., *Screening for the metabolic side effects of antipsychotic medication: findings of a 6-year quality improvement programme in the UK.* BMJ Open, 2015. **5**(10): p. e007633.
262. Severi, E., et al., *Assessment of cardiovascular risk in an Italian psychiatric outpatient sample: A chart review of patients treated with second-generation antipsychotics.* Int J Ment Health Nurs, 2018. **27**(3): p. 1002-1008.
263. Crawford, M.J., et al., *Assessment and treatment of physical health problems among people with schizophrenia: national cross-sectional study.* Br J Psychiatry, 2014. **205**(6): p. 473-7.
264. Lack, D., R.I. Holt, and D.S. Baldwin, *Poor monitoring of physical health in patients referred to a mood disorders service.* Ther Adv Psychopharmacol, 2015. **5**(1): p. 22-5.
265. Carney, R., T. Bradshaw, and A.R. Yung, *Monitoring of physical health in services for young people at ultra-high risk of psychosis.* Early Interv Psychiatry, 2018. **12**(2): p. 153-159.
266. Whyte, S., et al., *Quality of diabetes care in patients with schizophrenia and bipolar disorder: cross-sectional study.* Diabet Med, 2007. **24**(12): p. 1442-8.

267. Hippisley-Cox, J., et al., *Inequalities in the primary care of patients with coronary heart disease and serious mental health problems: a cross-sectional study.* Heart, 2007. **93**(10): p. 1256-62.
268. Roberts, L., et al., *Physical health care of patients with schizophrenia in primary care: a comparative study.* Fam Pract, 2007. **24**(1): p. 34-40.
269. Osborn, D.P., et al., *Inequalities in the provision of cardiovascular screening to people with severe mental illnesses in primary care: cohort study in the United Kingdom THIN Primary Care Database 2000-2007.* Schizophr Res, 2011. **129**(2-3): p. 104-10.
270. Hardy, S., P. Hinks, and R. Gray, *Screening for cardiovascular risk in patients with severe mental illness in primary care: a comparison with patients with diabetes.* J Ment Health, 2013. **22**(1): p. 42-50.
271. Woodhead, C., et al., *Cardiovascular disease treatment among patients with severe mental illness: a data linkage study between primary and secondary care.* Br J Gen Pract, 2016. **66**(647): p. e374-81.
272. Hetlevik, O., M. Solheim, and S. Gjesdal, *Use of GP services by patients with schizophrenia: a national cross-sectional register-based study.* BMC Health Serv Res, 2015. **15**: p. 66.
273. Rathmann, W., et al., *Diabetes treatment in people with type 2 diabetes and schizophrenia: Retrospective primary care database analyses.* Prim Care Diabetes, 2016. **10**(1): p. 36-40.
274. Gal, G., H. Munitz, and I. Levav, *Health care disparities among persons with comorbid schizophrenia and cardiovascular disease: a case-control epidemiological study.* Epidemiol Psychiatr Sci, 2016. **25**(6): p. 541-547.
275. Gal, G., H. Munitz, and I. Levav, *Health Care and Mortality among Persons with Severe Mental Illness.* Can J Psychiatry, 2017. **62**(4): p. 259-267.
276. Ritchie, S. and L. Muldoon, *Cardiovascular preventive care for patients with serious mental illness.* Can Fam Physician, 2017. **63**(11): p. e483-e487.
277. Kisely, S., L.A. Campbell, and Y. Wang, *Treatment of ischaemic heart disease and stroke in individuals with psychosis under universal healthcare.* Br J Psychiatry, 2009. **195**(6): p. 545-50.
278. Wu, S.I., et al., *Diagnostic procedures, revascularization, and inpatient mortality after acute myocardial infarction in patients with schizophrenia and bipolar disorder.* Psychosom Med, 2013. **75**(1): p. 52-9.
279. Attar, R., et al., *Treatment following myocardial infarction in patients with schizophrenia.* PLoS One, 2017. **12**(12): p. e0189289.
280. Bresee, L.C., et al., *Utilization of general and specialized cardiac care by people with schizophrenia.* Psychiatr Serv, 2012. **63**(3): p. 237-42.
281. Kurdyak, P., et al., *High mortality and low access to care following incident acute myocardial infarction in individuals with schizophrenia.* Schizophr Res, 2012. **142**(1-3): p. 52-7.
282. Blackburn, R., et al., *Statin prescribing for prevention of cardiovascular disease amongst people with severe mental illness: Cohort study in UK primary care.* Schizophr Res, 2018. **192**: p. 219-225.
283. Manderbacka, K., et al., *How does a history of psychiatric hospital care influence access to coronary care: a cohort study.* BMJ Open, 2012. **2**(2): p. e000831.
284. Bodén, R., et al., *Higher mortality after myocardial infarction in patients with severe mental illness: a nationwide cohort study.* J Intern Med, 2015. **277**(6): p. 727-36.
285. Bongiorno, D.M., et al., *Comorbid Psychiatric Disease Is Associated With Lower Rates of Thrombolysis in Ischemic Stroke.* Stroke, 2018. **49**(3): p. 738-740.
286. Laursen, T.M., et al., *Somatic hospital contacts, invasive cardiac procedures, and mortality from heart disease in patients with severe mental disorder.* Arch Gen Psychiatry, 2009. **66**(7): p. 713-20.
287. Björkenstam, C., et al., *Suicide in first episode psychosis: a nationwide cohort study.* Schizophr Res, 2014. **157**(1-3): p. 1-7.
288. Nyhlén, A., et al., *Causes of premature mortality in Swedish drug abusers: a prospective longitudinal study 1970-2006.* J Forensic Leg Med, 2011. **18**(2): p. 66-72.

289. Manrique-Garcia, E., et al., *Cannabis, schizophrenia and other non-affective psychoses: 35 years of follow-up of a population-based cohort.* Psychol Med, 2012. **42**(6): p. 1321-8.
290. Erol, A., et al., *Sex differences in the risk of rapid cycling and other indicators of adverse illness course in patients with bipolar I and II disorder.* Bipolar Disord, 2015. **17**(6): p. 670-6.
291. Petkari, E., F. Mayoral, and B. Moreno-Kustner, *Gender matters in schizophrenia-spectrum disorders: Results from a healthcare users epidemiological study in Malaga, Spain.* Compr Psychiatry, 2017. **72**: p. 136-143.
292. Phan, H.T., et al., *Sex Differences in Long-Term Mortality After Stroke in the INSTRUCT (INternational STRoke oUtComes sTudy): A Meta-Analysis of Individual Participant Data.* Circ Cardiovasc Qual Outcomes, 2017. **10**(2).
293. Campi, T.R., Jr., et al., *Effect of charted mental illness on reperfusion therapy in hospitalized patients with an acute myocardial infarction in Florida.* Medicine (Baltimore), 2017. **96**(34): p. e7788.
294. Kontopantelis, E., et al., *Primary care consultation rates among people with and without severe mental illness: a UK cohort study using the Clinical Practice Research Datalink.* BMJ Open, 2015. **5**(12): p. e008650.
295. Ayerbe, L., et al., *Disparities in the management of cardiovascular risk factors in patients with psychiatric disorders: a systematic review and meta-analysis.* Psychol Med, 2018. **48**(16): p. 2693-2701.
296. Himelhoch, S., et al., *Care and management of cardiovascular risk factors among individuals with schizophrenia and type 2 diabetes who smoke.* Gen Hosp Psychiatry, 2009. **31**(1): p. 30-2.
297. Helsedirektoratet [The Norwegian Directorate of Health]. *Norsk Pasientregister [The Norwegian Patient Registry]*. 2019 [cited 2019 May 22, 2019]; Available from: https://www.helsedirektoratet.no/tema/statistikk-registre-og-rapporter/helsedata-og-helseregistre/norsk-pasientregister-npr.
298. Helsedirektoratet [The Norwegian Directorate of Health]. *KUHR-databasen [The KUHR database]*. 2019 [cited 2019 May 22, 2019]; Available from: https://www.helsedirektoratet.no/tema/statistikk-registre-og-rapporter/helsedata-og-helseregistre/kuhr.
299. Folkehelseinstituttet [The Norwegian Institute of Public Health]. *Dødsårsaksregisteret [The Norwegian Cause of Death Registry]*. 2019 [cited 2019 May 22, 2019]; Available from: https://www.fhi.no/hn/helseregistre-og-registre/dodsarsaksregisteret/.
300. Folkehelseinstituttet [Norwegian Institute of Public Health]. *Dødsårsaker, nøkkeltall (LHF) – per 100 000, standardisert [Causes of death, key figures (LHF) - per 100,000, standardized]*. 2018 January 15, 2019]; Available from: http://www.norgeshelsa.no/norgeshelsa/.
301. Statistisk Sentralbyrå [Statistics Norway]. *Folkemengde og befolkningsendringar [Population and population changes]*. 2016 November 21, 2016]; Available from: http://statistikkbank.fhi.no/.
302. Helsedirektoratet [The Norwegian Directorate of Health]. *Aktivitetsdata for avtalespesialister 2009 [Data on activities by specialists in private practice 2009]*. 2010; Available from: https://helsedirektoratet.no/Lists/Publikasjoner/Attachments/504/Aktivitetsdata-for-avtalespesialister-2009-IS-1818.pdf.
303. Lützen, J., A.S. Fuglset, and I. Dahlstrøm, *Aktivitetsdata for avtalespesialister 2015 [Data on activities by specialists in private practice 2015]*. 2015, Helsedirektoratet [The Norwegian Directorate of Health]: Oslo.
304. Pedersen, A.G. and C.L. Ellingsen, *Data quality in the Causes of Death Registry.* Tidsskr Nor Laegeforen, 2015. **135**(8): p. 768-70.
305. Folkehelseinstituttet [The Norwegian Institute of Public Health]. *Legemeldinger om dødsfall er grunnlaget for dødsårsaksstatistikken [Medical reports on deaths are the basis for the cause of death statistics]*. 2015 25.03.2015 [cited 2019 January 22, 2019]; Available from: https://www.fhi.no/hn/helseregistre-og-registre/dodsarsaksregisteret/legemeldinger-om-dodsfall/.

306. Tøllefsen, I.M., et al., *Differing Procedures for Recording Mortality Statistics in Scandinavia.* Crisis, 2017. **38**(2): p. 123-130.
307. Phillips, D.E., et al., *A composite metric for assessing data on mortality and causes of death: the vital statistics performance index.* Popul Health Metr, 2014. **12**: p. 14.
308. Pearce, N., *Classification of epidemiological study designs.* Int J Epidemiol, 2012. **41**(2): p. 393-7.
309. The Organisation for Economic Co-operation and Development (OECD). *Definitions for Health Care Quality Indicators 2016-2017 HCQI Data Collection*. 2019 [cited 2019 March 13, 2019]; Available from: http://www.oecd.org/els/health-systems/Definitions-of-Health-Care-Quality-Indicators.pdf.
310. Brown, S., et al., *Twenty-five year mortality of a community cohort with schizophrenia.* Br J Psychiatry, 2010. **196**(2): p. 116-21.
311. Carstensen, B. and P. Dickman. *SAS-macro for splitting of follow-up data*. [Web page] 2007 December 2007 23rd November 2016]; Available from: http://bendixcarstensen.com/Lexis/Lexis.sas.
312. Jones, M.E. and A.J. Swerdlow, *Bias in the standardized mortality ratio when using general population rates to estimate expected number of deaths.* Am J Epidemiol, 1998. **148**(10): p. 1012-7.
313. Armstrong, B.G., *Comparing standardized mortality ratios.* Ann Epidemiol, 1995. **5**(1): p. 60-4.
314. Rothman, K.J., S. Greenland, and T.L. Lash, *Modern epidemiology*. 3rd ed. 2008, Philadelphia, US: Lippincott Williams & Wilkins.
315. Goldman, D.A. and J.D. Brender, *Are standardized mortality ratios valid for public health data analysis?* Stat Med, 2000. **19**(8): p. 1081-8.
316. Szklo, M. and F.J. Nieto, *Epidemiology: Beyond the basics*. 3rd ed. ed. 2014, United States of America.
317. Zou, G., *A modified poisson regression approach to prospective studies with binary data.* Am J Epidemiol, 2004. **159**(7): p. 702-706.
318. Skov, T., et al., *Prevalence proportion ratios: estimation and hypothesis testing.* Int J Epidemiol, 1998. **27**(1): p. 91-5.
319. Greenland, S., *Model-based estimation of relative risks and other epidemiologic measures in studies of common outcomes and in case-control studies.* Am J Epidemiol, 2004. **160**(4): p. 301-5.
320. Barros, A.J. and V.N. Hirakata, *Alternatives for logistic regression in cross-sectional studies: an empirical comparison of models that directly estimate the prevalence ratio.* BMC Med Res Methodol, 2003. **3**: p. 21.
321. McNutt, L.A., et al., *Estimating the relative risk in cohort studies and clinical trials of common outcomes.* Am J Epidemiol, 2003. **157**(10): p. 940-3.
322. Deddens, J.A. and M.R. Petersen, *Approaches for estimating prevalence ratios.* Occup Environ Med, 2008. **65**(7): p. 481, 501-6.
323. Chen, W., et al., *Comparison of robustness to outliers between robust poisson models and log-binomial models when estimating relative risks for common binary outcomes: a simulation study.* BMC Med Res Methodol, 2014. **14**: p. 82.
324. Porta, M., et al., *A dictionary of epidemiology*. 2014: Oxford University Press, USA.
325. Hernán, M.A., et al., *Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology.* Am J Epidemiol, 2002. **155**(2): p. 176-84.
326. Bhopal, R., *Concepts of epidemiology. Integrating the ideas, theories, principles and methods of epidemiology*. 2008, United Kingdom: Oxford University Press.
327. Williamson, E.J., et al., *Introduction to causal diagrams for confounder selection.* Respirology, 2014. **19**(3): p. 303-11.
328. Greenland, S., J. Pearl, and J.M. Robins, *Causal diagrams for epidemiologic research.* Epidemiology, 1999: p. 37-48.

329. Textor, J., J. Hardt, and S. Knuppel, *DAGitty: a graphical tool for analyzing causal diagrams.* Epidemiology, 2011. **22**(5): p. 745.
330. So, H.C., et al., *Exploring shared genetic bases and causal relationships of schizophrenia and bipolar disorder with 28 cardiovascular and metabolic traits.* Psychol Med, 2018: p. 1-13.
331. Hansen, V., B.K. Jacobsen, and E. Arnesen, *Cause-specific mortality in psychiatric patients after deinstitutionalisation.* Br J Psychiatry, 2001. **179**: p. 438-43.
332. Crump, C., et al., *Mortality in persons with mental disorders is substantially overestimated using inpatient psychiatric diagnoses.* J Psychiatr Res, 2013. **47**(10): p. 1298-303.
333. Allgulander, C., *Psychoactive drug use in a general population sample, Sweden: correlates with perceived health, psychiatric diagnoses, and mortality in an automated record-linkage study.* Am J Public Health, 1989. **79**(8): p. 1006-10.
334. Onyeka, I.N., et al., *Patterns and 14-year trends in mortality among illicit drug users in Finland: the HUUTI study.* Int J Drug Policy, 2014. **25**(6): p. 1047-53.
335. Bretteville-Jensen, A.L., et al., *Illicit use of opioid substitution drugs: prevalence, user characteristics, and the association with non-fatal overdoses.* Drug Alcohol Depend, 2015. **147**: p. 89-96.
336. Wilcox, H.C., K.R. Conner, and E.D. Caine, *Association of alcohol and drug use disorders and completed suicide: an empirical review of cohort studies.* Drug Alcohol Depend, 2004. **76 Suppl**: p. S11-9.
337. Lawrence, D., F. Mitrou, and S.R. Zubrick, *Smoking and mental illness: results from population surveys in Australia and the United States.* BMC Public Health, 2009. **9**: p. 285.
338. Fiedorowicz, J.G., J. He, and K.R. Merikangas, *The association between mood and anxiety disorders with vascular diseases and risk factors in a nationally representative sample.* J Psychosom Res, 2011. **70**(2): p. 145-54.
339. Swain, N.R., et al., *Associations between DSM-IV mental disorders and subsequent non-fatal, self-reported stroke.* J Psychosom Res, 2015. **79**(2): p. 130-6.
340. Jørgensen, M., et al., *Quality and Predictors of Diabetes Care Among Patients With Schizophrenia: A Danish Nationwide Study.* Psychiatr Serv, 2018. **69**(2): p. 179-185.
341. Mitchell, A.J., et al., *Is the prevalence of metabolic syndrome and metabolic abnormalities increased in early schizophrenia? A comparative meta-analysis of first episode, untreated and treated patients.* Schizophr Bull, 2013. **39**(2): p. 295-305.
342. Riedel, M., et al., *How representative of everyday clinical populations are schizophrenia patients enrolled in clinical trials?* Eur Arch Psychiatry Clin Neurosci, 2005. **255**(2): p. 143-8.
343. Arbus, C., et al., *Health management of older persons with chronically medicated psychotic disorders: the results of a survey in France.* Int Psychogeriatr, 2012. **24**(3): p. 496-502.
344. Chow, V., et al., *Asymptomatic left ventricular dysfunction with long-term clozapine treatment for schizophrenia: a multicentre cross-sectional cohort study.* Open Heart, 2014. **1**(1): p. e000030.
345. Chen, P.H., et al., *Physiological characteristics of patients with schizophrenia prematurely dying from circulatory diseases.* Asia Pac Psychiatry, 2016. **8**(3): p. 199-205.
346. Manchia, M., et al., *Clinicians' adherence to clinical practice guidelines for cardiac function monitoring during antipsychotic treatment: a retrospective report on 434 patients with severe mental illness.* BMC Psychiatry, 2017. **17**(1): p. 121.
347. Berling, I., et al., *A review of ECG and QT interval measurement use in a public psychiatric inpatient setting.* Australas Psychiatry, 2018. **26**(1): p. 50-55.
348. Swildens, W., et al., *Somatic Care with a Psychotic Disorder. Lower Somatic Health Care Utilization of Patients with a Psychotic Disorder Compared to Other Patient Groups and to Controls Without a Psychiatric Diagnosis.* Adm Policy Ment Health, 2016. **43**(5): p. 650-62.
349. Young, J.K. and D.A. Foster, *Cardiovascular procedures in patients with mental disorders.* Jama, 2000. **283**(24): p. 3198; author reply 3198-9.
350. Druss, B.G., et al., *Mental disorders and use of cardiovascular procedures after myocardial infarction.* Jama, 2000. **283**(4): p. 506-11.

351. Petersen, L.A., et al., *Process of care and outcome after acute myocardial infarction for patients with mental illness in the VA health care system: are there disparities?* Health Serv Res, 2003. **38**(1 Pt 1): p. 41-63.
352. Kisely, S., et al., *Inequitable access for mentally ill patients to some medically necessary procedures.* Cmaj, 2007. **176**(6): p. 779-84.
353. Li, Y., et al., *Mental illness, access to hospitals with invasive cardiac services, and receipt of cardiac procedures by Medicare acute myocardial infarction patients.* Health Serv Res, 2013. **48**(3): p. 1076-95.
354. Briskman, I., et al., *Impact of co-morbid mental illness on the diagnosis and management of patients hospitalized for medical conditions in a general hospital.* Int J Psychiatry Med, 2012. **43**(4): p. 339-48.
355. Rathore, S.S., et al., *Mental disorders, quality of care, and outcomes among older patients hospitalized with heart failure: an analysis of the national heart failure project.* Arch Gen Psychiatry, 2008. **65**(12): p. 1402-8.
356. Copeland, L.A., et al., *Serious mental illnesses associated with receipt of surgery in retrospective analysis of patients in the Veterans Health Administration.* BMC Surg, 2015. **15**: p. 74.
357. Schulman-Marcus, J., et al., *Comparison of Trends in Incidence, Revascularization, and In-Hospital Mortality in ST-Elevation Myocardial Infarction in Patients With Versus Without Severe Mental Illness.* Am J Cardiol, 2016. **117**(9): p. 1405-10.
358. Sulo, E., et al., *Coronary angiography and myocardial revascularization following the first acute myocardial infarction in Norway during 2001-2009: Analyzing time trends and educational inequalities using data from the CVDNOR project.* Int J Cardiol, 2016. **212**: p. 122-8.
359. Copeland, L.A., et al., *Postoperative complications in the seriously mentally ill: a systematic review of the literature.* Ann Surg, 2008. **248**(1): p. 31-8.
360. Hoang, U., M.J. Goldacre, and R. Stewart, *Avoidable mortality in people with schizophrenia or bipolar disorder in England.* Acta Psychiatr Scand, 2013. **127**(3): p. 195-201.
361. Liu, N.H., et al., *Excess mortality in persons with severe mental disorders: a multilevel intervention framework and priorities for clinical practice, policy and research agendas.* World Psychiatry, 2017. **16**(1): p. 30-40.
362. Hunt, G.E., et al., *Comorbidity of bipolar and substance use disorders in national surveys of general populations, 1990-2015: Systematic review and meta-analysis.* J Affect Disord, 2016. **206**: p. 321-330.
363. Vancampfort, D., et al., *Sedentary behavior and physical activity levels in people with schizophrenia, bipolar disorder and major depressive disorder: a global systematic review and meta-analysis.* World Psychiatry, 2017. **16**(3): p. 308-315.
364. Dipasquale, S., et al., *The dietary pattern of patients with schizophrenia: a systematic review.* J Psychiatr Res, 2013. **47**(2): p. 197-207.
365. Dickerson, F., et al., *Mortality in schizophrenia and bipolar disorder: Clinical and serological predictors.* Schizophr Res, 2016. **170**(1): p. 177-83.
366. Brown, S. and C. Mitchell, *Predictors of death from natural causes in schizophrenia: 10-year follow-up of a community cohort.* Soc Psychiatry Psychiatr Epidemiol, 2012. **47**(6): p. 843-7.
367. Tran, E., et al., *Cancer mortality in patients with schizophrenia: an 11-year prospective cohort study.* Cancer, 2009. **115**(15): p. 3555-62.
368. Hamer, M., E. Stamatakis, and A. Steptoe, *Psychiatric hospital admissions, behavioral risk factors, and all-cause mortality: the Scottish health survey.* Arch Intern Med, 2008. **168**(22): p. 2474-9.
369. Moradi, H., P.D. Harvey, and L. Helldin, *Correlates of risk factors for reduced life expectancy in schizophrenia: Is it possible to develop a predictor profile?* Schizophr Res, 2018. **201**: p. 388-392.

370. De Hert, M., et al., *Physical illness in patients with severe mental disorders. II. Barriers to care, monitoring and treatment guidelines, plus recommendations at the system and individual level.* World Psychiatry, 2011. **10**(2): p. 138-51.
371. Cradock-O'Leary, J., et al., *Use of general medical services by VA patients with psychiatric disorders.* Psychiatr Serv, 2002. **53**(7): p. 874-8.
372. Gorczynski, P., H. Patel, and R. Ganguli, *Adherence to Diabetes Medication in Individuals with Schizophrenia: A Systematic Review of Rates and Determinants of Adherence.* Clin Schizophr Relat Psychoses, 2017. **10**(4): p. 191-200.
373. Jakobsen, A.S., et al., *Effect of lifestyle coaching versus care coordination versus treatment as usual in people with severe mental illness and overweight: Two-years follow-up of the randomized CHANGE trial.* PLoS One, 2017. **12**(10): p. e0185881.
374. Kessing, L.V., et al., *Treatment with antipsychotics and the risk of diabetes in clinical practice.* Br J Psychiatry, 2010. **197**(4): p. 266-71.
375. Honkola, J., et al., *Psychotropic medications and the risk of sudden cardiac death during an acute coronary event.* Eur Heart J, 2012. **33**(6): p. 745-51.
376. Li, K.J., A.P. Greenstein, and L.E. Delisi, *Sudden death in schizophrenia.* Curr Opin Psychiatry, 2018. **31**(3): p. 169-175.
377. Ray, W.A., et al., *Atypical antipsychotic drugs and the risk of sudden cardiac death.* N Engl J Med, 2009. **360**(3): p. 225-35.
378. Ifteni, P., et al., *Sudden unexpected death in schizophrenia: autopsy findings in psychiatric inpatients.* Schizophr Res, 2014. **155**(1-3): p. 72-6.
379. Khan, A.A., et al., *Clozapine and incidence of myocarditis and sudden death - Long term Australian experience.* Int J Cardiol, 2017. **238**: p. 136-139.
380. Torniainen, M., et al., *Antipsychotic treatment and mortality in schizophrenia.* Schizophr Bull, 2015. **41**(3): p. 656-63.
381. Tiihonen, J., et al., *Mortality and Cumulative Exposure to Antipsychotics, Antidepressants, and Benzodiazepines in Patients With Schizophrenia: An Observational Follow-Up Study.* Am J Psychiatry, 2016. **173**(6): p. 600-6.
382. Aggarwal, A., A. Pandurangi, and W. Smith, *Disparities in breast and cervical cancer screening in women with mental illness: a systematic literature review.* Am J Prev Med, 2013. **44**(4): p. 392-8.
383. Jørgensen, M., et al., *Quality of care and clinical outcomes of chronic obstructive pulmonary disease in patients with schizophrenia. A Danish nationwide study.* Int J Qual Health Care, 2018. **30**(5): p. 351-357.
384. Bishop, J.R., et al., *Osteoporosis screening and treatment in women with schizophrenia: a controlled study.* Pharmacotherapy, 2004. **24**(4): p. 515-21.
385. Hsu, Y.H., et al., *Lower Incidence of End-Stage Renal Disease but Suboptimal Pre-Dialysis Renal Care in Schizophrenia: A 14-Year Nationwide Cohort Study.* PLoS One, 2015. **10**(10): p. e0140510.
386. Chochinov, H.M., et al., *Comparative health care use patterns of people with schizophrenia near the end of life: a population-based study in Manitoba, Canada.* Schizophr Res, 2012. **141**(2-3): p. 241-6.
387. Huang, H.K., et al., *Disparity of end-of-life care in cancer patients with and without schizophrenia: A nationwide population-based cohort study.* Schizophr Res, 2018. **195**: p. 434-440.
388. Shefer, G., et al., *Diagnostic overshadowing and other challenges involved in the diagnostic process of patients with mental illness who present in emergency departments with physical symptoms--a qualitative study.* PLoS One, 2014. **9**(11): p. e111682.
389. Graber, M.A., et al., *Effect of a patient's psychiatric history on physicians' estimation of probability of disease.* J Gen Intern Med, 2000. **15**(3): p. 204-6.
390. Atzema, C.L., M.J. Schull, and J.V. Tu, *The effect of a charted history of depression on emergency department triage and outcomes in patients with acute myocardial infarction.* Cmaj, 2011. **183**(6): p. 663-9.

391. Vistorte, A.O.R., et al., *Stigmatizing attitudes of primary care professionals towards people with mental disorders: A systematic review.* Int J Psychiatry Med, 2018. **53**(4): p. 317-338.
392. Harangozo, J., et al., *Stigma and discrimination against people with schizophrenia related to medical services.* Int J Soc Psychiatry, 2014. **60**(4): p. 359-66.
393. Mittal, D., et al., *Healthcare providers' attitudes toward persons with schizophrenia.* Psychiatr Rehabil J, 2014. **37**(4): p. 297-303.
394. Noblett, J.E., R. Lawrence, and J.G. Smith, *The attitudes of general hospital doctors toward patients with comorbid mental illness.* Int J Psychiatry Med, 2015. **50**(4): p. 370-82.
395. Schomerus, G., et al., *The stigma of alcohol dependence compared with other mental disorders: a review of population studies.* Alcohol Alcohol, 2011. **46**(2): p. 105-12.
396. Vahia, I.V., et al., *Adequacy of medical treatment among older persons with schizophrenia.* Psychiatr Serv, 2008. **59**(8): p. 853-9.
397. Sullivan, G., et al., *Influence of schizophrenia diagnosis on providers' practice decisions.* J Clin Psychiatry, 2015. **76**(8): p. 1068-74; quiz 1074.
398. Brämberg, E.B., et al., *Access to primary and specialized somatic health care for persons with severe mental illness: a qualitative study of perceived barriers and facilitators in Swedish health care.* BMC Fam Pract, 2018. **19**(1): p. 12.
399. Blanner Kristiansen, C., et al., *Promoting physical health in severe mental illness: patient and staff perspective.* Acta Psychiatr Scand, 2015. **132**(6): p. 470-8.
400. Gale, C.R., et al., *Association of mental disorders in early adulthood and later psychiatric hospital admissions and mortality in a cohort study of more than 1 million men.* Arch Gen Psychiatry, 2012. **69**(8): p. 823-31.
401. Morrison, D.S., *Homelessness as an independent risk factor for mortality: results from a retrospective cohort study.* Int J Epidemiol, 2009. **38**(3): p. 877-83.
402. Nielsen, S.F., et al., *Psychiatric disorders and mortality among people in homeless shelters in Denmark: a nationwide register-based cohort study.* Lancet, 2011. **377**(9784): p. 2205-14.
403. Montross, L.P., S. Zisook, and J. Kasckow, *Suicide among patients with schizophrenia: a consideration of risk and protective factors.* Ann Clin Psychiatry, 2005. **17**(3): p. 173-82.
404. Hakko, H., et al., *Genetic vulnerability and premature death in schizophrenia spectrum disorders: a 28-year follow-up of adoptees in the Finnish Adoptive Family Study of Schizophrenia.* Nord J Psychiatry, 2011. **65**(4): p. 259-65.
405. McLean, G., et al., *Standard cardiovascular disease risk algorithms underestimate the risk of cardiovascular disease in schizophrenia: evidence from a national primary care database.* Schizophr Res, 2014. **159**(1): p. 176-81.
406. Straus, S.M., et al., *Antipsychotics and the risk of sudden cardiac death.* Arch Intern Med, 2004. **164**(12): p. 1293-7.
407. Hou, P.Y., et al., *Risk factors for sudden cardiac death among patients with schizophrenia.* Schizophr Res, 2015. **168**(1-2): p. 395-401.
408. Khasawneh, F.T. and G.S. Shankar, *Minimizing cardiovascular adverse effects of atypical antipsychotic drugs in patients with schizophrenia.* Cardiol Res Pract, 2014. **2014**: p. 273060.
409. Perry, B.I., et al., *The association between first-episode psychosis and abnormal glycaemic control: systematic review and meta-analysis.* Lancet Psychiatry, 2016. **3**(11): p. 1049-1058.
410. Hansen, T., et al., *At-risk variant in TCF7L2 for type II diabetes increases risk of schizophrenia.* Biol Psychiatry, 2011. **70**(1): p. 59-63.
411. Wang, K., et al., *Classification of common human diseases derived from shared genetic and environmental determinants.* Nat Genet, 2017. **49**(9): p. 1319-1325.
412. Jakobsen, L., et al., *Severe Mental Illness and Clinical Outcome After Primary Percutaneous Coronary Intervention.* Am J Cardiol, 2017. **120**(4): p. 550-555.
413. Conley, R.R., et al., *Cardiovascular disease in relation to weight in deceased persons with schizophrenia.* Compr Psychiatry, 2005. **46**(6): p. 460-7.
414. Stubbs, B., et al., *Decreased pain sensitivity among people with schizophrenia: a meta-analysis of experimental pain induction studies.* Pain, 2015. **156**(11): p. 2121-31.

415. Nielsen, J., et al., *Unrecognised myocardial infarction in patients with schizophrenia.* Acta Neuropsychiatr, 2015. **27**(2): p. 106-12.
416. Weir-McCall, J.R., et al., *Prevalence of unrecognized myocardial infarction in a low-intermediate risk asymptomatic cohort and its relation to systemic atherosclerosis.* Eur Heart J Cardiovasc Imaging, 2017. **18**(6): p. 657-662.
417. Kanzaki, T., et al., *Increased Silent Brain Infarction Accompanied With High Prevalence of Diabetes and Dyslipidemia in Psychiatric Inpatients: A Cross-Sectional Study.* Prim Care Companion CNS Disord, 2015. **17**(2).
418. Garcia-Portilla, M.P., et al., *Impact of substance use on the physical health of patients with bipolar disorder.* Acta Psychiatr Scand, 2010. **121**(6): p. 437-45.
419. Brunner, S., et al., *Patients under Psychiatric Medication Undergoing Cardiac Surgery Have a Higher Risk for Adverse Events.* Thorac Cardiovasc Surg, 2016. **64**(7): p. 575-580.
420. Beck, C.A., et al., *Alcohol and drug use disorders among patients with myocardial infarction: associations with disparities in care and mortality.* PLoS One, 2013. **8**(9): p. e66551.
421. Benson, K. and A.J. Hartz, *A comparison of observational studies and randomized, controlled trials.* N Engl J Med, 2000. **342**(25): p. 1878-86.
422. Concato, J., N. Shah, and R.I. Horwitz, *Randomized, controlled trials, observational studies, and the hierarchy of research designs.* N Engl J Med, 2000. **342**(25): p. 1887-92.
423. Ioannidis, J.P., et al., *Comparison of evidence of treatment effects in randomized and nonrandomized studies.* Jama, 2001. **286**(7): p. 821-30.
424. MacLehose, R.R., et al., *A systematic review of comparisons of effect sizes derived from randomised and non-randomised studies.* Health Technol Assess, 2000. **4**(34): p. 1-154.
425. Hernan, M.A., et al., *Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease.* Epidemiology, 2008. **19**(6): p. 766-79.
426. Øiesvold, T., et al., *Diagnosing comorbidity in psychiatric hospital: challenging the validity of administrative registers.* BMC Psychiatry, 2013. **13**: p. 13.
427. Nesvåg, R., et al., *The quality of severe mental disorder diagnoses in a national health registry as compared to research diagnoses based on structured interview.* BMC Psychiatry, 2017. **17**(1): p. 93.
428. Vandenbroucke, J. and N. Pearce, *Point: incident exposures, prevalent exposures, and causal inference: does limiting studies to persons who are followed from first exposure onward damage epidemiology?* Am J Epidemiol, 2015. **182**(10): p. 826-33.
429. Heiberg, I.H., et al., *Total and cause-specific standardized mortality ratios in patients with schizophrenia and/or substance use disorder.* PLoS One, 2018. **13**(8): p. e0202028.
430. Nordentoft, M., T. Madsen, and I. Fedyszyn, *Suicidal behavior and mortality in first-episode psychosis.* J Nerv Ment Dis, 2015. **203**(5): p. 387-92.
431. Øiesvold, T., et al., *Classification of bipolar disorder in psychiatric hospital. A prospective cohort study.* BMC Psychiatry, 2012. **12**: p. 13.
432. Uggerby, P., et al., *The validity of the schizophrenia diagnosis in the Danish Psychiatric Central Research Register is good.* Dan Med J, 2013. **60**(2): p. A4578.
433. Santelmann, H., et al., *Test-retest reliability of schizoaffective disorder compared with schizophrenia, bipolar disorder, and unipolar depression--a systematic review and meta-analysis.* Bipolar Disord, 2015. **17**(7): p. 753-68.
434. Statistisk Sentralbyrå [Statistics Norway]. *Allmennlegetjenesten, 2015 [Public Health Services, 2015],*. 2015 June 24th, 2018]; Available from: https://www.ssb.no/helse/statistikker/fastlegetj/aar/2016-06-08?fane=om.
435. Khan, N.F., S.E. Harrison, and P.W. Rose, *Validity of diagnostic coding within the General Practice Research Database: a systematic review.* Br J Gen Pract, 2010. **60**(572): p. e128-36.
436. Bromet, E.J., et al., *Diagnostic shifts during the decade following first admission for psychosis.* Am J Psychiatry, 2011. **168**(11): p. 1186-94.

437. Toftdahl, N.G., M. Nordentoft, and C. Hjorthøj, *Prevalence of substance use disorders in psychiatric patients: a nationwide Danish population-based study.* Soc Psychiatry Psychiatr Epidemiol, 2016. **51**(1): p. 129-40.
438. Hansen, S.S., et al., *Psychoactive substance use diagnoses among psychiatric in-patients.* Acta Psychiatr Scand, 2000. **102**(6): p. 432-8.
439. McCormick, N., et al., *Validity of Diagnostic Codes for Acute Stroke in Administrative Databases: A Systematic Review.* PLoS One, 2015. **10**(8): p. e0135834.
440. McCormick, N., et al., *Validity of myocardial infarction diagnoses in administrative databases: a systematic review.* PLoS One, 2014. **9**(3): p. e92286.
441. McCormick, N., et al., *Validity of heart failure diagnoses in administrative databases: a systematic review and meta-analysis.* PLoS One, 2014. **9**(8): p. e104519.
442. Varmdal, T., et al., *Comparison of the validity of stroke diagnoses in a medical quality register and an administrative health register.* Scand J Public Health, 2016. **44**(2): p. 143-9.
443. Øie, L.R., et al., *Validation of intracranial hemorrhage in the Norwegian Patient Registry.* Brain Behav, 2018. **8**(2): p. e00900.
444. Sundbøll, J., et al., *Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study.* BMJ Open, 2016. **6**(11): p. e012832.
445. Pajunen, P., et al., *The validity of the Finnish Hospital Discharge Register and Causes of Death Register data on coronary heart disease.* Eur J Cardiovasc Prev Rehabil, 2005. **12**(2): p. 132-7.
446. Rix, T.A., et al., *Validity of the diagnoses atrial fibrillation and atrial flutter in a Danish patient registry.* Scand Cardiovasc J, 2012. **46**(3): p. 149-53.
447. Hald, S.M., et al., *Intracerebral hemorrhage: positive predictive value of diagnosis codes in two nationwide Danish registries.* Clin Epidemiol, 2018. **10**: p. 941-948.
448. Delekta, J., et al., *The validity of the diagnosis of heart failure (I50.0-I50.9) in the Danish National Patient Register.* Dan Med J, 2018. **65**(4).
449. Lasota, A.N., et al., *Validity of Peripheral Arterial Disease Diagnoses in the Danish National Patient Registry.* Eur J Vasc Endovasc Surg, 2017. **53**(5): p. 679-685.
450. Prior, A., et al., *Post-stroke mortality, stroke severity, and preadmission antipsychotic medicine use--a population-based cohort study.* PLoS One, 2014. **9**(1): p. e84103.
451. Riksrevisjonen [Office of the Auditor General], *Riksrevisjonens undersøkelse av medisinsk kodepraksis i helseforetakene [The Office of the Auditor General's investigation of medical coding practice within the health enterprises]*. 2017, Riksrevisjonen.
452. Winkler, V., J.J. Ott, and H. Becher, *Reliability of coding causes of death with ICD-10 in Germany.* Int J Public Health, 2010. **55**(1): p. 43-8.
453. Naghavi, M., et al., *Algorithms for enhancing public health utility of national causes-of-death data.* Popul Health Metr, 2010. **8**: p. 9.
454. Roulson, J., E.W. Benbow, and P.S. Hasleton, *Discrepancies between clinical and autopsy diagnosis and the value of post mortem histology; a meta-analysis and review.* Histopathology, 2005. **47**(6): p. 551-9.
455. Gulsvik, A.K., et al., *Diagnostic validity of fatal cerebral strokes and coronary deaths in mortality statistics: an autopsy study.* Eur J Epidemiol, 2011. **26**(3): p. 221-8.
456. Alfsen, G.C. and J. Mæhlen, *Obduksjonens betydning for registrering av dødsårsak [The value of autopsies for determining the cause of death]*. Tidsskr Nor Laegeforen, 2012. **132**(2): p. 147-51.
457. Alfsen, G.C. and L.G. Lyckander, *Does quality control of death certificates in hospitals have an impact on cause of death statistics?* Tidsskr Nor Laegeforen, 2013. **133**(7): p. 750-5.
458. Alperovitch, A., et al., *Do we really know the cause of death of the very old? Comparison between official mortality statistics and cohort study classification.* Eur J Epidemiol, 2009. **24**(11): p. 669-75.
459. Mieno, M.N., et al., *Accuracy of Death Certificates and Assessment of Factors for Misclassification of Underlying Cause of Death.* J Epidemiol, 2016. **26**(4): p. 191-8.

460. Deckert, A., *The existence of standard-biased mortality ratios due to death certificate misclassification - a simulation study based on a true story.* BMC Med Res Methodol, 2016. **16**: p. 8.
461. Cheng, T.J., et al., *Reporting of incorrect cause-of-death causal sequence on death certificates in the USA: using hypertension and diabetes as an educational illustration.* Postgrad Med J, 2012. **88**(1046): p. 690-3.
462. Agarwal, R., et al., *Overreporting of deaths from coronary heart disease in New York City hospitals, 2003.* Prev Chronic Dis, 2010. **7**(3): p. A47.
463. Modelmog, D., S. Rahlenbeck, and D. Trichopoulos, *Accuracy of death certificates: a population-based, complete-coverage, one-year autopsy study in East Germany.* Cancer Causes Control, 1992. **3**(6): p. 541-6.
464. Harriss, L.R., et al., *Accuracy of national mortality codes in identifying adjudicated cardiovascular deaths.* Aust N Z J Public Health, 2011. **35**(5): p. 466-76.
465. Coffey, S., et al., *Clinical information has low sensitivity for postmortem diagnosis of heart valve disease.* Heart, 2017. **103**(13): p. 1031-1035.
466. Ravakhah, K., *Death certificates are not reliable: revivification of the autopsy.* South Med J, 2006. **99**(7): p. 728-33.
467. Madsen, M., et al., *The validity of the diagnosis of acute myocardial infarction in routine statistics: a comparison of mortality and hospital discharge data with the Danish MONICA registry.* J Clin Epidemiol, 2003. **56**(2): p. 124-30.
468. Mahonen, M., et al., *The validity of the routine mortality statistics on coronary heart disease in Finland: comparison with the FINMONICA MI register data for the years 1983-1992. Finnish multinational MONItoring of trends and determinants in CArdiovascular disease.* J Clin Epidemiol, 1999. **52**(2): p. 157-66.
469. Lozano, R., et al., *Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010.* The Lancet, 2013. **380**(9859): p. 2095-2128.
470. Sweeting, J., J. Duflou, and C. Semsarian, *Postmortem analysis of cardiovascular deaths in schizophrenia: a 10-year review.* Schizophr Res, 2013. **150**(2-3): p. 398-403.
471. Nilsson, L.L. and B. Logdberg, *Dead and forgotten--postmortem time before discovery as indicator of social isolation and inadequate mental healthcare in schizophrenia.* Schizophr Res, 2008. **102**(1-3): p. 337-9.
472. Alfsen, G.C., *Medical autopsies after deaths outside hospital.* Tidsskr Nor Laegeforen, 2013. **133**(7): p. 756-9.
473. Varnik, P., et al., *Validity of suicide statistics in Europe in relation to undetermined deaths: developing the 2-20 benchmark.* Inj Prev, 2012. **18**(5): p. 321-5.
474. Tøllefsen, I.M., et al., *Are suicide deaths under-reported? Nationwide re-evaluations of 1800 deaths in Scandinavia.* BMJ Open, 2015. **5**(11): p. e009120.
475. Fugelstad, A., et al., *Drug-related deaths: Statistics based on death certificates miss one-third of cases.* Scand J Public Health, 2017: p. 1403494817745187.
476. Green, C.A., et al., *Assessing the accuracy of opioid overdose and poisoning codes in diagnostic information from electronic health records, claims data, and death records.* Pharmacoepidemiol Drug Saf, 2017. **26**(5): p. 509-517.
477. Beary, M., R. Hodgson, and H.J. Wildgust, *A critical review of major mortality risk factors for all-cause mortality in first-episode schizophrenia: clinical and research implications.* J Psychopharmacol, 2012. **26**(5 Suppl): p. 52-61.
478. Speyer, H., et al., *The CHANGE trial: no superiority of lifestyle coaching plus care coordination plus treatment as usual compared to treatment as usual alone in reducing risk of cardiovascular disease in adults with schizophrenia spectrum disorders and abdominal obesity.* World Psychiatry, 2016. **15**(2): p. 155-65.
479. Osborn, D., et al., *Clinical and cost-effectiveness of an intervention for reducing cholesterol and cardiovascular risk for people with severe mental illness in English primary care: a cluster randomised controlled trial.* Lancet Psychiatry, 2018.

480. Caemmerer, J., C.U. Correll, and L. Maayan, *Acute and maintenance effects of non-pharmacologic interventions for antipsychotic associated weight gain and metabolic abnormalities: a meta-analytic comparison of randomized controlled trials.* Schizophr Res, 2012. **140**(1-3): p. 159-68.
481. Mizuno, Y., et al., *Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis.* Schizophr Bull, 2014. **40**(6): p. 1385-403.
482. Gurusamy, J., et al., *Exercise, diet and educational interventions for metabolic syndrome in persons with schizophrenia: A systematic review.* Asian J Psychiatr, 2018. **36**: p. 73-85.
483. Gierisch, J.M., et al., *Pharmacologic and behavioral interventions to improve cardiovascular risk factors in adults with serious mental illness: a systematic review and meta-analysis.* J Clin Psychiatry, 2014. **75**(5): p. e424-40.
484. Singh, V.K., et al., *Impact of lifestyle modification on some components of metabolic syndrome in persons with severe mental disorders: A meta-analysis.* Schizophr Res, 2018. **202**: p. 17-25.
485. Fernandez-San-Martin, M.I., et al., *The effectiveness of lifestyle interventions to reduce cardiovascular risk in patients with severe mental disorders: meta-analysis of intervention studies.* Community Ment Health J, 2014. **50**(1): p. 81-95.
486. Bonfioli, E., et al., *Health promotion lifestyle interventions for weight management in psychosis: a systematic review and meta-analysis of randomised controlled trials.* BMC Psychiatry, 2012. **12**: p. 78.
487. McGinty, E.E., et al., *Interventions to Address Medical Conditions and Health-Risk Behaviors Among Persons With Serious Mental Illness: A Comprehensive Review.* Schizophr Bull, 2016. **42**(1): p. 96-124.
488. Vancampfort, D., et al., *Cardiorespiratory Fitness in Severe Mental Illness: A Systematic Review and Meta-analysis.* Sports Med, 2017. **47**(2): p. 343-352.
489. Tosh, G., et al., *General physical health advice for people with serious mental illness.* Cochrane Database Syst Rev, 2014(3): p. Cd008567.
490. Osborn, D.P., M.B. King, and I. Nazareth, *Participation in screening for cardiovascular risk by people with schizophrenia or similar mental illnesses: cross sectional study in general practice.* BMJ, 2003. **326**(7399): p. 1122-3.
491. Watkins, K.E., et al., *Association Between Quality Measures and Mortality in Individuals With Co-Occurring Mental Health and Substance Use Disorders.* J Subst Abuse Treat, 2016. **69**: p. 1-8.
492. Ward, M.C., D.T. White, and B.G. Druss, *A meta-review of lifestyle interventions for cardiovascular risk factors in the general medical population: lessons for individuals with serious mental illness.* J Clin Psychiatry, 2015. **76**(4): p. e477-86.
493. Kilbourne, A.M., et al., *Datapoints: are VA patients with serious mental illness dying younger?* Psychiatr Serv, 2009. **60**(5): p. 589.
494. Desai, M.M., et al., *Receipt of nutrition and exercise counseling among medical outpatients with psychiatric and substance use disorders.* J Gen Intern Med, 2002. **17**(7): p. 556-60.
495. Doran, T., K.A. Maurer, and A.M. Ryan, *Impact of Provider Incentives on Quality and Value of Health Care.* Annu Rev Public Health, 2017. **38**: p. 449-465.
496. Scott, A., et al., *The effect of financial incentives on the quality of health care provided by primary care physicians.* Cochrane Database Syst Rev, 2011(9): p. Cd008451.

Paper I

PLOS ONE

RESEARCH ARTICLE

Total and cause-specific standardized mortality ratios in patients with schizophrenia and/or substance use disorder

Ina H. Heiberg[1]*, Bjarne K. Jacobsen[1,2], Ragnar Nesvåg[3], Jørgen G. Bramness[4,5], Ted Reichborn-Kjennerud[6,7], Øyvind Næss[7,8], Eivind Ystrom[6,9,10], Christina M. Hultman[11], Anne Høye[1,5,6,12]

1 Center for Clinical Documentation and Evaluation (SKDE), Tromsø, Norway, **2** Department of Community Medicine, UiT—The Arctic University of Norway, Tromsø, Norway, **3** Nydalen DPS, Oslo University Hospital, Oslo, Norway, **4** Norwegian National Advisory Unit on Concurrent Substance Abuse and Mental Health Disorders, Innlandet Hospital Trust, Hamar, Norway, **5** Department of Clinical Medicine, Faculty of Health Sciences, UiT—The Arctic University of Norway, Tromsø, Norway, **6** Department of Mental Disorders, Norwegian Institute of Public Health, Oslo, Norway, **7** Institute of Clinical Medicine, University of Oslo, Oslo, Norway, **8** Institute of Health and Society, University of Oslo, Oslo, Norway, **9** Department of Psychology, University of Oslo, Oslo, Norway, **10** PharmacoEpidemiology and Drug Safety Research Group, School of Pharmacy, University of Oslo, Oslo, Norway, **11** Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden, **12** Division of Mental Health and Substance Abuse, University Hospital of North Norway, Tromsø, Norway

* ina.heiberg@skde.no

Citation: Heiberg IH, Jacobsen BK, Nesvåg R, Bramness JG, Reichborn-Kjennerud T, Næss Ø, et al. (2018) Total and cause-specific standardized mortality ratios in patients with schizophrenia and/or substance use disorder. PLoS ONE 13(8): e0202028. https://doi.org/10.1371/journal.pone.0202028

Editor: Chin-Kuo Chang, Institute of Psychiatry, UNITED KINGDOM

Received: December 20, 2017

Accepted: July 26, 2018

Published: August 23, 2018

Data Availability Statement: Confidentiality requirements according to Norwegian law prevents sharing of individual patient level data in public repositories. Application of legal basis and exemption from professional secrecy requirements for the use of personal health data in research may be sent to a regional committee for medical and health research ethics (https://helseforskning.etikkom.no/), and requests for the data to The Norwegian Patient Registry (https://helsedirektoratet.no/English) and the Cause of

Abstract

Individuals with schizophrenia or substance use disorder have a substantially increased mortality compared to the general population. Despite a high and probably increasing prevalence of comorbid substance use disorder in people with schizophrenia, the mortality in the comorbid group has been less studied and with contrasting results. We performed a nationwide open cohort study from 2009 to 2015, including all Norwegians aged 20–79 with schizophrenia and/or substance use disorder registered in any specialized health care setting in Norway, a total of 125,744 individuals. There were 12,318 deaths in the cohort, and total, sex-, age- and cause-specific standardized mortality ratios (SMRs) were calculated, comparing the number of deaths in patients with schizophrenia, schizophrenia only, substance use disorder only or a co-occurring diagnosis of schizophrenia and substance use disorder to the number expected if the patients had the age-, sex- and calendar-year specific death rates of the general population. The SMRs were 4.9 (95% CI 4.7–5.1) for all schizophrenia patients, 4.4 (95% CI 4.2–4.6) in patients with schizophrenia without substance use disorder, 6.6 (95% CI 6.5–6.8) in patients with substance use disorder only, and 7.4 (95% CI 7.0–8.2) in patients with both schizophrenia and substance use disorder. The SMRs were elevated in both genders, in all age groups and for all considered causes of death, and most so in the youngest. Approximately 27% of the excess mortality in all patients with schizophrenia was due to the raised mortality in the subgroup with comorbid SUD. The increased mortality in patients with schizophrenia and/or substance use disorder corresponded to more than 10,000 premature deaths, which constituted 84% of all deaths in the cohort. The persistent mortality gap highlights the importance of securing systematic screening and

Death Registry (https://www.fhi.no/en/). Information on annual number of deaths by sex, age and cause of death are freely available at http://statistikkbank.fhi.no/webview, and annual population numbers freely available at http://statistikkbank.fhi.no.

Funding: The study is funded by a research grant offered by the Regional Health Authorities in Northern Norway. Grant number: PFP1236-15. URL: https://helse-nord.no/. The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Competing interests: The authors have declared that no competing interests exist.

proper access to somatic health care, and a more effective prevention of premature death from external causes in this group.

Introduction

Individuals with schizophrenia have a two- to three-fold increased mortality compared to the general population [1–3] and a 10-20-year reduction in average life span [2, 4–6]. Individuals with substance use disorder (SUD) have an even higher risk of premature death, ranging from a four-fold increased mortality among persons with alcohol use disorder (AUD) [7–10] to a four to-15-fold increased mortality among opioid users [11–13]. A concurrent diagnosis of schizophrenia spectrum disorder (SCZ) and SUD (henceforth referred to as SCZ+SUD) is associated with a variety of detrimental outcomes, among these increased somatic morbidity [14–19], increased risk of fatal overdoses, violent behavior [20–23] and victimization [24, 25]. Despite these vulnerabilities and a high [26, 27], and probably increasing [28], prevalence of comorbid SUD in SCZ patients, the mortality in the comorbid group has been less studied and with contrasting results. Studies of SCZ individuals with co-morbid SUD have found both increased [29–34] and decreased [35] all-cause mortality, increased suicide mortality [36, 37], but no difference in cardiovascular mortality [38] compared to SCZ individuals without SUD. Studies of SUD individuals report both higher [39, 40], similar [12, 13, 40–43], and lower [44] mortality in individuals also diagnosed with a psychotic disorder, compared to individuals with SUD-only, depending on type of SUD and gender [40]. Only a few studies with complete national coverage have investigated all cause [30, 33, 34, 40] or cause-specific mortality [33, 34] in patients with SCZ-only, SUD-only or co-morbid SCZ and SUD, and neither of these reported results for different age groups or mortality from unnatural causes of death.

The aims of the present study were to (i) investigate standardized mortality ratios for all cause mortality (SMRs) in patients with SCZ, SCZ-only, SUD-only and SCZ+SUD, diagnosed in Norwegian psychiatric or somatic specialist health care, (ii) describe how much of the excess mortality that could be attributed to a concurrent diagnosis of SCZ and SUD, and (iii) investigate age-, sex-, and cause-specific SMRs in patients with SCZ-only, SUD-only or SCZ+SUD. We hypothesized that mortality in patients with SCZ and/or SUD would be increased compared to the general population for all main causes of death, and that patients with a concurrent diagnosis of SCZ and SUD would have particularly high SMRs.

Materials and methods

Study population

The study population included all in- and outpatients diagnosed with SCZ and/or SUD in the Norwegian specialized health care system during 2009–2015, who were 20–79 years old when they had their first consultation in the time bracket. Patients with SCZ and/or SUD were identified through the Norwegian Patient Registry (NPR), which is a mandatory national registry covering all patients receiving specialist health care (i.e. government-owned hospitals and outpatient clinics, publicly financed substance use treatment facilities and private health clinics with governmental reimbursement). Since 2009 the coverage in the NPR is almost 100% [45, 46]. The exception is private mental health clinics with governmental reimbursement, where the proportion of the episodes that were reported to the NPR increased from 76% in 2009 [47] to 97% in 2015 [48], but only 0.2% of patients in the present study were treated solely in these clinics. Patients were excluded if an invalid ID number (n = 6,178), a diagnosis of intellectual

disability (ICD-10 codes F70-F79) (n = 1,632), or inconsistent data regarding age, gender or emigration date (n = 666) were recorded.

Diagnostic categories

Diagnostic codes in the NPR follow the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) [49]. Patients were included in the SCZ group if a diagnosis of schizophrenia-related disorders (F20-F29) was recorded in the NPR during 2009–2015. The SUD group included patients with a diagnosis of mental and behavioral disorders due to use of psychoactive substances (F10-F19, excluding tobacco (F17)), and patients with at least one somatic diagnosis strongly indicating alcohol abuse (see list of ICD-10 codes in S1 Table). Patients identified by somatic diagnoses only constituted 4.1% of the SUD group. A total of 275 patients treated in substance use treatment facilities, with a diagnosis of SCZ, but no registered diagnosis of SUD (excluding pathological gambling (F63.0)), were included in the SCZ+SUD group. In subgroup analyses, we differentiated between patients with a non-alcohol SUD (F11-F16, F18-F19, Z50.3, Z71.5 and Z72.2), and patients with AUD only. Hard drug use disorder was deemed present if the patient was diagnosed with disorders due to use of opioids (F11), cocaine (F14), other stimulants (mostly amphetamines, F15), hallucinogens (F16), volatile solvents (F18), and multiple drug use and use of other psychoactive substances (F19).

Information on deaths

The Cause of Death Registry (CDR), which includes 98% of all deaths in Norway [50], provided data on the underlying cause of death, based on death certificates issued by physicians. The National Population Registry provided information about year of birth and date of death or emigration. Accurate linkage regarding mortality of the patients was obtained using the unique 11 digit personal ID number included in all the registries. Causes of death were coded according to ICD-10 [49] and divided into natural causes (A00-R99), unnatural causes (V01-Y98) and missing cause of death. Natural causes of death were further divided into cardiovascular (I00-I99), respiratory (J00-J99), cancer (C00-C97) and other natural causes. Unnatural causes of death were divided into poisoning (X40-X49), suicide (X60-X84 and Y87.0) and other unnatural causes.

The reference population included all residents in Norway aged 20–79 during 2009–2015. Annual number of deaths in gender-stratified five-year age groups for the reference population were obtained from the Norwegian Institute of Public Health [51], and annual population figures in the age groups 20–79 in the years 2009–2015 were obtained from Statistics Norway [52].

Follow-up

The study cohort was followed from the admission date of the index episode (their first consultation during 2009–2015). Patients already hospitalized before January 1, 2009, were followed from this date (n = 2,633). To account for diagnostic instability in SCZ patients, we defined an extended diagnostic spectrum covering schizophrenia (F20-F29), affective disorders (F30-F39), and personality disorder (F60). If a diagnosis of SCZ was ever recorded, the index episode was defined as the first episode with a diagnosis within the extended diagnostic spectrum. Follow-up ended on December 31, 2015, on the date of emigration from Norway, on December 31 in the year of the 79th birthday, or on the date of death, whichever came first.

Statistical analysis

For comparison with the mortality of the general population of Norway, SMRs with corresponding 95% confidence intervals were calculated for patients with SCZ, SCZ-only, SUD-only, and SCZ+SUD. SMR reflects the relative mortality of the patient group compared to that of the general population and is computed as the observed number of deaths divided by the expected number of deaths. The expected number of deaths was calculated as the total number of person-years at risk in each sex-, age group- and calendar year band, multiplied by the corresponding age- (5-year age groups), sex- and calendar-year specific (2009–2015) death rate in the general population. Age was defined as attained age at the end of each calendar year, as we did not have access to exact birth dates. Person-years at risk contributed by persons who moved from one age band to the next during follow-up was assigned to the respective sex-, age group- and calendar year bands, using the "lexis" method [53]. The number of excess deaths was calculated as the difference between observed and expected deaths.

Biased SMRs may be a major problem when the prevalence of exposure in the general population is high [54]. In contrast to SCZ, unnatural deaths in the SUD subgroup constitute a large proportion of unnatural deaths in the general population, implicating risk of biased SMRs for unnatural causes of death in this subgroup. We consequently investigated the impact on SMRs for poisoning, suicide and all-cause mortality in patients with SUD (SUD-only and SCZ+SUD combined), using an unexposed comparison group, rather than the general population, for calculation of the expected number of deaths. This unexposed comparison group constituted the Norwegian population excluding subjects with recorded SUD in specialized health care and corresponding deaths from the relevant age-/gender group in the reference population. The mortality rates in this unexposed population was calculated and applied when computing the expected number of deaths.

We also investigated the impact on SMRs of the temporal ordering of SCZ and SUD diagnoses in comorbid patients, and of varying inclusion criteria in a series of pre-specified sensitivity analyses (i) excluding patients treated solely in somatic hospitals during follow-up (e.g. older individuals with presumably stable mental illness suffering from somatic health problems), (ii) excluding patients diagnosed with SCZ as a secondary diagnosis only, and (iii) including only patients diagnosed with narrow schizophrenia (F20) in the SCZ group.

The analyses were conducted using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, N.C.)

Ethics

All patient data were fully de-identified when accessed by the investigators. In Norway, studies with de-identified information from medical health registries do not require participant consent. Legal basis and exemption from professional secrecy requirements for the use of personal health data in research was granted by the regional committee for medical and health research ethics (2014/72/REK nord).

Results

Characteristics of the study population

A total of 125,744 individuals were included in the study during 2009–2015. They were aged 20–79 at start of follow-up. Of these, 27,859 (22.2%) were registered with a diagnosis of SCZ, 20,537 (16.3%) with SCZ-only, 97,885 (77.8%) with SUD-only, and 7,322 (5.8%) with SCZ+SUD (Table 1). Men were overrepresented in the SUD groups (66.6% in SUD-only

Table 1. Characteristics of the study population. Patients aged 20–79 with schizophrenia spectrum disorder (SCZ) and/or substance use disorder (SUD).

				SCZ-only		SUD-only		SCZ+SUD	
Men									
	Patients, n (%)			10,509		65,175		5,126	
	Personyears, sum			48,776		250,350		26,873	
	Personyears, mean (SD)			4.6	(2.3)	3.8	(2.2)	5.2	(2.0)
	Age at start of follow-up, mean (SD)			43.4	(15.2)	43.5	(15.7)	35.2	(12.0)
	No. of patients with substance use disorder, n (%)								
		Alcohol use disorder		-		44,198	(67.8)	2,230	(43.5)
		Alcohol use disorder only		-		33,917	(52.0)	980	(19.1)
		Non-alcohol substance use disorder		-		31,258	(48.0)	3,984	(77.7)
			Cannabis use disorder	-		13,688	(21.0)	1,805	(35.2)
			Hard drug use disorders	-		23,073	(35.4)	3,202	(62.5)
		Non-alcohol substance use disorder only		-		20,977	(32.2)	2,734	(53.3)
		Unknown substance use disorder		-		0	(0.0)	162	(3.2)
	No. of health care episodes per person-year, median (IQR)								
		No. of admissions, mental care		0.2	(0.0–0.4)	0.0	(0.0–0.0)	0.3	(0.2–0.6)
		No. of outpatient visits, mental care		5.6	(1.1–16.5)	0.0	(0.0–2.0)	7.3	(1.9–19.0)
		No. of admissions, medical care		0.0	(0.0–0.2)	0.2	(0.0–0.4)	0.1	(0.0–0.3)
		No. of outpatient visits, medical care		0.6	(0.0–1.9)	1.5	(0.5–4.2)	0.9	(0.3–2.0)
		No. of admissions, SUD treatment		-		0.0	(0.0–0.2)	0.0	(0.0–0.1)
		No. of outpatient visits, SUD treatment		-		0.2	(0.0–3.9)	0.0	(0.0–1.8)
Women									
	Patients, n (%)			10,028		32,710		2,196	
	Personyears, sum			45,970		126,174		11,946	
	Personyears, mean (SD)			4.6	(2.3)	3.9	(2.2)	5.4	(1.9)
	Age at start of follow-up, mean (SD)			47.9	(16.1)	42.5	(16.2)	39.1	(14.0)
	No. of patients with substance use disorder, n (%)								
		Alcohol use disorder		-		20,800	(63.6)	965	(43.9)
		Alcohol use disorder only		-		15,471	(47.3)	442	(20.1)
		Non-alcohol substance use disorder		-		17,239	(52.7)	1,641	(74.7)
			Cannabis use disorder	-		4,573	(14.0)	433	(19.7)
			Hard drug use disorders	-		11,834	(36.2)	1,247	(56.8)
		Non-alcohol substance use disorder only		-		11,910	(36.4)	1,118	(50.9)
		Unknown substance use disorder		-		0	(0.0)	113	(5.1)
	No. of health care episodes per person-year, median (IQR)								
		No. of admissions, mental care		0.2	(0.0–0.4)	0.0	(0.0–0.2)	0.4	(0.2–0.7)
		No. of outpatient visits, mental care		5.8	(1.2–17.0)	0.8	(0.0–6.1)	8.4	(2.5–21.6)
		No. of admissions, medical care		0.1	(0.0–0.3)	0.2	(0.0–0.5)	0.2	(0.0–0.5)
		No. of outpatient visits, medical care		1.0	(0.2–3.1)	2.4	(0.9–6.0)	1.5	(0.6–3.3)
		No. of admissions, SUD treatment		-		0.0	(0.0–0.0)	0.0	(0.0–0.0)
		No. of outpatient visits, SUD treatment		-		0.0	(0.0–3.7)	0.0	(0.0–1.6)

Abbreviations: SCZ, schizophrenia spectrum disorder; SUD, substance use disorder; SCZ+SUD, concurrent diagnoses of schizophrenia and substance use disorder; SD, standard deviation; IQR, interquartile range.

https://doi.org/10.1371/journal.pone.0202028.t001

and 70.1% in SCZ+SUD). In patients with SUD, AUD was most common in patients with SUD-only (66.4%), whereas non-alcohol SUD was most common in comorbid patients (76.5%).

Table 2. Number of deaths (overall and in different age groups) and mean age of death, according to sex. Patients aged 20–79 with schizophrenia spectrum disorder (SCZ) and/or substance use disorder (SUD).

			SCZ-only		SUD-only		SCZ+SUD	
Men								
	Deaths, n		972		7,334		423	
		Age at death 20–39, n (%)	90	(9.3)	847	(11.5)	170	(40.2)
		Age at death 40–59, n (%)	295	(30.3)	2,445	(33.3)	171	(40.4)
		Age at death 60–79, n (%)	587	(60.4)	4,042	(55.1)	82	(19.4)
	Age at death, mean (SD)		60.3	(13.6)	58.6	(13.7)	45.3	(14.2)
Women								
	Deaths, n		832		2,592		165	
		Age at death 20–39, n (%)	42	(5.0)	256	(9.9)	34	(20.6)
		Age at death 40–59, n (%)	198	(23.8)	928	(35.8)	75	(45.5)
		Age at death 60–79, n (%)	592	(71.2)	1,408	(54.3)	56	(33.9)
	Age at death, mean (SD)		64.0	(12.3)	59.0	(13.6)	52.5	(14.2)

Abbreviations: SCZ, schizophrenia spectrum disorder; SUD, substance use disorder; SCZ+SUD, concurrent diagnoses of schizophrenia and substance use disorder; SD, standard deviation.

https://doi.org/10.1371/journal.pone.0202028.t002

All-cause mortality

Of the 125,744 individuals included, 12,318 (9.8%) died during follow-up (Table 2). Mean age at death was highest in patients with SCZ-only (62.0 years) and lowest in patients with SCZ +SUD (47.3 years), and particularly low in comorbid men (45.3 years). Comparing with the expected number of deaths based on the mortality of the general population, we found a SMR of 4.9 (95% CI 4.7–5.1) in SCZ patients (with or without SUD), and SMRs of 4.4 (95% CI 4.2–4.6), 6.6 (95% CI 6.5–6.7) and 7.4 (95% CI 6.9–8.1) in patients with SCZ-only, SUD-only, and SCZ+SUD, respectively, corresponding to 10,328 excess deaths (of which 18% were in SCZ patients). In men, the SMRs for patients with SCZ (with or without SUD), SCZ-only, SUD-only, and SCZ+SUD were 5.1 (95% CI 4.8–5.4), 4.5 (95% CI 4.2–4.8), 6.4 (95% CI 6.2–6.5) and 7.6 (95% CI 6.9–8.4), respectively. In women, the corresponding figures were 4.6 (95% CI 4.3–4.9), 4.3 (95% CI 4.0–4.6), 7.4 (95% CI 7.1–7.6) and 7.0 (95% CI 6.0–8.2). All-cause mortality was elevated for both genders and in all age groups (Fig 1), but the SMRs were consistently

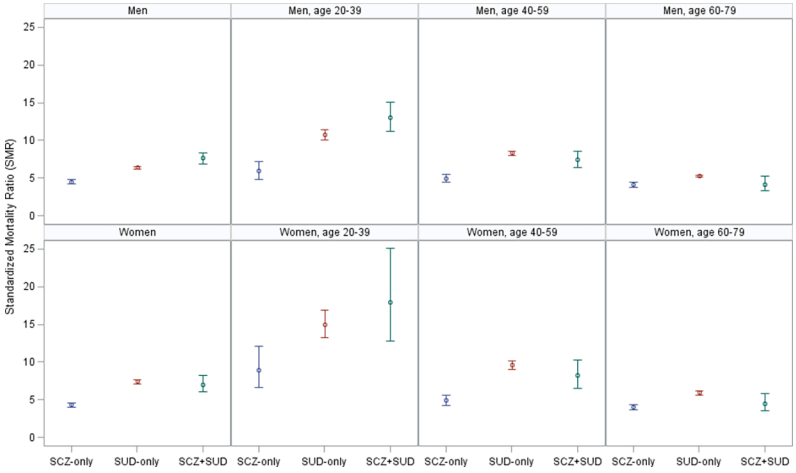


Fig 1. All-cause age, gender, and calendar-year standardized mortality ratios according to gender and age among patients with schizophrenia and/or substance use disorders.

https://doi.org/10.1371/journal.pone.0202028.g001

Table 3. All-cause age, gender, and calendar-year standardized mortality ratios among patients aged 20–79 with substance use disorders only (SUD-only) or concurrent SUD and schizophrenia related disorders (SCZ+SUD), according to type of SUD.

		SUD-only			SCZ+SUD		
		Obs	SMR[a]	(95% CI)	Obs	SMR[a]	(95% CI)
Men		7,334	6.4	(6.2–6.5)	423	7.6	(6.9–8.3)
	AUD-only	5,109	5.9	(5.7–6.0)	120	5.4	(4.5–6.4)
	Non-alcohol SUD	2,225	8.0	(7.7–8.3)	295	9.4	(8.4–10.5)
	Unknown SUD	0			8	4.0	(2.0–8.0)
Women		2,592	7.4	(7.1–7.7)	165	7.0	(6.0–8.2)
	AUD-only	1,520	7.0	(6.6–7.3)	47	6.4	(4.8–8.5)
	Non-alcohol SUD	1,072	8.0	(7.5–8.5)	111	7.4	(6.1–8.9)
	Unknown SUD	0			7	6.9	(3.3–14.4)

Abbreviations: SUD, substance use disorder; SCZ+SUD, concurrent diagnoses of schizophrenia and substance use disorder; Obs, observed deaths; SMR, standardized mortality ratio; 95% CI, 95% confidence interval; AUD, Alcohol Use Disorder.

[a] The standard population used for the sex- and calendar year specific age standardization was the annual population of Norway aged 20–79 in the years 2009–2015.

https://doi.org/10.1371/journal.pone.0202028.t003

higher in the youngest age groups. Women aged 20–39 years with SUD had particularly high SMRs; 15 in the SUD-only group and 18 in the SCZ+SUD group.

Sensitivity analyses (i) excluding patients treated solely in somatic hospitals during follow-up, or (ii) patients with a secondary diagnosis of SCZ only indicated decreased SMRs for SCZ-only (both models) and SUD-only (model ii), whereas application of a narrow definition of SCZ (F20) (model iii) resulted in moderately increased SMRs for SCZ-only (S2 Table).

Impact of a concurrent diagnosis of SCZ and SUD

Overall, comorbid patients had higher all-cause SMRs than patients with SCZ-only or SUD-only. However, when stratified according to sex and type of SUD (Table 3), SMRs were similar in SUD patients with or without comorbid SCZ, except in comorbid men with a non-alcohol SUD who had higher SMR than men with non-alcohol SUD-only. Comorbid patients aged 20–39, 40–59 and 60–69 had 107%, 57% and 6% higher numbers of deaths compared to what could be expected if the same age-specific SMRs as patients with SCZ-only had applied, whereas application of age-specific SMRs for SUD-only in the comorbid had smaller impact on hypothetical numbers of death. Thus, the major reason for the high SMRs in comorbid patients was the SUD component. In this total Norwegian patient population, approximately 27% of the excess number of deaths in all patients with SCZ was due to the raised mortality in the subgroup with comorbid SUD. This effect was strongest in men and in the youngest.

Supplementary analyses examining the temporal ordering of SCZ and SUD diagnoses in comorbid patients showed that SCZ and SUD were mostly co-occurring: 39% had both diagnoses within three months, 55% within one year and 70% within two years. One in four comorbid patients had a SUD diagnosis more than three months prior to the SCZ diagnosis, whereas 36% had a SCZ diagnosis more than three months prior to the SUD diagnosis. The SMRs tended to be higher when the SUD diagnosis preceded the SCZ diagnosis, and were highest when the first diagnosis of SCZ and SUD during follow-up were recorded within a short time interval (S3 Table).

Cause specific mortality

We found elevated mortality from all considered causes of death in all subgroups (Table 4). In both men and women, the highest SMRs were observed for poisoning, suicides and respiratory

Table 4. Cause-specific age, gender, and calendar-year standardized mortality ratios among men and women aged 20–79 with schizophrenia-related disorders (SCZ) and/or substance use disorders (SUD).

					SCZ-only			SUD-only			SCZ+SUD		
					Obs	SMR[a]	95% CI	Obs	SMR[a]	95% CI	Obs	SMR[a]	95% CI
Men													
	Natural causes				775	4.2	(3.9–4.5)	5,293	5.4	(5.3–5.6)	182	4.6	(4.0–5.3)
			Age 20–39		17	3.3	(2.1–5.3)	141	5.5	(4.6–6.4)	24	5.7	(3.8–8.5)
			Age 40–59		211	4.7	(4.1–5.3)	1,555	6.9	(6.6–7.2)	86	5.1	(4.1–6.3)
			Age 60–79		547	4.1	(3.8–4.5)	3,597	5.0	(4.8–5.2)	72	3.9	(3.1–5.0)
		Subtype											
			Cardiovascular		200	3.9	(3.4–4.5)	1,252	4.7	(4.4–4.9)	35	3.3	(2.4–4.6)
			Respiratory		123	8.5	(7.1–10.1)	617	8.0	(7.4–8.7)	30	13.1	(9.1–18.7)
			Cancer		197	2.6	(2.3–3.0)	1,180	2.9	(2.7–3.1)	30	1.9	(1.3–2.7)
			Other		255	6.1	(5.4–6.9)	2,244	10.2	(9.8–10.7)	87	8.3	(6.7–10.3)
	Unnatural causes				186	6.9	(5.9–7.9)	1,837	13.3	(12.7–13.9)	228	16.3	(14.3–18.5)
			Age 20–39		72	7.8	(6.2–9.8)	684	14.1	(13.1–15.2)	140	17.4	(14.8–20.6)
			Age 40–59		76	6.4	(5.1–8.0)	807	14.2	(13.3–15.3)	81	16.0	(12.9–19.9)
			Age 60–79		38	6.4	(4.6–8.7)	346	10.4	(9.4–11.6)	7	7.6	(3.6–16.0)
		Subtype											
			Poisoning		30	4.6	(3.2–6.5)	903	27.5	(25.8–29.3)	115	29.0	(24.2–34.9)
			Suicide		115	11.6	(9.7–13.9)	499	9.9	(9.0–10.8)	87	16.0	(13.0–19.8)
			Other		41	3.8	(2.8–5.2)	435	7.9	(7.2–8.7)	26	5.6	(3.8–8.3)
	Missing				11	1.6	(0.9–2.8)	204	5.4	(4.7–6.2)	13	5.5	(3.2–9.5)
Women													
	Natural causes				703	3.9	(3.6–4.2)	1,921	6.0	(5.8–6.3)	90	4.4	(3.6–5.4)
			Age 20–39		8	3.0	(1.5–6.0)	46	5.2	(3.9–7.0)	8	7.9	(4.0–15.8)
			Age 40–59		146	4.2	(3.6–4.9)	608	7.4	(6.8–8.0)	40	5.2	(3.8–7.0)
			Age 60–79		549	3.9	(3.6–4.2)	1,267	5.6	(5.3–5.9)	42	3.6	(2.6–4.8)
		Subtype											
			Cardiovascular		150	4.3	(3.7–5.1)	306	5.4	(4.8–6.1)	17	5.1	(3.2–8.2)
			Respiratory		126	7.1	(6.0–8.4)	292	10.0	(8.9–11.2)	22	13.4	(8.9–20.4)
			Cancer		239	2.7	(2.4–3.1)	451	2.8	(2.5–3.0)	19	1.7	(1.1–2.7)
			Other		188	4.7	(4.1–5.5)	872	12.6	(11.8–13.4)	32	7.2	(5.1–10.1)
	Unnatural causes				113	9.9	(8.2–11.9)	629	23.2	(21.4–25.0)	74	30.9	(24.6–38.9)
			Age 20–39		29	15.7	(10.9–22.6)	201	26.7	(23.2–30.6)	26	32.4	(22.1–47.7)
			Age 40–59		47	9.7	(7.3–12.9)	305	25.8	(23.1–28.9)	35	29.9	(21.5–41.7)
			Age 60–79		37	7.8	(5.7–10.8)	123	15.8	(13.2–18.8)	13	30.9	(18.0–53.3)
		Subtype											
			Poisoning		11	5.1	(2.8–9.2)	263	44.7	(39.6–50.4)	25	43.5	(29.4–64.4)
			Suicide		77	19.0	(15.2–23.8)	248	22.7	(20.0–25.7)	38	36.7	(26.7–50.4)
			Other		25	4.8	(3.2–7.1)	118	11.4	(9.5–13.7)	11	14.1	(7.8–25.4)
	Missing				16	5.0	(3.1–8.2)	42	6.7	(5.0–9.1)	1	nr	nr

Abbreviations: Obs, observed deaths; SMR, standardized mortality ratio; 95% CI, 95% confidence interval; nr, Not reportable because of small samples (no. of deaths < 5) within the data category.

[a] The standard population used for the sex- and calendar year specific age standardization was the annual population of Norway aged 20–79 in the years 2009–2015.

https://doi.org/10.1371/journal.pone.0202028.t004

diseases. Women had higher SMRs for unnatural death than men in all age groups, and higher SMRs for suicides. SMRs for natural causes of death did not differ much with age neither for men nor for women. For unnatural causes of death, SMRs in people with SCZ-only were stable across age groups, except in women aged 20–39, who had elevated SMRs compared to other age groups. In patients with SUD, SMRs in the age group 20–59 were elevated compared to age 60–79, except in comorbid women who had a 30-fold increased SMR across all age groups.

Overall, 73% of excess number of deaths were from natural causes. In SCZ-only and SUD-only, natural causes accounted for 82% and 73% of all deaths, respectively, with cancer and cardiovascular disease being the most common causes. In the SCZ+SUD group, unnatural causes accounted for 54% of all deaths. Women with SUD-only had higher SMRs than men with SUD-only for nearly all considered causes of death. Women with SUD (with or without SCZ) had particularly high SMRs (approximately 45) for poisoning.

Deaths due to poisoning and suicide in SUD patients in our sample constituted a large proportion of all deaths from these causes in Norway in the years 2009–2015 (52% and 22%, respectively). In a supplementary analysis we assessed the bias in SMRs for poisoning and suicide for patients with SUD (SUD-only and SCZ+SUD combined) using an unexposed comparison group (e.g. no diagnosis of SUD in specialized health care), rather than the general population, to calculate expected deaths. This resulted in a three-fold increase in SMR for poisoning in men and a doubled SMR for poisoning in women (from 27.7 to 82.9 in men, and from 44.6 to 98.5 in women), whereas SMRs for suicides increased from 10.5 to 13.7 in men and from 23.9 to 33.8 in women. The SMRs for all-cause mortality were also affected (increased from 6.4 to 7.3 in men, and from 7.3 to 7.9 in women).

Discussion

Our study shows that patients in specialized health care with SCZ, SCZ-only or SUD (with or without SCZ) had a five-, four- and seven-fold increased total mortality, respectively, compared to the general population. Mortality was elevated for both genders, in all age groups and for all considered causes of death, with the highest SMRs observed for poisoning, suicides and respiratory diseases. Very high SMRs for poisoning were noted in women with SUD (with or without SCZ). The highest SMRs were found in the age group 20–39, mainly due to unnatural causes of death.

The excess mortality corresponded to more than 10 000 premature deaths (84% of all deaths in the cohort). About 27% of the excess deaths in SCZ patients could be attributed to SUD (or factors associated with SUD). The nearly five-fold increased mortality in SCZ (with and without SUD) was substantially higher than reported in meta-analyses [1, 55], and also higher than reported in a recent Nordic study [56]. The omission of patients in primary care, and the relatively short follow-up, may have led to a selection of more severe cases, oversampling patients with many health care episodes and patients with increased suicide risk. Inclusion of older individuals suffering from somatic health problems, such as cardiovascular and respiratory diseases, is another explanation of the elevated SMR in SCZ patients, as shown in the sensitivity analysis. Differences in case finding criteria might also have contributed, also shown in the sensitivity analyses, whereas survivor bias resulting from inclusion of prevalent cases would have the opposite effect. Also, catchment of SCZ might be higher in Norway compared to countries without universal health care. Another contributing explanation might be the rising mortality gap in schizophrenia patients compared to the general population reported in recent studies [1, 57, 58], partly explained by decreased mortality from cardiovascular disease in the general population [59, 60].

The increased all cause and suicide mortality, as well as the similar cardiovascular mortality in comorbid patients, is in accordance with some previous studies [29–34, 38], but not in line with a study reporting decreased mortality in persons with co-occurring psychosis and cannabis use/abuse, compared to psychosis only [35]. In the present study, mortality from cannabis use disorder was not studied separately, due to few deaths and suspicion of selective recording of less severe cases in comorbid patients.

Overall, a co-occurring diagnosis of SCZ also conferred increased SMRs in SUD patients. However, when stratified according to type of SUD, we found similar SMRs for non-alcohol

SUD patients with and without SCZ, in accordance with other studies [12, 13, 41, 42], and similar SMRs in AUD patients with and without SCZ, in contrast to a 50-year follow-up study of AUD persons [39]. Differences in length of follow-up may be one explanation for the latter finding. Furthermore, when stratified according to gender, we found increased SMR in comorbid men, but not in comorbid women, in accordance with a study conducted in inpatients [40]. Thus, in our study, the increased SMRs in comorbid patients, both genders combined, was explained by the high proportion of young comorbid men with a non-alcohol SUD. The eight-to-nine-fold increased SMR in patients with non-alcohol SUD with and without SCZ, is similar to [61] or higher than [12, 31] reported elsewhere. Norway has one of the highest rates of injecting drug users among hard drug users [62], which may have contributed to this finding.

The very high all cause SMRs found among young patients were similar to [63] or higher than [31, 64] reported earlier. Previous studies have found excess mortality to be highest the year following a first diagnosis of severe mental illness, due to increased mortality from unnatural causes of death [2, 65]. Besides low expected death rates in the youngest in the general population, the inverse relationship between the SMR and age may thus partly be explained by the inclusion of presumably more incident cases in the youngest and more prevalent cases among the oldest in our study, and may have been amplified by survivor bias, treatment-compliant patients in our sample and lower suicide rates with increasing age in SCZ patients [66]. Comorbid women did not, however, experience a decrease in SMR with increasing age, but had very high mortality across all age groups. We found very high SMRs for poisoning and suicide in women with SUD, which confirms earlier findings [60, 67], and high SMRs for respiratory diseases, probably associated with increased smoking prevalence in individuals with severe mental disorders [68]. The increased mortality due to suicide in patients with SCZ was more pronounced than reported in a systematic review [1], but of similar magnitude as reported in a sample with comparable age span [37].

The excess mortality in patients with severe mental illness has been ascribed to a wide range of factors, both at the individual level, health system level and at the societal level [69]. Explanations include lifestyle factors [38, 70] (such as smoking, substance use, physical inactivity and unhealthy diet), poorer socioeconomic conditions [71], suboptimal use of or access to medical care [72], and metabolic side effects of high dosages of antipsychotic medication [73], as well as higher levels of suicides, poisoning, violent behavior [20–23] and victimization [24, 25]. It is thus a huge challenge to address the complex needs of patients with severe mental illness in combination with SUD, both with regard to general improvement of outcome as well as prevention of premature mortality. Despite the well known high association between SUD and SCZ there is no evidence supporting one specific treatment strategy for patients with dual diagnoses [69, 74, 75]. Likewise, there is little evidence for successful interventions addressing somatic risk factors in patients with severe mental disorders [70, 76], although evidence-based interventions for smoking cessation and weight reduction in persons with severe mental illness exist [69]. The universal health care system in Norway, designed to prevent socioeconomic differences in health care, has unfortunately not been able to address these issues. Generally, a population approach for prevention is considered the key avenue for non-communicable diseases, e.g. cardiovascular diseases and cancer [77]. The patients here studied clearly constitute a high-risk group, but there is limited knowledge of effective intervention and treatment strategies to use with these vulnerable patients [4]. An approach that includes both individual focused and system focused interventions is probably needed, involving both primary and integrated specialist health care. Further research is needed to pinpoint effective system focused interventions specifically aiming at reaching the high-risk subgroup with mental illness. The extremely high mortality risk in young patients highlights the need for such efforts to be implemented in the younger age groups.

Strengths and limitations

The major strength of this study is the use of unselected and complete nationwide registry data of recent date, covering all specialist health care settings, and with no bias associated with selective self-reporting. The inclusion of outpatients and patients treated solely in somatic hospitals also enabled more generalizable risk estimates. The CDR is found to provide high quality data on the underlying cause of death [78]. Also, the validity of a schizophrenia diagnosis in hospital case registries is good when compared to diagnoses based on structured research interviews [79, 80]. Furthermore, in Norway, treatment of psychosis is mainly a specialist task, with free admission to hospital treatment and a maximum annual cost of 2205 NOK (approximately 235 €) for outpatient treatment, implying high coverage for SCZ in the NPR.

The relatively short follow-up is a limitation, which also precluded analysis of secular trends in SMRs. Another important limitation is the lack of control for unmeasured individual risk factors associated with mortality. However, studies adjusting for such factors [30, 38, 81] still revealed an increased mortality after adjustment. The SMRs in the current study may be prone both to under- and overestimation. We found underestimated SMRs for unnatural causes of death in SUD patients when the general population, rather than an unexposed population, was used as reference. Survivor bias in comorbid patients may also have resulted in underestimation, as patients would have to live long enough to receive both diagnoses. On the other hand, underreporting of less severe SUD in specialized care may have led to overestimated SMRs in all groups, although a higher detection rate of less severe SUD in comorbid patients (Berkson's bias) may be suspected. SCZ and SUD were identified independently of time, ignoring the possibility that the two diagnoses were not co-occurring. However, supplementary analyses showed that a majority of comorbid patients had both diagnosed within a year. We were not able to differentiate between patients with a primary psychotic disorder that co-occurs with SUD and patients with substance-induced psychosis, although we found indications that patients with a SUD diagnosis preceding SCZ had worse outcomes. We found a 26% prevalence of SUD in SCZ patients during a mean follow-up of four years, which is similar to a previous Norwegian study [27] SUD diagnoses in the NPR have not been subject to formal validity checks [80], but a Norwegian validation study found hospital diagnosis of SUD to be fairly valid, although only 31% classified with SUD by expert opinion was identified in administrative data [79] Another Nordic study found nearly 50% underreporting of SUD in individuals with schizophrenia in the Danish Psychiatric Register [82]. However, a sensitivity analysis identifying SUD patients from hospital data only did not change results appreciably in the study by Hjorthøj et al [30]. We had no information concerning frequency and level of past and current substance abuse, nor information concerning prescriptions for treatment of SUD. Finally, this study included only patients in specialized health care, possibly implying higher mortality than would be found among patients with SCZ and/or SUD in the general population. The generalizability of these findings is therefore to specialized care settings with similar health care systems and socioeconomic features.

Conclusion

Our study demonstrates that patients with SCZ and/or SUD who receives specialized health care have a substantially elevated risk of premature mortality compared to the general population for both natural and unnatural causes of death. The high mortality in these vulnerable patients, and the differences in causes of death between the subgroups in our study, call for complex intervention strategies addressing several aspects of prevention, follow-up and treatment at all levels of primary and specialist health care. Young patients and women with SUD (with or without SCZ) have for unnatural causes particularly high mortality compared to the

general population. The high proportion of deaths directly linked to poisoning in SUD patients urgently calls for a more effective societal prevention of SUD-related unnatural deaths.

Disclaimer

Data from the Norwegian Patient Registry have been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Norwegian Patient Registry is intended nor should be inferred.

Supporting information

S1 Table. List of somatic diagnosis indicating alcohol abuse or drug abuse.
(DOCX)

S2 Table. Sensitivity-analysis for all-cause age, gender, and calendar-year standardized mortality ratios among men and women aged 20–79 with schizophrenia-related disorders (SCZ) and/or substance use disorders (SUD).
(DOCX)

S3 Table. All-cause age, gender, and calendar-year standardized mortality ratios among patients aged 20–79 with schizophrenia-related disorders (SCZ) and a concurrent substance use disorder (SUD), according to the temporal ordering of SCZ and SUD diagnosis.
(DOCX)

Author Contributions

Conceptualization: Ina H. Heiberg, Bjarne K. Jacobsen, Ragnar Nesvåg, Jørgen G. Bramness, Ted Reichborn-Kjennerud, Øyvind Næss, Eivind Ystrom, Christina M. Hultman, Anne Høye.

Data curation: Ina H. Heiberg.

Formal analysis: Ina H. Heiberg, Bjarne K. Jacobsen, Anne Høye.

Funding acquisition: Ragnar Nesvåg, Ted Reichborn-Kjennerud, Øyvind Næss, Eivind Ystrom, Christina M. Hultman, Anne Høye.

Investigation: Ina H. Heiberg, Bjarne K. Jacobsen, Ragnar Nesvåg, Jørgen G. Bramness, Anne Høye.

Methodology: Ina H. Heiberg, Bjarne K. Jacobsen, Anne Høye.

Project administration: Anne Høye.

Supervision: Bjarne K. Jacobsen, Ragnar Nesvåg, Anne Høye.

Validation: Ina H. Heiberg, Bjarne K. Jacobsen, Ragnar Nesvåg, Jørgen G. Bramness, Ted Reichborn-Kjennerud, Øyvind Næss, Eivind Ystrom, Christina M. Hultman, Anne Høye.

Visualization: Ina H. Heiberg.

Writing – original draft: Ina H. Heiberg, Bjarne K. Jacobsen, Ragnar Nesvåg, Jørgen G. Bramness, Anne Høye.

Writing – review & editing: Ina H. Heiberg, Bjarne K. Jacobsen, Ragnar Nesvåg, Jørgen G. Bramness, Ted Reichborn-Kjennerud, Øyvind Næss, Eivind Ystrom, Christina M. Hultman, Anne Høye.

References

1. Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? Arch Gen Psychiatry. 2007; 64(10):1123–31. Epub 2007/10/03. https://doi.org/10.1001/archpsyc.64.10.1123 PMID: 17909124.
2. Nordentoft M, Wahlbeck K, Hällgren J, Westman J, Ösby U, Alinaghizadeh H, et al. Excess mortality, causes of death and life expectancy in 270,770 patients with recent onset of mental disorders in Denmark, Finland and Sweden. PLoS One. 2013; 8(1):e55176. Epub 2013/02/02. https://doi.org/10.1371/journal.pone.0055176 PMID: 23372832; PubMed Central PMCID: PMCPmc3555866.
3. Olfson M, Gerhard T, Huang C, Crystal S, Stroup TS. Premature Mortality Among Adults With Schizophrenia in the United States. JAMA Psychiatry. 2015:1–10. Epub 2015/10/29. https://doi.org/10.1001/jamapsychiatry.2015.1737 PMID: 26509694.
4. Hjorthøj C, Stürup AE, McGrath JJ, Nordentoft M. Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis. The lancet Psychiatry. 2017. Epub 2017/02/27. https://doi.org/10.1016/s2215-0366(17)30078-0 PMID: 28237639.
5. Chang CK, Hayes RD, Perera G, Broadbent MT, Fernandes AC, Lee WE, et al. Life expectancy at birth for people with serious mental illness and other major disorders from a secondary mental health care case register in London. PLoS One. 2011; 6(5):e19590. Epub 2011/05/26. https://doi.org/10.1371/journal.pone.0019590 PMID: 21611123; PubMed Central PMCID: PMCPmc3097201.
6. Lawrence D, Hancock KJ, Kisely S. The gap in life expectancy from preventable physical illness in psychiatric patients in Western Australia: retrospective analysis of population based registers. Bmj. 2013; 346:f2539. Epub 2013/05/23. https://doi.org/10.1136/bmj.f2539 PMID: 23694688; PubMed Central PMCID: PMCPmc3660620.
7. Chesney E, Goodwin GM, Fazel S. Risks of all-cause and suicide mortality in mental disorders: a meta-review. World Psychiatry. 2014; 13(2):153–60. Epub 2014/06/04. https://doi.org/10.1002/wps.20128 PMID: 24890068; PubMed Central PMCID: PMCPmc4102288.
8. Roerecke M, Rehm J. Alcohol use disorders and mortality: a systematic review and meta-analysis. Addiction (Abingdon, England). 2013; 108(9):1562–78. Epub 2013/05/01. https://doi.org/10.1111/add.12231 PMID: 23627868.
9. Wahlbeck K, Westman J, Nordentoft M, Gissler M, Laursen TM. Outcomes of Nordic mental health systems: life expectancy of patients with mental disorders. The British journal of psychiatry: the journal of mental science. 2011; 199(6):453–8. Epub 2011/05/20. https://doi.org/10.1192/bjp.bp.110.085100 PMID: 21593516.
10. Westman J, Wahlbeck K, Laursen TM, Gissler M, Nordentoft M, Hällgren J, et al. Mortality and life expectancy of people with alcohol use disorder in Denmark, Finland and Sweden. Acta Psychiatr Scand. 2015; 131(4):297–306. Epub 2014/09/23. https://doi.org/10.1111/acps.12330 PMID: 25243359; PubMed Central PMCID: PMCPmc4402015.
11. Degenhardt L, Bucello C, Mathers B, Briegleb C, Ali H, Hickman M, et al. Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies. Addiction (Abingdon, England). 2010; 106(1):32–51. Epub 2010/11/09. https://doi.org/10.1111/j.1360-0443.2010.03140.x PMID: 21054613.
12. Arendt M, Munk-Jørgensen P, Sher L, Jensen SO. Mortality among individuals with cannabis, cocaine, amphetamine, MDMA, and opioid use disorders: a nationwide follow-up study of Danish substance users in treatment. Drug and alcohol dependence. 2011; 114(2–3):134–9. Epub 2010/10/26. https://doi.org/10.1016/j.drugalcdep.2010.09.013 PMID: 20971585.
13. Bogdanowicz KM, Stewart R, Broadbent M, Hatch SL, Hotopf M, Strang J, et al. Double trouble: Psychiatric comorbidity and opioid addiction-all-cause and cause-specific mortality. Drug and alcohol dependence. 2015; 148:85–92. Epub 2015/01/13. https://doi.org/10.1016/j.drugalcdep.2014.12.025 PMID: 25578253.
14. Esse K, Fossati-Bellani M, Traylor A, Martin-Schild S. Epidemic of illicit drug use, mechanisms of action/addiction and stroke as a health hazard. Brain and behavior. 2011; 1(1):44–54. Epub 2012/03/09. https://doi.org/10.1002/brb3.7 PMID: 22398980; PubMed Central PMCID: PMCPMC3217673.
15. Batki SL, Meszaros ZS, Strutynski K, Dimmock JA, Leontieva L, Ploutz-Snyder R, et al. Medical comorbidity in patients with schizophrenia and alcohol dependence. Schizophr Res. 2009; 107(2–3):139–46. Epub 2008/11/22. https://doi.org/10.1016/j.schres.2008.10.016 PMID: 19022627; PubMed Central PMCID: PMCPmc2649875.
16. Dickey B, Normand SL, Weiss RD, Drake RE, Azeni H. Medical morbidity, mental illness, and substance use disorders. Psychiatric services (Washington, DC). 2002; 53(7):861–7. Epub 2002/07/04. https://doi.org/10.1176/appi.ps.53.7.861 PMID: 12096170.
17. Adrian M, Barry SJ. Physical and mental health problems associated with the use of alcohol and drugs. Substance use & misuse. 2003; 38(11–13):1575–614. Epub 2003/10/30. PMID: 14582571.

18. Maraj S, Figueredo VM, Lynn Morris D. Cocaine and the heart. Clinical cardiology. 2010; 33(5):264–9. Epub 2010/06/01. https://doi.org/10.1002/clc.20746 PMID: 20513064.

19. Frasch K, Larsen JI, Cordes J, Jacobsen B, Wallenstein Jensen SO, Lauber C, et al. Physical illness in psychiatric inpatients: comparison of patients with and without substance use disorders. The International journal of social psychiatry. 2013; 59(8):757–64. Epub 2012/10/05. https://doi.org/10.1177/0020764012456803 PMID: 23034284.

20. Fazel S, Gulati G, Linsell L, Geddes JR, Grann M. Schizophrenia and violence: systematic review and meta-analysis. PLoS medicine. 2009; 6(8):e1000120. Epub 2009/08/12. https://doi.org/10.1371/journal.pmed.1000120 PMID: 19668362; PubMed Central PMCID: PMCPmc2718581.

21. Volavka J. Violence in schizophrenia and bipolar disorder. Psychiatria Danubina. 2013; 25(1):24–33. Epub 2013/03/09. PMID: 23470603.

22. Witt K, van Dorn R, Fazel S. Risk factors for violence in psychosis: systematic review and meta-regression analysis of 110 studies. PLoS One. 2013; 8(2):e55942. Epub 2013/02/19. https://doi.org/10.1371/journal.pone.0055942 PMID: 23418482; PubMed Central PMCID: PMCPmc3572179.

23. Large M, Mullin K, Gupta P, Harris A, Nielssen O. Systematic meta-analysis of outcomes associated with psychosis and co-morbid substance use. The Australian and New Zealand journal of psychiatry. 2014; 48(5):418–32. Epub 2014/03/05. https://doi.org/10.1177/0004867414525838 PMID: 24589980.

24. Latalova K, Kamaradova D, Prasko J. Violent victimization of adult patients with severe mental illness: a systematic review. Neuropsychiatric disease and treatment. 2014; 10:1925–39. Epub 2014/10/23. https://doi.org/10.2147/NDT.S68321 PMID: 25336958; PubMed Central PMCID: PMCPmc4200170.

25. Maniglio R. Severe mental illness and criminal victimization: a systematic review. Acta Psychiatr Scand. 2009; 119(3):180–91. Epub 2008/11/20. https://doi.org/10.1111/j.1600-0447.2008.01300.x PMID: 19016668.

26. Hartz SM, Pato CN, Medeiros H, Cavazos-Rehg P, Sobell JL, Knowles JA, et al. Comorbidity of severe psychotic disorders with measures of substance use. JAMA Psychiatry. 2014; 71(3):248–54. Epub 2014/01/03. https://doi.org/10.1001/jamapsychiatry.2013.3726 PMID: 24382686; PubMed Central PMCID: PMCPmc4060740.

27. Nesvåg R, Knudsen GP, Bakken IJ, Høye A, Ystrom E, Surén P, et al. Substance use disorders in schizophrenia, bipolar disorder, and depressive illness: a registry-based study. Soc Psychiatry Psychiatr Epidemiol. 2015; 50(8):1267–76. Epub 2015/02/15. https://doi.org/10.1007/s00127-015-1025-2 PMID: 25680837.

28. Westermeyer J. Comorbid schizophrenia and substance abuse: a review of epidemiology and course. The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions. 2006; 15(5):345–55. Epub 2006/09/13. https://doi.org/10.1080/10550490600860114 PMID: 16966190.

29. Schmidt LM, Hesse M, Lykke J. The impact of substance use disorders on the course of schizophrenia—a 15-year follow-up study: dual diagnosis over 15 years. Schizophr Res. 2011; 130(1–3):228–33. Epub 2011/05/20. https://doi.org/10.1016/j.schres.2011.04.011 PMID: 21592731.

30. Hjorthøj C, Østergaard ML, Benros ME, Toftdahl NG, Erlangsen A, Andersen JT, et al. Association between alcohol and substance use disorders and all-cause and cause-specific mortality in schizophrenia, bipolar disorder, and unipolar depression: a nationwide, prospective, register-based study. The lancet Psychiatry. 2015; 2(9):801–8. Epub 2015/08/19. https://doi.org/10.1016/S2215-0366(15)00207-2 PMID: 26277044.

31. Reininghaus U, Dutta R, Dazzan P, Doody GA, Fearon P, Lappin J, et al. Mortality in schizophrenia and other psychoses: a 10-year follow-up of the ÆSOP first-episode cohort. Schizophr Bull. 2015; 41(3):664–73. Epub 2014/09/30. https://doi.org/10.1093/schbul/sbu138 PMID: 25262443; PubMed Central PMCID: PMCPmc4393685.

32. Allgulander C. Psychoactive drug use in a general population sample, Sweden: correlates with perceived health, psychiatric diagnoses, and mortality in an automated record-linkage study. Am J Public Health. 1989; 79(8):1006–10. Epub 1989/08/01. PMID: 2751014; PubMed Central PMCID: PMCPmc1349896.

33. Björkenstam E, Ljung R, Burström B, Mittendorfer-Rutz E, Hallqvist J, Weitoft GR. Quality of medical care and excess mortality in psychiatric patients—a nationwide register-based study in Sweden. BMJ Open. 2012; 2:e000778. Epub 2012/03/01. https://doi.org/10.1136/bmjopen-2011-000778 PMID: 22368297; PubMed Central PMCID: PMCPmc3289986.

34. Lumme S, Pirkola S, Manderbacka K, Keskimaki I. Excess Mortality in Patients with Severe Mental Disorders in 1996–2010 in Finland. PLoS One. 2016; 11(3):e0152223. Epub 2016/03/25. https://doi.org/10.1371/journal.pone.0152223 PMID: 27010534; PubMed Central PMCID: PMCPmc4807083.

35. Koola MM, McMahon RP, Wehring HJ, Liu F, Mackowick KM, Warren KR, et al. Alcohol and cannabis use and mortality in people with schizophrenia and related psychotic disorders. J Psychiatr Res. 2012;

46(8):987–93. Epub 2012/05/19. https://doi.org/10.1016/j.jpsychires.2012.04.019 PMID: 22595870; PubMed Central PMCID: PMCPmc3392453.

36. Björkenstam C, Björkenstam E, Hjern A, Bodén R, Reutfors J. Suicide in first episode psychosis: a nationwide cohort study. Schizophr Res. 2014; 157(1–3):1–7. Epub 2014/06/05. https://doi.org/10.1016/j.schres.2014.05.010 PMID: 24893904.

37. Limosin F, Loze JY, Philippe A, Casadebaig F, Rouillon F. Ten-year prospective follow-up study of the mortality by suicide in schizophrenic patients. Schizophr Res. 2007; 94(1–3):23–8. Epub 2007/06/19. https://doi.org/10.1016/j.schres.2007.04.031 PMID: 17574389.

38. Kilbourne AM, Morden NE, Austin K, Ilgen M, McCarthy JF, Dalack G, et al. Excess heart-disease-related mortality in a national study of patients with mental disorders: identifying modifiable risk factors. General hospital psychiatry. 2009; 31(6):555–63. Epub 2009/11/07. https://doi.org/10.1016/j.genhosppsych.2009.07.008 PMID: 19892214; PubMed Central PMCID: PMCPmc4033835.

39. Mattisson C, Bogren M, Öjehagen A, Nordström G, Horstmann V. Mortality in alcohol use disorder in the Lundby Community Cohort—a 50 year follow-up. Drug and alcohol dependence. 2011; 118(2–3):141–7. Epub 2011/04/09. https://doi.org/10.1016/j.drugalcdep.2011.03.008 PMID: 21474255.

40. Steingrímsson S, Sigurdsson MI, Aspelund T, Sigfússon S, Magnusson A. Total population-based study of the impact of substance use disorders on the overall survival of psychiatric inpatients. Nord J Psychiatry. 2016; 70(3):161–6. Epub 2015/09/01. https://doi.org/10.3109/08039488.2015.1062143 PMID: 26317284.

41. Sørensen HJ, Jepsen PW, Haastrup S, Juel K. Drug-use pattern, comorbid psychosis and mortality in people with a history of opioid addiction. Acta Psychiatr Scand. 2005; 111(3):244–9. Epub 2005/02/11. https://doi.org/10.1111/j.1600-0447.2004.00445.x PMID: 15701109.

42. Nyhlén A, Fridell M, Hesse M, Krantz P. Causes of premature mortality in Swedish drug abusers: a prospective longitudinal study 1970–2006. Journal of forensic and legal medicine. 2011; 18(2):66–72. Epub 2011/02/15. https://doi.org/10.1016/j.jflm.2011.01.003 PMID: 21315300.

43. Manrique-Garcia E, Zammit S, Dalman C, Hemmingsson T, Andreasson S, Allebeck P. Cannabis, schizophrenia and other non-affective psychoses: 35 years of follow-up of a population-based cohort. Psychol Med. 2012; 42(6):1321–8. Epub 2011/10/18. https://doi.org/10.1017/S0033291711002078 PMID: 21999906.

44. Nyhlén A, Fridell M, Bäckström M, Hesse M, Krantz P. Substance abuse and psychiatric co-morbidity as predictors of premature mortality in Swedish drug abusers: a prospective longitudinal study 1970–2006. BMC Psychiatry. 2011; 11:122. Epub 2011/08/02. https://doi.org/10.1186/1471-244X-11-122 PMID: 21801441; PubMed Central PMCID: PMCPmc3163521.

45. Helsedirektoratet [The Norwegian Directorate of Health]. Aktivitetsdata for somatisk spesialisthelsetjeneste 2009 [Data on activities in specialized somatic health services 2009] Oslo2010. Available from: https://helsedirektoratet.no/Lists/Publikasjoner/Attachments/525/Aktivitetsdata-for-somatisk-spesialisthelsetjeneste-2009-IS-1800.pdf.

46. Helsedirektoratet [The Norwegian Directorate of Health]. Aktivitetsdata for psykisk helsevern for voksne og tverrfaglig spesialisert behandling av rusmiddelmisbruk 2010 [Activity data for mental health care for adults and children interdisciplinary specialized drug abuse treatment 2010] Oslo2011. Available from: https://helsedirektoratet.no/Lists/Publikasjoner/Attachments/518/Aktivitetsdata-for-psykisk-helsevern-for-voksne-og-tverrfaglig-spesialisert-behandling-av-rusmiddelmisbruk-2010-IS-1911.pdf.

47. Helsedirektoratet [The Norwegian Directorate of Health]. Aktivitetsdata for avtalespesialister 2009 [Data on activities by specialists in private practice 2009] Oslo2010. Available from: https://helsedirektoratet.no/Lists/Publikasjoner/Attachments/504/Aktivitetsdata-for-avtalespesialister-2009-IS-1818.pdf.

48. Helsedirektoratet [The Norwegian Directorate of Health]. Aktivitetsdata for avtalespesialister 2015 [Data on activities by specialists in private practice 2015] Oslo2016. Available from: https://helsedirektoratet.no/Lists/Publikasjoner/Attachments/1180/Aktivitetsdata%20for%20avtalespesialister%202015.pdf.

49. World Health Organization. International Statistical Classification of Diseases and Related Health Problems 10th Revision: World Health Organization; 2004.

50. Pedersen AG, Ellingsen CL. Data quality in the Causes of Death Registry. Tidsskrift for den Norske laegeforening: tidsskrift for praktisk medicin, ny raekke. 2015; 135(8):768–70. Epub 2015/05/08. https://doi.org/10.4045/tidsskr.14.1065 PMID: 25947599.

51. Norwegian Institute of Public Health. Dødsfall etter kjønn, alder og detaljert dødsårsak [Deaths by sex, age and cause of death] 2015 [December 1, 2015]. Available from: http://statistikkbank.fhi.no/webview/.

52. Statistics Norway. Folkemengde og befolkningsendringar [Population and population changes] 2016 [November 21, 2016]. Available from: http://statistikkbank.fhi.no/.

53. Carstensen B, Dickman P. SAS-macro for splitting of follow-up data [Web page]. 2007 [updated December 200723rd November 2016]. Available from: http://bendixcarstensen.com/Lexis/Lexis.sas.

54. Jones ME, Swerdlow AJ. Bias in the standardized mortality ratio when using general population rates to estimate expected number of deaths. American journal of epidemiology. 1998; 148(10):1012–7. Epub 1998/11/26. PMID: 9829874.

55. Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. JAMA Psychiatry. 2015; 72(4):334–41. Epub 2015/02/12. https://doi.org/10.1001/jamapsychiatry.2014.2502 PMID: 25671328; PubMed Central PMCID: PMCPmc4461039.

56. Laursen TM, Wahlbeck K, Hällgren J, Westman J, Ösby U, Alinaghizadeh H, et al. Life expectancy and death by diseases of the circulatory system in patients with bipolar disorder or schizophrenia in the Nordic countries. PLoS One. 2013; 8(6):e67133. Epub 2013/07/05. https://doi.org/10.1371/journal.pone.0067133 PMID: 23826212; PubMed Central PMCID: PMCPmc3691116.

57. Høye A, Jacobsen BK, Hansen V. Increasing mortality in schizophrenia: are women at particular risk? A follow-up of 1111 patients admitted during 1980–2006 in Northern Norway. Schizophr Res. 2011; 132 (2–3):228–32. Epub 2011/08/27. https://doi.org/10.1016/j.schres.2011.07.021 PMID: 21868200.

58. Nielsen RE, Uggerby AS, Jensen SO, McGrath JJ. Increasing mortality gap for patients diagnosed with schizophrenia over the last three decades—a Danish nationwide study from 1980 to 2010. Schizophr Res. 2013; 146(1–3):22–7. Epub 2013/03/26. https://doi.org/10.1016/j.schres.2013.02.025 PMID: 23523021.

59. Laursen TM, Nordentoft M. Heart disease treatment and mortality in schizophrenia and bipolar disorder —changes in the Danish population between 1994 and 2006. J Psychiatr Res. 2011; 45(1):29–35. Epub 2010/06/16. https://doi.org/10.1016/j.jpsychires.2010.04.027 PMID: 20546788.

60. Ösby U, Westman J, Hällgren J, Gissler M. Mortality trends in cardiovascular causes in schizophrenia, bipolar and unipolar mood disorder in Sweden 1987–2010. European journal of public health. 2016; 26 (5):867–71. Epub 2016/01/10. https://doi.org/10.1093/eurpub/ckv245 PMID: 26748100; PubMed Central PMCID: PMCPmc5054269.

61. Onyeka IN, Beynon CM, Hannila ML, Tiihonen J, Föhr J, Tuomola P, et al. Patterns and 14-year trends in mortality among illicit drug users in Finland: the HUUTI study. The International journal on drug policy. 2014; 25(6):1047–53. Epub 2014/08/26. https://doi.org/10.1016/j.drugpo.2014.07.008 PMID: 25151335.

62. Bretteville-Jensen AL, Lillehagen M, Gjersing L, Andreas JB. Illicit use of opioid substitution drugs: prevalence, user characteristics, and the association with non-fatal overdoses. Drug and alcohol dependence. 2015; 147:89–96. Epub 2014/12/30. https://doi.org/10.1016/j.drugalcdep.2014.12.002 PMID: 25543167.

63. Kiviniemi M, Suvisaari J, Pirkola S, Häkkinen U, Isohanni M, Hakko H. Regional differences in five-year mortality after a first episode of schizophrenia in Finland. Psychiatric services (Washington, DC). 2010; 61(3):272–9. Epub 2010/03/03. https://doi.org/10.1176/appi.ps.61.3.272 PMID: 20194404.

64. Chang CK, Hayes RD, Broadbent M, Fernandes AC, Lee W, Hotopf M, et al. All-cause mortality among people with serious mental illness (SMI), substance use disorders, and depressive disorders in southeast London: a cohort study. BMC Psychiatry. 2010; 10:77. Epub 2010/10/06. https://doi.org/10.1186/1471-244X-10-77 PMID: 20920287; PubMed Central PMCID: PMCPmc2958993.

65. Walter F, Carr MJ, Mok PLH, Astrup A, Antonsen S, Pedersen CB, et al. Premature Mortality Among Patients Recently Discharged From Their First Inpatient Psychiatric Treatment. JAMA Psychiatry. 2017; 74(5):485–92. Epub 2017/03/16. https://doi.org/10.1001/jamapsychiatry.2017.0071 PMID: 28296989; PubMed Central PMCID: PMCPmc5417353.

66. Sørensen HJ, Larsen JT, Mors O, Nordentoft M, Mortensen PB, Petersen L. Analysis of risk factors for schizophrenia with two different case definitions: a nationwide register-based external validation study. Schizophr Res. 2015; 162(1–3):74–8. Epub 2015/01/27. https://doi.org/10.1016/j.schres.2015.01.018 PMID: 25620118.

67. Wilcox HC, Conner KR, Caine ED. Association of alcohol and drug use disorders and completed suicide: an empirical review of cohort studies. Drug and alcohol dependence. 2004; 76 Suppl:S11–9. Epub 2004/11/24. https://doi.org/10.1016/j.drugalcdep.2004.08.003 PMID: 15555812.

68. Lawrence D, Mitrou F, Zubrick SR. Smoking and mental illness: results from population surveys in Australia and the United States. BMC Public Health. 2009; 9:285. Epub 2009/08/12. https://doi.org/10.1186/1471-2458-9-285 PMID: 19664203; PubMed Central PMCID: PMCPmc2734850.

69. Liu NH, Daumit GL, Dua T, Aquila R, Charlson F, Cuijpers P, et al. Excess mortality in persons with severe mental disorders: a multilevel intervention framework and priorities for clinical practice, policy and research agendas. World Psychiatry. 2017; 16(1):30–40. Epub 2017/01/28. https://doi.org/10.1002/wps.20384 PMID: 28127922; PubMed Central PMCID: PMCPmc5269481.

70. Beary M, Hodgson R, Wildgust HJ. A critical review of major mortality risk factors for all-cause mortality in first-episode schizophrenia: clinical and research implications. Journal of psychopharmacology (Oxford, England). 2012; 26(5 Suppl):52–61. Epub 2012/04/03. https://doi.org/10.1177/0269881112440512 PMID: 22465947.

71. Gale CR, Batty GD, Osborn DP, Tynelius P, Whitley E, Rasmussen F. Association of mental disorders in early adulthood and later psychiatric hospital admissions and mortality in a cohort study of more than 1 million men. Arch Gen Psychiatry. 2012; 69(8):823–31. Epub 2012/08/08. https://doi.org/10.1001/archgenpsychiatry.2011.2000 PMID: 22868936; PubMed Central PMCID: PMCPmc4170756.

72. Mitchell AJ, Lord O. Do deficits in cardiac care influence high mortality rates in schizophrenia? A systematic review and pooled analysis. Journal of psychopharmacology (Oxford, England). 2010; 24(4 Suppl):69–80. Epub 2010/10/15. https://doi.org/10.1177/1359786810382056 PMID: 20923922; PubMed Central PMCID: PMCPmc2951596.

73. Correll CU, Detraux J, De Lepeleire J, De Hert M. Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. World Psychiatry. 2015; 14(2):119–36. Epub 2015/06/05. https://doi.org/10.1002/wps.20204 PMID: 26043321; PubMed Central PMCID: PMCPmc4471960.

74. Hunt GE, Siegfried N, Morley K, Sitharthan T, Cleary M. Psychosocial interventions for people with both severe mental illness and substance misuse. The Cochrane database of systematic reviews. 2013; (10):Cd001088. Epub 2013/10/05. https://doi.org/10.1002/14651858.CD001088.pub3 PMID: 24092525.

75. Murthy P, Chand P. Treatment of dual diagnosis disorders. Curr Opin Psychiatry. 2012; 25(3):194–200. Epub 2012/03/08. https://doi.org/10.1097/YCO.0b013e328351a3e0 PMID: 22395768.

76. Speyer H, Christian Brix Norgaard H, Birk M, Karlsen M, Storch Jakobsen A, Pedersen K, et al. The CHANGE trial: no superiority of lifestyle coaching plus care coordination plus treatment as usual compared to treatment as usual alone in reducing risk of cardiovascular disease in adults with schizophrenia spectrum disorders and abdominal obesity. World Psychiatry. 2016; 15(2):155–65. Epub 2016/06/07. https://doi.org/10.1002/wps.20318 PMID: 27265706; PubMed Central PMCID: PMCPmc4911772.

77. Rose G. Sick individuals and sick populations. Int J Epidemiol. 2001; 30(3):427–32; discussion 33–4. Epub 2001/06/21. PMID: 11416056.

78. Phillips DE, Lozano R, Naghavi M, Atkinson C, Gonzalez-Medina D, Mikkelsen L, et al. A composite metric for assessing data on mortality and causes of death: the vital statistics performance index. Population health metrics. 2014; 12:14. Epub 2014/07/02. https://doi.org/10.1186/1478-7954-12-14 PMID: 24982595; PubMed Central PMCID: PMCPmc4060759.

79. Øiesvold T, Nivison M, Hansen V, Skre I, Østensen L, Sørgaard KW. Diagnosing comorbidity in psychiatric hospital: challenging the validity of administrative registers. BMC Psychiatry. 2013; 13:13. Epub 2013/01/10. https://doi.org/10.1186/1471-244X-13-13 PMID: 23297686; PubMed Central PMCID: PMCPmc3544620.

80. Nesvåg R, Jönsson EG, Bakken IJ, Knudsen GP, Bjella TD, Reichborn-Kjennerud T, et al. The quality of severe mental disorder diagnoses in a national health registry as compared to research diagnoses based on structured interview. BMC Psychiatry. 2017; 17(1):93. Epub 2017/03/16. https://doi.org/10.1186/s12888-017-1256-8 PMID: 28292279; PubMed Central PMCID: PMCPmc5351165.

81. Osborn DP, Levy G, Nazareth I, Petersen I, Islam A, King MB. Relative risk of cardiovascular and cancer mortality in people with severe mental illness from the United Kingdom's General Practice Research Database. Arch Gen Psychiatry. 2007; 64(2):242–9. Epub 2007/02/07. https://doi.org/10.1001/archpsyc.64.2.242 PMID: 17283292.

82. Hansen SS, Munk-Jørgensen P, Guldbæk B, Solgård T, Lauszus KS, Albrechtsen N, et al. Psychoactive substance use diagnoses among psychiatric in-patients. Acta Psychiatr Scand. 2000; 102(6):432–8. Epub 2001/01/06. PMID: 11142432.

S1 Table. List of somatic diagnosis indicating alcohol abuse or drug abuse.

ICD-10 code	Description
E24.4	Alcohol-induced pseudo-Cushing syndrome
E52	Niacin deficiency [pellagra]
G31.2	Degeneration of nervous system due to alcohol
G62.1	Alcoholic polyneuropathy
G72.1	Alcoholic myopathy
I42.6	Alcoholic cardiomyopathy
K29.2	Alcoholic gastritis
K70	Alcoholic liver disease
K86.0	Alcohol-induced chronic pancreatitis
O35.4	Maternal care for (suspected) damage to fetus from alcohol
O35.5	Maternal care for (suspected) damage to fetus by drugs
Z50.2	Alcohol rehabilitation
Z50.3	Drug rehabilitation
Z71.4	Alcohol abuse counselling and surveillance
Z71.5	Drug abuse counselling and surveillance
Z72.1	Alcohol use
Z72.2	Drug use

S2 Table. Sensitivity-analysis for all-cause age, gender, and calendar-year standardized mortality ratios among men and women aged 20-79 with schizophrenia-related disorders (SCZ) and/or substance use disorders (SUD).

	SCZ-only			SUD-only			SCZ+SUD		
	Obs	SMR	(95 % CI)	Obs	SMR	(95 % CI)	Obs	SMR	(95 % CI)
Men									
Original model	972	4.5	(4.2-4.8)	7,334	6.4	(6.2-6.5)	423	7.6	(6.9-8.3)
(i) Excluding patients in somatic hospitals	678	3.8	(3.5-4.1)	3,419	5.7	(5.5-5.9)	324	7.8	(7.0-8.7)
(ii) Primary diagnosis only [a]	669	3.8	(3.5-4.1)	7,412	6.4	(6.3-6.6)	346	7.3	(6.6-8.2)
(iii) SCZ defined as F20 only	670	5.2	(4.8-5.6)	7,530	6.4	(6.3-6.6)	227	7.9	(7.0-9.0)
Women									
Original model	832	4.3	(4.0-4.6)	2,592	7.4	(7.1-7.7)	165	7.0	(6.0-8.2)
(i) Excluding patients in somatic hospitals	591	3.6	(3.3-4.0)	1,226	6.2	(5.9-6.5)	105	6.5	(5.4-7.9)
(ii) Primary diagnosis only [a]	570	3.6	(3.3-3.9)	2,620	7.4	(7.1-7.7)	137	6.6	(5.6-7.9)
(iii) SCZ defined as F20 only	469	5.0	(4.6-5.5)	2,680	7.3	(7.0-7.6)	77	9.3	(7.4-11.6)

Abbreviations: Obs, observed deaths; SMR, standardized mortality ratio; 95 % CI, 95 % confidence interval; AUD, Alcohol Use Disorder.

[a] The number of patient in the SUD-only group increases, and the number of comorbid patients decreases, when a secondary diagnosis no longer qualifies for a SCZ diagnosis.

S3 Table. All-cause age, gender, and calendar-year standardized mortality ratios among patients aged 20-79 with schizophrenia-related disorders (SCZ) and a concurrent substance use disorder (SUD), according to the temporal ordering of SCZ and SUD diagnosis

	1 month			3 months			6 months		
	Obs	SMR	(95 % CI)	Obs	SMR	(95 % CI)	Obs	SMR	(95 % CI)
SCZ preceding SUD diagnosis	189	5.5	(4.8-6.4)	161	5.2	(4.4-6.1)	146	5.3	(4.5-6.2)
SUD preceding SCZ diagnosis	167	8.4	(7.2-9.8)	145	7.9	(6.7-9.3)	121	7.6	(6.4-9.1)
Both diagnosis within specified time frame	217	9.8	(8.6-11.2)	267	9.9	(8.8-11.1)	306	8.3	(8.3-10.4)

Abbreviations: Obs, observed deaths; SMR, standardized mortality ratio; 95% CI, 95% confidence interval

Paper II

Acta Psychiatrica Scandinavica

Acta Psychiatr Scand 2019: 139: 558–571

DOI: 10.1111/acps.13017

Undiagnosed cardiovascular disease prior to cardiovascular death in individuals with severe mental illness

I. H. Heiberg[1], B. K. Jacobsen[1,2,3], L. Balteskard[1], J. G. Bramness[4,5], Ø. Næss[6,7], E. Ystrom[8,9,10], T. Reichborn-Kjennerud[6,8], C. M. Hultman[11,12], R. Nesvåg[5,13], A. Høye[1,5,14]

Heiberg IH, Jacobsen BK, Balteskard L, Bramness JG, Næss Ø, Ystrom E, Reichborn-Kjennerud T, Hultman CM, Nesvåg R, Høye A. Undiagnosed cardiovascular disease prior to cardiovascular death in individuals with severe mental illness.

Objective: To examine whether individuals with schizophrenia (SCZ) or bipolar disorder (BD) had equal likelihood of not being diagnosed with cardiovascular disease (CVD) prior to cardiovascular death, compared to individuals without SCZ or BD.
Methods: Multivariate logistic regression analysis including nationwide data of 72 451 cardiovascular deaths in the years 2011–2016. Of these, 814 had a SCZ diagnosis and 673 a BD diagnosis in primary or specialist health care.
Results: Individuals with SCZ were 66% more likely (OR: 1.66; 95% CI: 1.39–1.98), women with BD were 38% more likely (adjusted OR: 1.38; 95% CI: 1.04–1.82), and men with BD were equally likely (OR: 0.88, 95% CI: 0.63–1.24) not to be diagnosed with CVD prior to cardiovascular death, compared to individuals without SMI. Almost all (98%) individuals with SMI and undiagnosed CVD had visited primary or specialized somatic health care prior to death, compared to 88% among the other individuals who died of CVD.
Conclusion: Individuals with SCZ and women with BD are more likely to die due to undiagnosed CVD, despite increased risk of CVD and many contacts with primary and specialized somatic care. Strengthened efforts to prevent, recognize, and treat CVD in individuals with SMI from young age are needed.

Significant outcomes

- In this nationwide study, we found a considerable under diagnosis of cardiovascular disease (CVD) prior to cardiovascular death in individuals with schizophrenia (SCZ). Similar relationships were found for women, but not men, with bipolar disorder (BD).
- The higher likelihood of undiagnosed CVD applied to all main types of cardiovascular death and was particularly pronounced in the youngest.
- Almost all individuals with SMI and undiagnosed CVD prior to cardiovascular death were in contact with primary or specialized somatic health care in the observation period before death, demonstrating that opportunities for identification and management of CVD risk factors exist.

Limitations

- Information on antipsychotic medications and history of CVD prior to the study period was lacking.
- As for other studies based on health registries, the diagnostic quality has not been established for all disease categories.

[1]Center for Clinical Documentation and Evaluation (SKDE), [2]Department of Community Medicine, UiT – The Arctic University of Norway, [3]Centre for Sami Health Research, Department of Community Medicine, UiT – The Arctic University of Norway, Tromsø, [4]Norwegian National Advisory Unit on Concurrent Substance Abuse and Mental Health Disorders, Innlandet Hospital Trust, Hamar, [5]Department of Clinical Medicine, UiT – The Arctic University of Norway, Tromsø, [6]Institute of Clinical Medicine, University of Oslo, [7]Institute of Health and Society, University of Oslo, [8]Department of Mental Disorders, Norwegian Institute of Public Health, [9]Department of Psychology, University of Oslo, [10]PharmacoEpidemiology and Drug Safety Research Group, School of Pharmacy, University of Oslo, Oslo, Norway, [11]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden, [12]Icahn School of Medicine, Mt Sinai Hospital, New York, NY, USA, [13]Norwegian Medical Association, Oslo, and [14]Division of Mental Health and Substance Abuse, University Hospitalof North Norway, Tromsø, Norway

Key words: schizophrenia; bipolar disorder; cardiovascular diseases; death; adult; treatment delay; delayed diagnosis

Ina H. Heiberg, Center for Clinical Documentation and Evaluation (SKDE), postbox 6, 9038 Tromsø, Norway. E-mail: ina.heiberg@skde.no

Accepted for publication February 25, 2019

Introduction

Individuals with schizophrenia (SCZ) or bipolar disorder [BD; henceforth referred to as severe mental illness (SMI)] have impaired cardiovascular health (1, 2). A higher incidence of cardiovascular disease (CVD) in individuals with SMI has been documented (3, 4), as well as increased mortality from CVD compared to the general population (5, 6). Cardiovascular mortality has been reduced by 50% in the general population since 2000 (7), but remain high among individuals with SMI (8, 9). A recent study found that Norwegians with SCZ treated in specialized health care in the period 2009–2015 had a fourfold to fivefold increased risk of cardiovascular death compared to the general population (10), which is substantially higher than the doubled risk reported in earlier studies (11, 12).

Excess cardiovascular mortality in individuals with SMI is often attributed to socioeconomic disadvantage (13), lifestyle factors such as unhealthy diet, physical inactivity, smoking, and alcohol abuse (14), and metabolic side-effects of antipsychotic medication (15). It is also a substantial overlap between genetic risk for SMI and genetic risk for type I diabetes, hypertension, cardiac dysrhythmia, and non-rheumatic heart disease (16), indicating additional frailty for CVD in individuals with SMI. There is, however, a rising concern that suboptimal health care, including underdiagnosis and treatment delay of CVD, may also contribute to the elevated cardiovascular mortality among individuals with SMI (17, 18). Meta-analytic studies have reported inferior preventive care regarding CVD risk factors in patients with SMI, compared to others (19–21). Large population-based cohort studies have reported lower or similar rates of recorded CVDs such as atrial fibrillation, hypertension, and ischemic heart disease (IHD) in individuals with SMI, compared to others (1, 22–24), in spite of increased risk of CVD. Lower prescriptions rates for cardiovascular medication in individuals with SMI compared to others have also been reported (25–27), possibly implying underdiagnosis and under-treatment of CVD in these individuals. Furthermore, in a survey of mental health service users, 39% reported not having discussed CVD risk factors with healthcare professionals the previous year (28).

While evidence regarding the prevalence of undiagnosed CVD in individuals with SMI is accumulating, mortality from undiagnosed CVD in individuals with SMI is less studied. Exceptions include two nationwide Swedish studies, where the proportion of individuals who died from IHD undiagnosed 1 month prior to an IHD death was higher in individuals with SCZ compared to others (23), but not significantly different between individuals with or without BD (29). Importantly, when restricting the analysis to people who were previously diagnosed with IHD, SCZ was only modestly associated with higher IHD mortality, which indicates that premature cardiovascular deaths in individuals with SMI may be prevented if CVDs were identified and treated (30–32). To clarify reasons for premature cardiovascular deaths in individuals with SMI, it is important to investigate to what extent these individuals are in contact with and treated in primary or specialized somatic health care prior to cardiovascular death. SCZ and BD often have an early onset and a chronic course, which makes it more likely to assume that the presence of SMI may have affected the detection and treatment of CVD in the years, possibly decades, leading up to a cardiovascular death. We chose not to merge SCZ and BD into one SMI group, as they often differ with regard to symptom expression, socioeconomic background of patients, and healthcare utilization. Previous studies (23, 29, 33) did

not differentiate between sexes, although sex is associated with severity of both SMI (34–36) and CVD (37), and healthcare utilization (38, 39). We therefore present sex-specific analyses, to facilitate identification of groups at particularly risk of fatal undiagnosed CVD.

Aims of the study

We examined whether individuals with and without schizophrenia or bipolar disorder had equal likelihood of not being diagnosed with cardiovascular disease prior to cardiovascular death. Secondary aims were to describe sex-specific differences between individuals with schizophrenia and bipolar disorder, and to describe demographic characteristics, comorbidity, and healthcare utilization in individuals with schizophrenia or bipolar disorder and undiagnosed cardiovascular disease prior to death.

Material and methods

Data sources

We obtained mortality data for the period 2011–2016 from the Norwegian Cause of Death Registry (CDR), and diagnostic data on individuals with SMI and/or CVD and information on use of primary and specialized health care from the Norwegian Directorate of Health's system for control and payment of health reimbursements in primary care (the KUHR database) and the Norwegian Patient Registry (NPR) for the period 2008–2016.

Nearly all healthcare services in Norway are publicly funded, which ensures representative and almost complete data in national health registries. The CDR provides 98% complete information on causes of death based on standardized certificates completed by the physician who examined the deceased (40). The CDR also receives notifications of autopsy findings and may request supplementary information from physicians, healthcare institutions, and clinical registries such as the Medical Birth Registry and the Cancer Registry. In approximately half of all cases, the underlying cause of death is determined using automated classification software (16, 17), which process data according to the rules of ICD-10, whereas the remaining cases are set by professional coders (supervised by physicians), based on the death certificate and any supplementary information.

The KUHR database contains information on consultations in primary care (i.e., visits at general practitioners' (GP) offices, home visits by GPs, and emergency room visits). As GPs are funded mainly on a fee-for-service basis, the completeness of reported contacts in the KUHR database is considered to be almost 100%. The NPR contains information on all contacts in specialized health care in Norway (i.e., government-owned hospitals and out-patient clinics, publicly financed substance use treatment facilities, and private health clinics with governmental reimbursement). Since 2008, the coverage in the NPR has been almost 100%, except for substance use treatment facilities which were included from 2009, and private somatic health clinics with governmental reimbursement, in which approximately 85% of all contacts were reported in the study period (41, 42).

Diagnostic codes in the CDR and the NPR follow the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), whereas diagnostic codes for primary care contacts in the KUHR database follow the International Classification of Primary Care 2nd Edition (ICPC-2). Accurate linkage across data sources was obtained using an encrypted personal identification number included in all registries.

Subject inclusion criteria and diagnostic categories

Deceased individuals aged 18 years or older were included if a diagnosis of CVD (ICD-10 codes I00–I82) was recorded as underlying cause of death in the death certificate. The study included deaths in the years 2011–2016, securing at least 3 years of observation time in the NPR and the KUHR database prior to death (as information concerning healthcare utilization during 2008–2016 was included).

Cardiovascular causes of death were subdivided into IHD (I20–I25), other forms of heart disease (OHD, I30–I52) and cerebrovascular diseases (I60–I69). IHD was further subdivided into myocardial infarction (MI, ICD-10 codes I21–I22 and I25.2), and OHD was further subdivided into heart failure (ICD-10, codes I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43, and I50) and arrhythmia (ICD-10, codes I44.1–I44.3, I45.6, I45.9, and I47–I49). Foreign citizens and individuals registered as having died abroad were excluded ($N = 132$).

Individuals were included in the SMI group if a diagnosis of SCZ (ICD-10 code F20 or ICPC-2 code P72) or BD (ICD-10 codes F30–F31 or ICPC-2 code P73) was recorded in the NPR or the KUHR database during the years 2008–2016, or in the death certificate. Individuals diagnosed with both SCZ and BD ($N = 97$) were included in the SCZ group only.

A diagnosis of CVD was considered present if ICD-10-codes I00–I82 or G45, or corresponding ICPC-2 diagnoses (codes K70–K71, K74–K80, K82–K84, K86–K87, and K89–K94) were recorded in the NPR or the KUHR database in the period from inclusion (January 1, 2008) and up to 1 month prior to death. Diagnoses of CVD recorded only within the last month prior to death were not counted to avoid including CVDs secondary to other fatal diseases.

Analysis and statistical methods

Sex, age, and use of primary and specialized somatic care (the latter including all contacts in government-owned hospitals, out-patient clinics, and private health clinics with governmental reimbursement with a somatic diagnosis), and comorbidity up to 1 month prior to death were used to assess group comparability. Mean score on the Charlson comorbidity index (CCI) (43) was used to describe somatic comorbidity recorded in primary or specialized somatic care, and was modified to exclude CVD (i.e., MI, heart failure, peripheral vascular disease, and cerebrovascular disease), applying weights from Quan et al. (44). Continuous variables, with the exception of CCI, were presented as medians with the 25 and 75 percentile and compared using the Kruskal–Wallis test. Chi-square tests were used to compare proportions. Significant results were followed by post hoc tests with Bonferroni correction for multiple comparisons to assess whether there were any differences between the three groups (45). A two-tailed P-value < 0.05 was considered statistically significant.

We applied the following analytic strategy: First, the proportion of people who had not been diagnosed with CVD prior to cardiovascular death was computed and compared across the three groups. Second, crude sex-specific odds ratios (ORs) for not being diagnosed with CVD prior to cardiovascular death were calculated using logistic regression and reported with corresponding 95% confidence intervals (CI). Third, we adjusted for age at death adding a linear variable with six categories (age 18–49, 50–59, 60–69, 70–79, 80–89, and 90 years or above). No linear interactions between age and diagnostic groups were found. Sex- and age-stratified ORs were also calculated, applying age-groups 18–59, 60–79, and 80 years or above. Finally, we included in the model the modified mean score on the CCI and recorded substance use disorders (SUD, see diagnostic codes in Table S1). Subgroup analyses were conducted for individuals with IHD, MI, OHD, or cerebrovascular disease as underlying cause of death. To test the consistency of study findings, we also conducted additional analysis to assess the impact of (i) excluding individuals with dementia (see codes in Table S1), (ii) excluding cases with causes of death that should not be considered underlying causes of death (46), (iii) including CVD diagnosis during the last month prior to death, (iv) applying CVD recorded in specialized somatic care only as dependent variable, (v) including cases with CVD as contributing cause of death, and (vi) adjustment for observation time. All analyses were performed using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethics

All patient data were fully de-identified when accessed by the investigators. In Norway, studies with de-identified information from medical health registries do not require participant consent. Legal basis and exemption from professional secrecy requirements for the use of personal health data in research were granted by the Regional Committee for Medical and Health Research Ethics (2014/72/REK nord).

Results

Characteristics of the study population

A total of 72 451 Norwegian citizens aged 18 years or older who died due to CVD in the period 2011–2016 were included in the study (Table 1). Of these, 814 (1.1%) were registered with SCZ and 673 (0.9%) with BD. During the study period, most individuals with SCZ (55%) had their SCZ diagnosis recorded in primary care only, while 35% had a SCZ diagnosis recorded in both primary and specialized health care, 8% in specialized health care only, and 3% in the CDR only (results not shown in the tables). Among individuals with BD, 37% had a BD diagnosis in primary care only, 47% both in primary and specialized health care, 15% in specialized health care only, and 1% in the CDR only.

Women were in majority in all three groups (SCZ, BD, and no SMI; Table 1). Men and women with SMI died 9 and 7 years younger, respectively, than men and women without SMI. Nearly 75% of individuals without SMI died at ages 80 years or above, whereas less than half of individuals with SMI who died of CVD reached this age. IHD was the most common cause of cardiovascular death and accounted for nearly 40% of all deaths in the

Table 1. Cardiovascular deaths among individuals with schizophrenia, bipolar disorder, or no severe mental illness who died at ages 18 years or above, according to sex, age, and cause of death

	Schizophrenia	Bipolar disorder	No severe mental illness	*P*-value	*Post hoc* comparisons
Men					
Deaths, *n*	384	291	33 015		
Age at death, mean (SD)	70.9 (14.3)	70.9 (13.0)	79.8 (12.1)	<0.0001	SCZ, BD < No SMI
Age 18–59 at death, *n* (%)	80 (20.8)	57 (19.6)	2330 (7.1)	<0.0001	No SMI < SCZ, BD
Age 60–79 at death, *n* (%)	181 (47.1)	154 (52.9)	10 853 (32.9)	<0.0001	No SMI < SCZ, BD
Age ≥ 80 at death, *n* (%)	123 (32.0)	80 (27.5)	19 832 (60.1)	<0.0001	SCZ, BD < No SMI
Underlying cause of death, *n* (%)					
I20–I25 Ischemic heart diseases	175 (45.6)	117 (40.2)	13 969 (42.3)	0.311	–
Myocardial infarction	102 (26.6)	65 (22.3)	8510 (25.8)	0.381	–
I30–I52 Other forms of heart disease	100 (26.0)	68 (23.4)	8422 (25.5)	0.676	–
Heart failure	45 (11.7)	28 (9.6)	3863 (11.7)	0.542	–
Arrhythmia	23 (6.0)	8 (2.7)	1988 (6.0)	0.064	–
I60–I69 Cerebrovascular diseases	70 (18.2)	71 (24.4)	6825 (20.7)	0.128	–
Other cardiovascular diseases†	39 (10.2)	35 (12.0)	3799 (11.5)	0.689	–
Women					
Deaths, *n*	430	382	37 949		
Age at death, mean (SD)	80.5 (13.3)	79.3 (12.6)	86.7 (9.5)	<0.0001	BD < SCZ < No SMI
Age 18–59 at death, n (%)	42 (9.8)	26 (6.8)	761 (2.0)	<0.0001	No SMI < BD < SCZ
Age 60–79 at death, n (%)	117 (27.2)	132 (34.6)	5446 (14.4)	<0.0001	No SMI < SCZ < BD
Age ≥ 80 at death, *n* (%)	271 (63.0)	224 (58.6)	31 742 (83.6)	<0.0001	SCZ, BD < NO SMI
Underlying cause of death, *n* (%)					
I20–I25 Ischemic heart diseases	152 (35.3)	135 (35.3)	11 883 (31.3)	0.064	–
Myocardial infarction	92 (21.4)	87 (22.8)	7532 (19.8)	0.310	–
I30–I52 Other forms of heart disease	123 (28.6)	101 (26.4)	12 004 (31.6)	0.040	–
Heart failure	60 (14.0)	58 (15.2)	5797 (15.3)	0.768	–
Arrhythmia	25 (5.8)	14 (3.7)	3162 (8.3)	0.001	BD < No SMI
I60–I69 Cerebrovascular diseases	114 (26.5)	96 (25.1)	9696 (25.6)	0.852	–
Other cardiovascular diseases†	41 (9.5)	50 (13.1)	4366 (11.5)	0.286	–

BD, bipolar disorder; SCZ, schizophrenia; SD, standard deviation; SMI, severe mental illness.
†Other cardiovascular diseases: ICD-10 codes I00–I15, I26–I28, and I70–I82.

three groups. No significant differences in causes of cardiovascular deaths were noted across groups.

Men with SCZ had lower frequency of GP visits and specialized somatic out-patient visits, but similar frequency of emergency room visits and somatic admissions, compared to men without SMI, whereas women with SCZ had higher frequency of emergency room visits, lower frequency of specialized somatic out-patient visits, but similar frequency of GP visits and somatic hospital admissions compared to women without SMI (Table 2). Individuals with BD had higher frequency of both primary and specialized somatic care compared to individuals with SCZ, and also higher frequency of GP visits, emergency room visits, and somatic hospital admissions compared to individuals without SMI. Individuals with SMI had higher frequency of SUD compared to individuals without SMI, and women with SMI also higher prevalence of diagnosed chronic obstructive pulmonary disease (COPD) and dementia compared to women without SMI (Table 2).

Undiagnosed CVD prior to cardiovascular death

Twenty-three per cent of individuals with SCZ who died from CVD had not been diagnosed with CVD in primary or specialized somatic health care prior to death, compared to 17% in individuals with BD and 11% in individuals without SMI ($P < 0.0001$). The highest proportion of undiagnosed CVD prior to cardiovascular death was found in individuals who died at ages 18–59, of whom 60% of individuals with SCZ, 37% of individuals with BD, and 44% of individuals without SMI were undiagnosed with CVD prior to death (Fig. 1).

Most individuals with diagnosed CVD prior to death had their CVD diagnosis recorded both in primary and specialized somatic care, but individuals with SCZ least so (74% in individuals with SCZ, compared to 79% in individuals with BD and 80% in individuals without SMI, $P = 0.012$, results not shown in the tables). A slightly higher proportion of individuals with SCZ had their CVD diagnosis recorded only in specialized somatic health care prior to death (11% in individuals with SCZ, compared to 9% of individuals with BD, and 6% of individuals without SMI, $P = 0.050$, results not shown in tables).

Unadjusted analyses showed that individuals with SCZ or BD had 132% and 56% higher odds, respectively, of not being diagnosed with CVD prior to cardiovascular death, compared to individuals without SMI (OR 2.32; 95% CI: 1.97–2.74

Table 2. Healthcare utilization and comorbidity in individuals with schizophrenia, bipolar disorder, or no severe mental illness who died from CVD at ages 18 years or above, according to sex

	Schizophrenia	Bipolar disorder	No severe mental illness	*P*-value	*Post hoc* comparisons
Men	384	291	33 015		
Patients according to healthcare sector, *n* (%)					
General practitioner	366 (95.3)	290 (99.7)	32 058 (97.1)	0.004	SCZ, No SMI < BD
Emergency room	283 (73.7)	240 (82.5)	23 570 (71.4)	0.000	SCZ, No SMI < BD
Specialized somatic care	337 (87.8)	278 (95.5)	30 880 (93.5)	<0.0001	SCZ < BD, No SMI
Specialized mental care	248 (64.6)	200 (68.7)	2840 (8.6)	<0.0001	No SMI < SCZ, BD
No healthcare use	5 (1.3)	0 (0.0)	478 (1.4)	0.115	–
No. of healthcare contacts per person-year, median (25/75 percentile)					
GP visits	6.3 (3.0–12.3)	9.6 (5.6–15.2)	7.6 (3.9–13.3)	<0.0001	SCZ < No SMI < BD
Emergency room visits	0.5 (0.3–1.0)	0.7 (0.3–1.5)	0.5 (0.3–0.9)	<0.0001	SCZ, No SMI < BD
Somatic admissions	0.5 (0.2–1.0)	0.7 (0.3–1.2)	0.6 (0.3–1.1)	0.001	SCZ, No SMI < BD
Somatic out-patient visits	1.0 (0.3–2.3)	2.1 (0.8–3.6)	2.0 (0.8–3.9)	<0.0001	SCZ < BD, No SMI
Patients with selected comorbidities, *n* (%)					
Diabetes	90 (23.4)	74 (25.4)	7551 (22.9)	0.568	–
COPD	65 (16.9)	65 (22.3)	5775 (17.5)	0.092	–
Substance use disorder	55 (14.3)	72 (24.7)	1846 (5.6)	<0.0001	No SMI < SCZ < BD
Dementia	77 (20.1)	66 (22.7)	5901 (17.9)	0.058	–
Modified CCI, mean (SD)	1.11 (1.8)	1.35 (1.8)	1.24 (1.7)	0.017	SCZ < BD, No SMI
No CC groups, *n* (%)	217 (56.5)	129 (44.3)	15 996 (48.5)	0.003	BD, No SMI < SCZ
≥2 CC groups, *n* (%)	71 (18.5)	69 (23.7)	7042 (21.3)	0.243	–
Women	430	382	37 949		
Patients according to healthcare sector, *n* (%)					
General practitioner	405 (94.2)	375 (98.2)	36 221 (95.4)	0.175	–
Emergency room	338 (88.0)	302 (79.1)	27 983 (84.8)	0.005	–
Specialized somatic care	399 (92.8)	368 (96.3)	35 898 (94.6)	0.082	–
Specialized mental care	251 (58.4)	240 (62.8)	3134 (8.3)	<0.0001	No SMI < SCZ, BD
No healthcare use	5 (1.2)	1 (0.3)	579 (1.5)	0.110	–
No. of healthcare contacts per person-year, median (25/75 percentile)					
GP visits	6.4 (2.9–12.5)	9.3 (5.0–16.3)	7.1 (3.6–12.4)	<0.0001	SCZ, No SMI < BD
Emergency room visits	0.5 (0.3–1.1)	0.6 (0.3–1.1)	0.5 (0.3–0.9)	<0.0001	No SMI < SCZ, BD
Somatic admissions	0.5 (0.3–0.9)	0.7 (0.3–1.2)	0.5 (0.3–1.0)	0.000	SCZ, No SMI < BD
Somatic out-patient visits	1.2 (0.5–2.3)	1.5 (0.7–3.1)	1.5 (0.6–2.9)	<0.0001	SCZ < No SMI < BD
Patients with selected comorbidities, *n* (%)					
Diabetes	92 (21.4)	82 (21.5)	6902 (18.2)	0.061	–
COPD	78 (18.1)	78 (20.4)	4805 (12.7)	<0.0001	No SMI < SCZ, BD
Substance use disorder	17 (4.0)	45 (11.8)	748 (2.0)	<0.0001	No SMI < SCZ < BD
Dementia	158 (36.7)	123 (32.2)	10 006 (26.4)	<0.0001	No SMI < SCZ, BD
Modified CCI, mean (SD)	1.25 (1.6)	1.37 (1.6)	1.08 (1.5)	<0.0001	No SMI < BD
No CC groups, *n* (%)	204 (47.4)	154 (40.3)	19 518 (51.4)	<0.0001	BD < No SMI
≥2 CC groups, *n* (%)	80 (18.6)	82 (21.5)	6227 (16.4)	0.016	No SMI < BD

BD, bipolar disorder; CC groups, Charlson Comorbidity groups; COPD, chronic obstructive pulmonary disease; GP, general practitioner; Modified CCI, Charlson comorbidity index modified to exclude CVD (e.g., myocardial infarction, heart failure, peripheral vascular disease, and cerebrovascular disease); SCZ, schizophrenia; SD, standard deviation; SMI, severe mental illness.

in individuals with SCZ and OR: 1.56; 95% CI: 1.27–1.92 in individuals with BD, results not shown in tables). After adjustment for age at death and comorbidities, we found that individuals with SCZ were 66% more likely (OR: 1.66; 95% CI: 1.39–1.98), women with BD were 38% more likely (OR: 1.38; 95% CI: 1.04–1.82), and men with BD were equally likely (OR: 0.88, 95% CI: 0.63–1.24) not to be diagnosed with CVD prior to cardiovascular death, compared to individuals without SMI (Fig. 2). Recorded SUD and higher medical comorbidity were negatively associated with the odds of undiagnosed CVD (results not shown), but inclusion of these covariates did not alter results notably compared to the age-adjusted models (Table 3).

Subgroup analyses according to cause of death with adjustment for age at death and comorbidities showed that individuals with SCZ had higher odds of not being diagnosed with CVD prior to death for all main causes of cardiovascular death (Table 3). Women with SCZ had particularly high odds of undiagnosed CVD prior to a MI death. Individuals with BD had similar odds of undiagnosed CVD prior to cardiovascular death as individuals without SMI, except that women with BD who died from cerebrovascular disease had higher odds of undiagnosed CVD (Table 3).

The sensitivity analyses (Figure S1) confirmed the main results; SCZ (in both men and women) and BD in women were associated with increased odds of not being diagnosed with CVD prior to

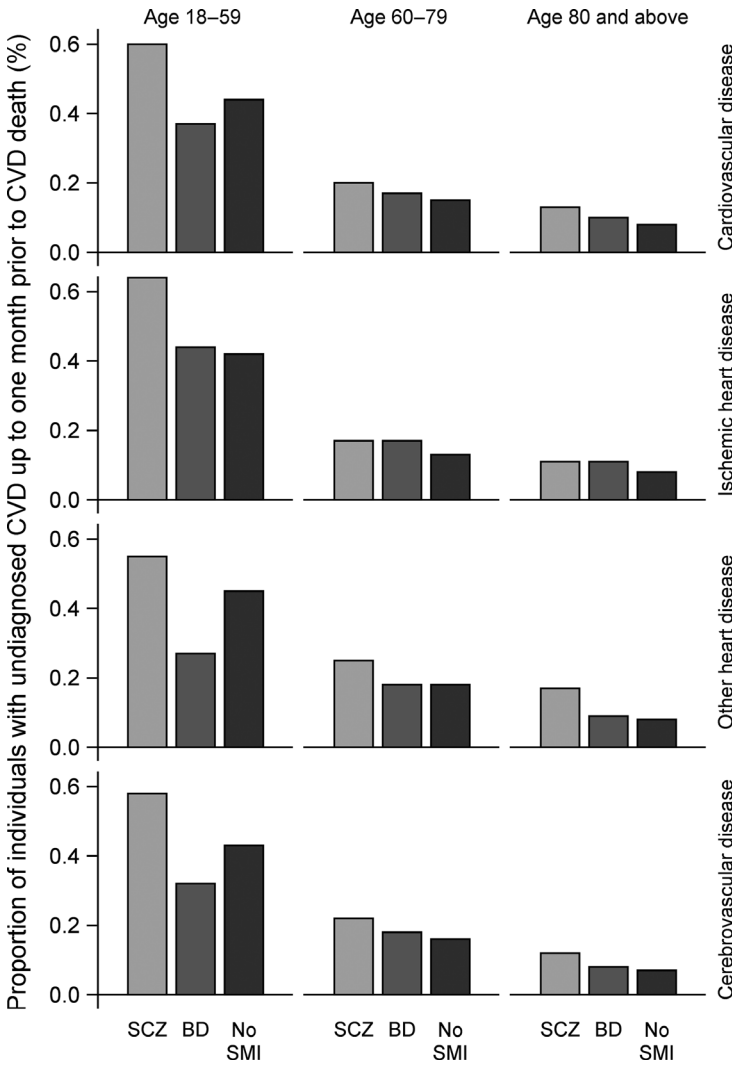


Fig. 1. Proportion of individuals with schizophrenia, bipolar disorder, and no severe mental illness (no SMI) who were undiagnosed with cardiovascular disease up to one month prior to cardiovascular death, according to cause of death, age at death, and patient group.

CVD death, whereas no association was found for BD in men.

Characteristics of individuals with undiagnosed CVD

Individuals with SMI who died from undiagnosed CVD died approximately 10 years younger than individuals with undiagnosed CVD without SMI (Table S2). Individuals with SMI and undiagnosed CVD had lower likelihood of dying in a nursing home, and individuals with SCZ and undiagnosed CVD had a higher likelihood of death at home, compared to individuals without SMI. No differences with regard to cause of death were found between the three groups (results not shown).

Almost all (98%) individuals with SMI and undiagnosed CVD had visited primary or specialized somatic health care prior to death, compared to 88% among individuals without SMI (results not shown in tables). Eighty-eight per cent of individuals with SCZ and 97% of individuals with BD had visits in primary care in the observation period, compared to 78% of individuals without SMI, and a majority of individuals with SMI had also been in contact with specialized somatic health care prior to death (73% of individuals with SCZ, and 84% in individuals with BD, compared to 70% of individuals without SMI). Having no healthcare contacts up to 1 month prior to death was uncommon in individuals with SMI (5% and 1% in individuals with SCZ or BD, respectively), while this was the case for 12% of individuals without SMI. Individuals with BD and undiagnosed CVD prior to death had more GP contacts and more admissions in specialized somatic care, compared to individuals without SMI who died from undiagnosed CVD, and individuals with SMI more emergency room visits (Table S2).

Compared to individuals with SMI and diagnosed CVD prior to death, individuals with SMI and undiagnosed CVD prior to death died

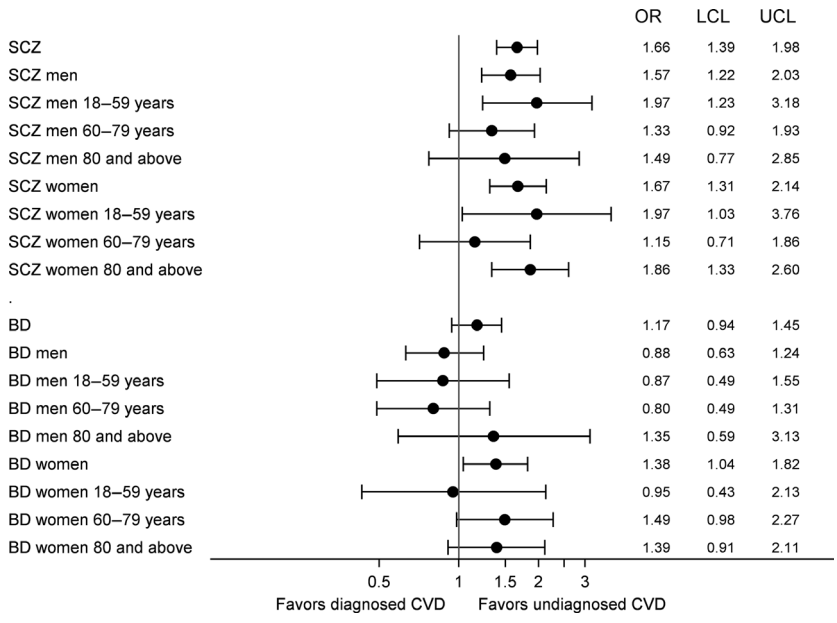


Fig. 2. Adjusted odds ratios with 95% upper (UCL) and lower (UCL) confidence limits for not being diagnosed with cardiovascular disease prior to cardiovascular death in individuals with schizophrenia or bipolar disorder, according to sex and age-group.

younger, more often at home (SCZ only), less often in a nursing home, more often at places outside home and healthcare institutions (BD only), and more often from IHD (SCZ only) (Table S2). They also had fewer healthcare contacts in primary care, fewer admissions and out-patient visits in specialized somatic care prior to death, and more recorded SUD than individuals with SMI and diagnosed CVD.

Discussion

In this study based on the entire Norwegian population, we found that men and women with SCZ and women with BD were more likely to be undiagnosed with CVD prior to cardiovascular death, even though most had been in contact with primary or specialized somatic care prior to death. The higher odds of undiagnosed CVD applied to all main causes of cardiovascular death and was most pronounced in the youngest.

The higher level of undiagnosed CVD prior to cardiovascular death in individuals with SCZ is in accordance with earlier studies reporting doubled risk of unforeseen death in individuals with SCZ, CVD being the most common cause (33), and also in accordance with studies reporting a decreased likelihood in individuals with SCZ of being diagnosed with somatic illness in the early courses of diseases (24, 47). It is also in accordance with a Swedish registry study, in which the proportion of individuals who died from IHD undiagnosed up to 1 month prior to an IHD death was higher in individuals with SCZ, compared to individuals without SCZ (23). Our study extends these earlier findings by documenting that the higher likelihood of undiagnosed CVD prior to death in individuals with SCZ may be related to the low age at death, and by documenting that the higher likelihood of undiagnosed CVD prior to death in individuals with SCZ applies to all main causes of cardiovascular death and is particularly pronounced for deaths from MI in women with SCZ. Our finding of similar odds of undiagnosed CVD prior to an IHD death in individuals with BD is also in accordance with earlier findings (29), but the increased odds of undiagnosed CVD prior to a cerebrovascular death in women with BD is a novel finding. Earlier studies have found an increased incidence of vascular disease in women with BD, but not in men with BD (48, 49). An increased risk of adverse illness course in women with BD has been reported (34) and may also contribute to this finding. We also observed higher levels of somatic out-patient visits in men with BD, including a higher level of somatic out-patient visits with a CVD diagnosis ($P = 0.001$, results not shown), indicating increased healthcare seeking and/or increased referral rates to specialized somatic care in men with BD, compared to women with BD. The finding may not be a stable finding, however, and should be replicated in independent studies.

We do not assume that cardiovascular deaths always can be prevented, as they may result from sudden and unpredictable events such as MI and stroke. Nevertheless, differences between groups found for the same causes of death in our study suggest that other mechanisms are also at work,

Table 3. Subgroup analyses showing odds ratios with 95% confidence intervals for not being diagnosed with CVD prior to cardiovascular death, according to sex, patient group, cause of death, and model specifications

	Crude OR (95% CI)§	Adjusted for age† OR (95% CI)§	Adjusted for age, SUD, and comorbidity‡ OR (95% CI)§
Both genders			
Ischemic heart disease			
Schizophrenia	**2.40** (1.87–3.07)	**1.64** (1.26–2.12)	**1.70** (1.30–2.22)
Bipolar disorder	1.23 (0.88–1.73)	0.84 (0.59–1.19)	0.92 (0.64–1.31)
Myocardial infarction			
Schizophrenia	**2.49** (1.83–3.39)	**1.85** (1.33–2.56)	**1.99** (1.42–2.78)
Bipolar disorder	1.37 (0.92–2.05)	1.05 (0.69–1.60)	1.14 (0.74–1.74)
Other forms of heart disease (I30–I52)			
Schizophrenia	**2.69** (1.91–3.79)	**1.82** (1.27–2.61)	**1.85** (1.28–2.67)
Bipolar disorder	**1.67** (1.06–2.65)	1.00 (0.62–1.61)	1.08 (0.67–1.76)
Cerebrovascular			
Schizophrenia	**1.77** (1.23–2.54)	1.43 (0.99–2.06)	**1.47** (1.01–2.13)
Bipolar disorder	**1.74** (1.19–2.54)	1.38 (0.93–2.03)	1.45 (0.98–2.15)
Men			
Ischemic heart disease			
Schizophrenia	**2.40** (1.72–3.34)	1.42 (0.99–2.03)	**1.47** (1.02–2.11)
Bipolar disorder	1.24 (0.76–2.00)	0.70 (0.42–1.16)	0.78 (0.47–1.31)
Myocardial infarction			
Schizophrenia	**2.00** (1.30–3.09)	1.40 (0.87–2.23)	1.48 (0.92–2.38)
Bipolar disorder	**1.65** (0.93–2.90)	1.09 (0.60–2.00)	1.20 (0.65–2.21)
Other forms of heart disease (I30–I52)			
Schizophrenia	**3.20** (1.95–5.26)	1.73 (0.99–3.02)	1.73 (0.98–3.06)
Bipolar disorder	1.95 (0.96–3.96)	0.90 (0.43–1.90)	0.98 (0.46–2.09)
Cerebrovascular			
Schizophrenia	**2.78** (1.62–4.78)	**1.80** (1.02–3.16)	1.75 (0.99–3.09)
Bipolar disorder	1.32 (0.67–2.58)	0.91 (0.45–1.81)	0.96 (0.47–1.92)
Women			
Ischemic heart disease			
Schizophrenia	**2.41** (1.67–3.50)	**1.85** (1.26–2.72)	**1.91** (1.29–2.83)
Bipolar disorder	1.26 (0.78–2.03)	0.94 (0.58–1.53)	0.99 (0.61–1.62)
Myocardial infarction			
Schizophrenia	**3.19** (2.06–4.93)	**2.47** (1.57–3.89)	**2.68** (1.68–4.27)
Bipolar disorder	1.20 (0.68–2.14)	0.97 (0.54–1.74)	1.03 (0.57–1.86)
Other forms of heart disease (I30–I52)			
Schizophrenia	**2.34** (1.46–3.76)	**1.82** (1.12–2.96)	**1.85** (1.13–3.03)
Bipolar disorder	1.50 (0.82–2.76)	1.06 (0.57–1.96)	1.14 (0.61–2.14)
Cerebrovascular			
Schizophrenia	1.30 (0.80–2.11)	1.13 (0.69–1.85)	1.23 (0.75–2.03)
Bipolar disorder	**2.04** (1.28–3.24)	**1.68** (1.05–2.71)	**1.77** (1.09–2.87)

CI, confidence interval; OR, odds ratio; SUD, substance use disorder.
†Adjusted for age-group at death (categories 18–49, 50–59, 60–69, 70–79, 80–89, and 90 and above).
‡Adjusted for age-group at death (see note †), SUD, and comorbidities (modified Charlson Index).
§Bold figures: Significant association at *P*-value < 0.05.

both at individual, provider, and system level. Current risk prediction algorithms for CVD have been shown to underestimate the risk in individuals with SCZ, particularly in younger men (50), and may likely lead to lower detection rates in individuals with SCZ compared to others. Also, unclear responsibility with regard to physical health examination in patients with SMI (51), complexity of care and misinterpretation of physical complaints as psychosomatic symptoms (52), as well as separation between primary and secondary health care and between somatic and psychiatric health care, may contribute to underdiagnosis. General stigma toward people with SMI (53), particularly those with comorbid SUD, has also been reported (54), although our results showed a negative association between recorded SUD and undiagnosed CVD. Given the overlap in genetic risk factors for SMI and CVD (16), it could be that individuals with SMI are more susceptible to CVD. Genetic risk for a severe outcome would under other circumstances imply an increased alertness in clinicians. Under these assumptions, reduced access to screening and treatment would have a disproportionate effect in the SMI population.

The ability to recognize somatic symptoms and seek timely somatic care may be impaired in individuals with SMI due to negative symptoms, cognitive impairment, and social isolation. Increased pain tolerance (55), as well as increased risk of silent CVD (56) not associated with traditional cardiovascular risk factors (57), has also been reported in individuals with SCZ, possibly affecting healthcare seeking. Reduced or delayed healthcare seeking has been reported earlier for older non-affective psychotic patients, especially regarding CVD (58).

In our study, undiagnosed CVD was associated with young age at death. Individuals with SCZ have increased the prevalence of risk factors for early cardiovascular mortality (59) and are at increased risk of dying at ages when healthcare providers may not usually suspect CVD. There is also a possibility that younger patients are prescribed higher doses of antipsychotic medicine due to more severe symptoms at an early stage in the disease course and hence are at higher risk of adverse cardiac effects such as arrhythmias, deviations in blood pressure, heart failure, myocarditis, and sudden death (60–65). Both typical and atypical antipsychotic medication have been associated with sudden cardiac death (66, 67), through mechanisms such as QTc interval lengthening (68), possibly leading to fatal arrhythmias, and myocarditis and cardiomyopathy associated with clozapine use (69). The possibility of more lethal, or faster progressing, CVD in individuals with SMI may also influence the odds for not having CVD diagnosed prior to cardiovascular death.

Strengths and limitations

The main strength of this study is the use of unselected, complete nationwide data on all individuals who died of CVD during a 6-year period, including complete diagnostic data from both primary

and specialized health care, and individuals without any healthcare contacts in the observation period prior to death. However, some limitations need attention. First, we had no information concerning history of CVD prior to the study period. Stable, long-term and currently untreated CVDs may thus have led to misclassification of undiagnosed CVD in this study. As individuals with SMI have higher lethality from CVD (70–72), our findings probably underestimate the real difference between individuals with and without SMI. It could be, however, that people with SMI to a larger extent live with, for example, untreated valve insufficiency, which is not treated due to contraindications to major surgery (such as smoking), although newer, less invasive techniques may have reduced this potential disparity. We did not have information on prescription of cardiovascular medication, but it is unlikely that such prescriptions would not be accompanied by a CVD diagnosis in primary care.

Second, we lacked information on antipsychotic prescriptions, which made us unable to study the association between antipsychotic medication and sudden cardiac death. We observed, however, a similar (SCZ) or lower (BD) likelihood of fatal arrhythmias in individuals with SMI, compared to individuals without SMI.

Third, we had no information on the severity of CVD. However, as the study included only deceased individuals, control for differences in medical need may be approximated by the fact that they all died from the same underlying causes of death. Also, studies of undiagnosed MI in the general population (73) and in individuals with SMI (71) have reported similar demographic characteristics, similar coronary risk profiles, and similar mortality among persons with diagnosed and previously undiagnosed MI.

Fourth, the validity of diagnoses is a concern when using administrative registry data. Previous studies have found high agreement between DSM-IV diagnosis and clinical diagnoses of SMI in the NPR (74), and valid information regarding stroke (75). Also, in other Nordic registries, the validity of cardiovascular diagnoses in general (76, 77), atrial fibrillation and atrial flutter (78), and intracerebral hemorrhage (79) have been found to be high, whereas the validity of heart failure diagnoses (80) and peripheral arterial disease diagnoses (81) may be questionable. The accuracy of diagnoses in the KUHR database has not yet been established. According to Statistics Norway, about 0.3% of main diagnoses set by the GP in the KUHR database in 2015 were assumed to have an incorrect diagnostic code (82), and the validity of diagnostic coding in general practice registries in other countries has been found good, particularly for chronic diseases (83). We included persons with a diagnosis of affective disorder (ICPC-2 code P73) in the BD group, which may have led to an inclusion of individuals with severe depression but not BD.

The CDR is found to provide high-quality information on causes of death (84). Autopsy is considered as the gold standard for determination of causes of death, but is infrequently undertaken in Norway. During the period 2008–2013, the proportion of autopsies in Norway remained stable at 7.5%, equally distributed between medical and forensic autopsies (85). A Norwegian study from 2011 reported very good agreement between autopsy findings and mortality statistics for both stroke and coronary heart disease in the CDR (86). An earlier Norwegian study investigating to what extent underlying cause of death based on the death certificate was changed when taking into account autopsy results, found a substantial (17%) underreporting of cardiovascular deaths, particularly in the young and old, and in women (87). The decision to perform an autopsy is, however, not made at random, and findings from such studies may therefore not be directly transferable to other cases. The most common error is that immediate or intermediate causes of death are registered as the underlying cause of death (88). We found, however, similar results when we included all deaths with CVD as underlying or contributing cause of death, as shown in the sensitivity analysis. We had no data on sudden death (ICD-10 code R98), possibly implying underestimated cardiovascular deaths. However, only about 2% of underlying causes of death in Norway in the years 2011–2016 were assigned to unknown or unspecified causes (R96–R99) (7). Longer postmortem time before discovery in individuals with SCZ compared to others has also been reported (89), possibly affecting the reliability of cause of death codes in individuals with SCZ.

Fifth, although it is possible to enter at least three diagnoses per primary care contact, 85% of these encounters had only one recorded diagnosis, both in individuals with and without SMI. There is therefore a possibility that only the SMI diagnosis was recorded, even if CVD may have been the subject of the consultation. However, among individuals with SMI, only 17% of the primary healthcare encounters included a SMI diagnosis, so it seems reasonable to assume that any recognized CVD would be recorded at some point in the observation period. Also, analysis with recorded CVD in specialized health care only as dependent variable

gave similar results, as shown in the sensitivity analysis.

Furthermore, individuals with SMI have a substantially increased risk of premature death from suicides and accidents, particularly in the youngest age-groups (10, 90). As persons with SMI included in our study must have lived long enough to develop CVD, this may have introduced survivor bias. Substance abuse and low socioeconomic status, which are associated with increased risk of accidental death, and also increased CVD risk, were, however, not associated with increased risk of undiagnosed IHD (23, 29) or increased risk of unforeseen death (33) in earlier studies.

Finally, the findings are representative of individuals with severe CVD in countries with publicly funded and readily available health services for both somatic and mental disorders.

Clinical implications

Persons with SMI constitute a subgroup at particularly high risk of early and severe CVD (50). In our study, almost all individuals with SMI with undiagnosed CVD prior to cardiovascular death utilized primary or specialized somatic care in the observation period preceding death, showing that opportunities for identification and management of cardiovascular disease exist. Hence, a diagnosis of SCZ or BD should act as a trigger for enhanced screening for CVD among the youngest patients, and antipsychotic medicine in younger patient groups should be carefully selected in order to minimize cardiovascular risk. Furthermore, there is a need to define more accurately the responsibility for maintaining follow-up and treatment of CVD risk factors and early CVD in patients with SMI. Albeit death from undiagnosed CVD cannot always be prevented, the results from our study indicate that improved health care at a structural level should be specifically directed toward younger patients. Improved recognition, monitoring, and treatment of individual CVD risk factors should be stressed. Further research is strongly needed, to investigate age-differentiated risk factors and interventions both at the system level and at the individual level.

Acknowledgements

This study was supported by a research grant from the Northern Norway Regional Health Authority (PFP1236-15).

Declaration of interest

None.

References

1. Kilbourne AM, Morden NE, Austin K et al. Excess heart-disease-related mortality in a national study of patients with mental disorders: identifying modifiable risk factors. Gen Hosp Psychiatry 2009;**31**:555–563.
2. Foguet-Boreu Q, Fernandez San Martin MI, Flores Mateo G et al. Cardiovascular risk assessment in patients with a severe mental illness: a systematic review and meta-analysis. BMC Psychiatry, 2016;**16**:141.
3. Fan Z, Wu Y, Shen J, Ji T, Zhan R. Schizophrenia and the risk of cardiovascular diseases: a meta-analysis of thirteen cohort studies. J Psychiatr Res 2013;**47**:1549–1556.
4. Prieto ML, Cuéllar-Barboza AB, Bobo WV et al. Risk of myocardial infarction and stroke in bipolar disorder: a systematic review and exploratory meta-analysis. Acta Psychiatr Scand 2014;**130**:342–353.
5. Westman J, Hällgren J, Wahlbeck K, Erlinge D, Alfredsson L, Osby U. Cardiovascular mortality in bipolar disorder: a population-based cohort study in Sweden. BMJ Open 2013;**3**:e002373.
6. Hjorthøj C, Stürup AE, McGrath JJ, Nordentoft M. Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis. Lancet Psychiatry 2017;**4**:295–301.
7. Norwegian Institute of Public Health. Dødsårsaker, nøkkeltall (LHF) – per 100 000, standardisert [Causes of death, key figures (LHF) – per 100,000, standardized]. 2018 [January 15, 2019]; Available from: http://www.norgeshelsa.no/norgeshelsa/
8. Laursen TM, Nordentoft M. Heart disease treatment and mortality in schizophrenia and bipolar disorder – changes in the Danish population between 1994 and 2006. J Psychiatr Res 2011;**45**:29–35.
9. Ösby U, Westman J, Hällgren J, Gissler M. Mortality trends in cardiovascular causes in schizophrenia, bipolar and unipolar mood disorder in Sweden 1987–2010. Eur J Public Health 2016;**26**:867–871.
10. Heiberg IH, Jacobsen BK, Nesvåg R et al. Total and cause-specific standardized mortality ratios in patients with schizophrenia and/or substance use disorder. PLoS One 2018;**13**:e0202028.
11. Hansen V, Jacobsen BK, Arnesen E. Cause-specific mortality in psychiatric patients after deinstitutionalisation. Br J Psychiatry 2001;**179**:438–443.
12. Høye A, Jacobsen BK, Hansen V. Increasing mortality in schizophrenia: are women at particular risk? A follow-up of 1111 patients admitted during 1980–2006 in Northern Norway. Schizophr Res 2011;**132**:228–232.
13. Manrique-Garcia E, Sidorchuk A, Hallqvist J, Moradi T. Socioeconomic position and incidence of acute myocardial infarction: a meta-analysis. J Epidemiol Community Health 2011;**65**:301–309.
14. von Hausswolff-Juhlin Y, Bjartveit M, Lindström E, Jones P. Schizophrenia and physical health problems. Acta Psychiatr Scand Suppl 2009;**000**:15–21.
15. Tek C, Kucukgoncu S, Guloksuz S, Woods SW, Srihari VH, Annamalai A. Antipsychotic-induced weight gain in first-episode psychosis patients: a meta-analysis of differential effects of antipsychotic medications. Early Interv Psychiatry 2016;**10**:193–202.
16. Wang K, Gaitsch H, Poon H, Cox NJ, Rzhetsky A. Classification of common human diseases derived from shared genetic and environmental determinants. Nat Genet 2017;**49**:1319–1325.

17. Druss BG, Bradford WD, Rosenheck RA, Radford MJ, Krumholz HM. Quality of medical care and excess mortality in older patients with mental disorders. Arch Gen Psychiatry 2001;**58**:565–572.
18. Mitchell AJ, Lord O. Do deficits in cardiac care influence high mortality rates in schizophrenia? A systematic review and pooled analysis. J Psychopharmacol 2010;**24**(4 Suppl):69–80.
19. Lord O, Malone D, Mitchell AJ. Receipt of preventive medical care and medical screening for patients with mental illness: a comparative analysis. Gen Hosp Psychiatry 2010;**32**:519–543.
20. Mitchell AJ, Delaffon V, Vancampfort D, Correll CU, De Hert M. Guideline concordant monitoring of metabolic risk in people treated with antipsychotic medication: systematic review and meta-analysis of screening practices. Psychol Med 2012;**42**:125–147.
21. Ayerbe L, Forgnone I, Addo J, Siguero A, Gelati S, Ayis S. Hypertension risk and clinical care in patients with bipolar disorder or schizophrenia; a systematic review and meta-analysis. J Affect Disord 2017;**225**:665–670.
22. Gabilondo A, Alonso-Moran E, Nuño-Solinis R, Orueta JF, Iruin A. Comorbidities with chronic physical conditions and gender profiles of illness in schizophrenia. Results from PREST, a new health dataset. J Psychosom Res, 2017;**93**:102–109.
23. Crump C, Winkleby MA, Sundquist K, Sundquist J. Comorbidities and mortality in persons with schizophrenia: a Swedish national cohort study. Am J Psychiatry 2013;**170**:324–333.
24. MuNk-Jørgensen P, Mors O, Mortensen PB, Ewald H. The schizophrenic patient in the somatic hospital. Acta Psychiatr Scand Suppl 2000;**102**:96–99.
25. Lahti M, Tiihonen J, Wildgust H et al. Cardiovascular morbidity, mortality and pharmacotherapy in patients with schizophrenia. Psychol Med 2012;**42**: 2275–2285.
26. Laursen TM, Mortensen PB, MacCabe JH, Cohen D, Gasse C. Cardiovascular drug use and mortality in patients with schizophrenia or bipolar disorder: a Danish population-based study. Psychol Med 2014;**44**:1625–1637.
27. Skrede S, Tvete IF, Tanum L, Steen VM, Bramness JG. Incident users of antipsychotic agents and future use of cholesterol-lowering drugs: an observational, pharmacoepidemiologic study. J Clin Psychiatry 2015;**76**:e111–e116.
28. Pitman AL, Osborn DP, Wright CA, Nazareth I, King MB. Cardiovascular screening of people with severe mental illness in England: views of service users and providers. Psychiatr Serv 2011;**62**:1338–1345.
29. Crump C, Sundquist K, Winkleby MA, Sundquist J. Comorbidities and mortality in bipolar disorder: a Swedish national cohort study. JAMA Psychiatry 2013;**70**:931–939.
30. World Health Organization. Prevention of cardiovascular disease: guidelines for assessment and management of total cardiovascular risk. Geneva, Switzerland: World Health Organization, 2007.
31. Cohn JN, Hoke L, Whitwam W et al. Screening for early detection of cardiovascular disease in asymptomatic individuals. Am Heart J 2003;**146**:679–685.
32. Newby DE, Adamson PD, Berry C et al. Coronary CT angiography and 5-year risk of myocardial infarction. N Engl J Med 2018;**379**:924–933.
33. Copeland LA, Zeber JE, Rosenheck RA, Miller AL. Unforeseen inpatient mortality among veterans with schizophrenia. Med Care 2006;**44**:110–116.
34. Erol A, Winham SJ, McElroy SL et al. Sex differences in the risk of rapid cycling and other indicators of adverse illness course in patients with bipolar I and II disorder. Bipolar Disord 2015;**17**:670–676.
35. Petkari E, Mayoral F, Moreno-Kustner B. Gender matters in schizophrenia-spectrum disorders: results from a health-care users epidemiological study in Malaga, Spain. Compr Psychiatry 2017;**72**:136–143.
36. Abel KM, Drake R, Goldstein JM. Sex differences in schizophrenia. Int Rev Psychiatry 2010;**22**:417–428.
37. Phan HT, Blizzard CL, Reeves MJ et al. Sex differences in long-term mortality after stroke in the INSTRUCT (INternational STRoke oUtComes sTudy): a meta-analysis of individual participant data. Circ Cardiovasc Qual Outcomes 2017;**10**:e003436.
38. Campi TR Jr, George S, Villacís D, Ward-Peterson M, Barengo NC, Zevallos JC. Effect of charted mental illness on reperfusion therapy in hospitalized patients with an acute myocardial infarction in Florida. Medicine (Baltimore) 2017;**96**:e7788.
39. Kontopantelis E, Olier I, Planner C et al. Primary care consultation rates among people with and without severe mental illness: a UK cohort study using the Clinical Practice Research Datalink. BMJ Open 2015;**5**:e008650.
40. Pedersen AG, Ellingsen CL. Data quality in the causes of death registry. Tidsskr Nor Laegeforen 2015;**135**:768–770.
41. Helsedirektoratet [The Norwegian Directorate of Health]. *Aktivitetsdata for avtalespesialister 2009 [Data on activities by specialists in private practice 2009]*. 2010; Available from: https://helsedirektoratet.no/Lists/Publikasjoner/Attachments/504/Aktivitetsdata-for-avtalespesialister-2009-IS-1818.pdf
42. Lützen J, Fuglset AS, Dahlstrøm I. Aktivitetsdata for avtalespesialister 2015 [Data on activities by specialists in private practice 2015]. Oslo: Helsedirektoratet [The Norwegian Directorate of Health], 2015.
43. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;**40**:373–383.
44. Quan H, Li B, Couris CM et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol 2011;**173**:676–682.
45. Elliott AC, Hynan LS. A SAS® macro implementation of a multiple comparison post hoc test for a Kruskal–Wallis analysis. Comput Methods Programs Biomed 2011;**102**:75–80.
46. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet, 2015;**385**:117–171.
47. Oud MJ, Meyboom-de Jong B. Somatic diseases in patients with schizophrenia in general practice: their prevalence and health care. BMC Fam Pract, 2009;**10**:32.
48. Fiedorowicz JG, He J, Merikangas KR. The association between mood and anxiety disorders with vascular diseases and risk factors in a nationally representative sample. J Psychosom Res 2011;**70**:145–154.
49. Swain NR, Lim CC, Levinson D et al. Associations between DSM-IV mental disorders and subsequent non-fatal, self-reported stroke. J Psychosom Res 2015;**79**:130–136.
50. McLean G, Martin JL, Martin DJ, Guthrie B, Mercer SW, Smith DJ. Standard cardiovascular disease risk algorithms underestimate the risk of cardiovascular disease in schizophrenia: evidence from a national primary care database. Schizophr Res 2014;**159**:176–181.

51. De Hert M, Cohen D, Bobes J et al. Physical illness in patients with severe mental disorders. II. Barriers to care, monitoring and treatment guidelines, plus recommendations at the system and individual level. World Psychiatry, 2011;**10**:138–151.
52. Jones S, Howard L, Thornicroft G. 'Diagnostic overshadowing': worse physical health care for people with mental illness. Acta Psychiatr Scand 2008;**118**:169–171.
53. Harangozo J, Reneses B, Brohan E et al. Stigma and discrimination against people with schizophrenia related to medical services. Int J Soc Psychiatry 2014;**60**:359–366.
54. Schomerus G, Lucht M, Holzinger A, Matschinger H, Carta MG, Angermeyer MC. The stigma of alcohol dependence compared with other mental disorders: a review of population studies. Alcohol Alcohol 2011;**46**:105–112.
55. Stubbs B, Thompson T, Acaster S, Vancampfort D, Gaughran F, Correll CU. Decreased pain sensitivity among people with schizophrenia: a meta-analysis of experimental pain induction studies. Pain 2015;**156**:2121–2131.
56. Nielsen J, Juel J, Alzuhairi KS et al. Unrecognised myocardial infarction in patients with schizophrenia. Acta Neuropsychiatr 2015;**27**:106–112.
57. Weir-McCall JR, Fitzgerald K, Papagiorcopulo CJ et al. Prevalence of unrecognized myocardial infarction in a low-intermediate risk asymptomatic cohort and its relation to systemic atherosclerosis. Eur Heart J Cardiovasc Imaging 2017;**18**:657–662.
58. Swildens W, Termorshuizen F, de Ridder A, Smeets H, Engelhard IM. Somatic care with a psychotic disorder. lower somatic health care utilization of patients with a psychotic disorder compared to other patient groups and to controls without a psychiatric diagnosis. Adm Policy Ment Health, 2016;**43**:650–662.
59. Chung KH, Chen PH, Kuo CJ, Tsai SY, Huang SH, Wu WC. Risk factors for early circulatory mortality in patients with schizophrenia. Psychiatry Res 2018;**267**:7–11.
60. Straus SM, Bleumink GS, Dieleman JP et al. Antipsychotics and the risk of sudden cardiac death. Arch Intern Med 2004;**164**:1293–1297.
61. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical antipsychotic drugs and the risk of sudden cardiac death. N Engl J Med 2009;**360**:225–235.
62. Ifteni P, Correll CU, Burtea V, Kane JM, Manu P. Sudden unexpected death in schizophrenia: autopsy findings in psychiatric inpatients. Schizophr Res 2014;**155**:72–76.
63. Hou PY, Hung GC, Jhong JR, Tsai SY, Chen CC, Kuo CJ. Risk factors for sudden cardiac death among patients with schizophrenia. Schizophr Res 2015;**168**:395–401.
64. Khasawneh FT, Shankar GS. Minimizing cardiovascular adverse effects of atypical antipsychotic drugs in patients with schizophrenia. Cardiol Res Pract 2014;**2014**:273060.
65. Torniainen M, Mittendorfer-Rutz E, Tanskanen A et al. Antipsychotic treatment and mortality in schizophrenia. Schizophr Bull 2015;**41**:656–663.
66. Honkola J, Hookana E, Malinen S et al. Psychotropic medications and the risk of sudden cardiac death during an acute coronary event. Eur Heart J 2012;**33**:745–751.
67. Li KJ, Greenstein AP, Delisi LE. Sudden death in schizophrenia. Curr Opin Psychiatry 2018;**31**:169–175.
68. Zhai D, Lang Y, Dong G et al. QTc interval lengthening in first-episode schizophrenia (FES) patients in the earliest stages of antipsychotic treatment. Schizophr Res 2017;**179**:70–74.
69. Khan AA, Ashraf A, Baker D et al. Clozapine and incidence of myocarditis and sudden death – Long term Australian experience. Int J Cardiol 2017;**238**:136–139.
70. Kugathasan P, Laursen TM, Grøntved S, Jensen SE, Aagaard J, Nielsen RE. Increased long-term mortality after myocardial infarction in patients with schizophrenia. Schizophr Res 2018;**199**:103–108.
71. Bodén R, Molin E, Jernberg T, Kieler H, Lindahl B, Sundström J. Higher mortality after myocardial infarction in patients with severe mental illness: a nationwide cohort study. J Intern Med 2015;**277**:727–736.
72. Prior A, Laursen TM, Larsen KK et al. Post-stroke mortality, stroke severity, and preadmission antipsychotic medicine use–a population-based cohort study. PLoS One 2014;**9**:e84103.
73. Sheifer SE, Manolio TA, Gersh BJ. Unrecognized myocardial infarction. Ann Intern Med 2001;**135**:801–811.
74. Nesvåg R, Jönsson EG, Bakken IJ et al. The quality of severe mental disorder diagnoses in a national health registry as compared to research diagnoses based on structured interview. BMC Psychiatry 2017;**17**:93.
75. Varmdal T, Bakken IJ, Janszky I et al. Comparison of the validity of stroke diagnoses in a medical quality register and an administrative health register. Scand J Public Health 2016;**44**:143–149.
76. Sundbøll J, Adelborg K, Munch T et al. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. BMJ Open 2016;**6**: e012832.
77. Pajunen P, Koukkunen H, Ketonen M et al. The validity of the Finnish Hospital Discharge Register and Causes of Death Register data on coronary heart disease. Eur J Cardiovasc Prev Rehabil 2005;**12**:132–137.
78. Rix TA, Riahi S, Overvad K, Lundbye-Christensen S, Schmidt EB, Joensen AM. Validity of the diagnoses atrial fibrillation and atrial flutter in a Danish patient registry. Scand Cardiovasc J 2012;**46**:149–153.
79. Hald SM, Kring Sloth C, Hey SM et al. Intracerebral hemorrhage: positive predictive value of diagnosis codes in two nationwide Danish registries. Clin Epidemiol 2018;**10**:941–948.
80. Delekta J, Hansen SM, AlZuhairi KS, Bork CS, Joensen AM. The validity of the diagnosis of heart failure (I50.0–I50.9) in the Danish National Patient Register. Dan Med J, 2018;**65**:A5470.
81. Lasota AN, Overvad K, Eriksen HH, Tjønneland A, Schmidt EB, Grønholdt MM. Validity of peripheral arterial disease diagnoses in the danish national patient registry. Eur J Vasc Endovasc Surg 2017;**53**:679–685.
82. Statistics Norway. *Allmennlegetjenesten, 2015 [Public Health Services, 2015]*, 2015 [June 24th, 2018]; Available from: https://www.ssb.no/helse/statistikker/fastlegetj/aar/2016-06-08?fane=om
83. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. Br J Gen Pract 2010;**60**:e128–e136.
84. Phillips DE, Lozano R, Naghavi M et al. A composite metric for assessing data on mortality and causes of death: the vital statistics performance index. Popul Health Metr 2014;**12**:14.
85. Folkehelseinstituttet [The Norwegian Institute of Public Health]. Legemeldinger om dødsfall er grunnlaget for dødsårsaksstatistikken [Medical reports on deaths are the basis for the cause of death statistics]. 2015, 25.03.2015 [cited 2019 January 22, 2019]; Available from: https://www.fhi.no/hn/helseregistre-og-registre/dodsarsaksregisteret/legemeldinger-om-dodsfall/.
86. Gulsvik AK, Gulsvik A, Svendsen E, Mæhle BO, Thelle DS, Wyller TB. Diagnostic validity of fatal cerebral

strokes and coronary deaths in mortality statistics: an autopsy study. Eur J Epidemiol 2011;**26**:221–228.
87. Alfsen GC, Mæhlen J. Obduksjonens betydning for registrering av dødsårsak [The value of autopsies for determining the cause of death]. Tidsskr Nor Laegeforen 2012;**132**:147–151.
88. Eriksson A, Stenlund H, Ahlm K et al. Accuracy of death certificates of cardiovascular disease in a community intervention in Sweden. Scand J Public Health 2013;**41**:883–889.
89. Nilsson LL, Logdberg B. Dead and forgotten–postmortem time before discovery as indicator of social isolation and inadequate mental healthcare in schizophrenia. Schizophr Res 2008;**102**:337–339.
90. Nordentoft M, Madsen T, Fedyszyn I. Suicidal behavior and mortality in first-episode psychosis. J Nerv Ment Dis 2015;**203**:387–392.

Supporting Information

Additional Supporting Information may be found in the online version of this article:
Figure S1. Results of sensitivity analyses.
Table S1. List of diagnoses describing psychiatric comorbidity.
Table S2. Characteristics of deaths, health care utilization and comorbidity in the subgroups with undiagnosed and diagnosed CVD prior to cardiovascular death.

Supporting Information

Table S1. List of diagnoses describing psychiatric comorbidity

Variable	ICD-10 code	ICPC-2 code	Description
Dementia	F00		Dementia in Alzheimer disease
	F01		Vascular dementia
	F02		Dementia in other diseases classified elsewhere
	F03		Unspecified dementia
	F05.1		Delirium superimposed on dementia
	G30		Alzheimer disease
	G31.1		Senile degeneration of brain, not elsewhere classified
		P70	Dementia
Substance use related disorders	F10-16, F18-F19		Mental and behavioral disorders due to use of psychoactive substances, except tobacco (F17)
	E24.4		Alcohol-induced pseudo-Cushing syndrome
	E52		Niacin deficiency [pellagra]
	G31.2		Degeneration of nervous system due to alcohol
	G62.1		Alcoholic polyneuropathy
	G72.1		Alcoholic myopathy
	I42.6		Alcoholic cardiomyopathy
	K29.2		Alcoholic gastritis
	K70		Alcoholic liver disease
	K86.0		Alcohol-induced chronic pancreatitis
	O35.4		Maternal care for (suspected) damage to fetus from alcohol
	O35.5		Maternal care for (suspected) damage to fetus by drugs
	Z50.2		Alcohol rehabilitation
	Z50.3		Drug rehabilitation
	Z71.4		Alcohol abuse counselling and surveillance
	Z71.5		Drug abuse counselling and surveillance
	Z72.1		Alcohol use
	Z72.2		Drug use
		P15	Chronic alcohol abuse
		P16	Acute alcohol abuse
		P18	Medication abuse
		P19	Drug abuse

Table S2. Characteristics of deaths, health care utilization and comorbidity in the subgroups with undiagnosed and diagnosed CVD prior to cardiovascular death.

	Schizophrenia		Bipolar disorder		No severe mental illness		p-value	Post hoc comparisons
Individuals with undiagnosed CVD prior to CVD death								
Deaths, n	186		112		8,020			
Age at death, mean (SD)	66.1	(17.0)	68.5	(14.7)	76.8	(16.4)	<.0001	SCZ, BD < No SMI
Age 18-59 at death, n (%)	73	(39.2)	31	(27.7)	1,351	(16.8)	<.0001	No SMI < BD < SCZ
Age 60-79 at death, n (%)	61	(32.8)	50	(44.6)	2,475	(30.9)	0.007	No SMI < BD
Age ≥ 80 at death, n (%)	52	(28.0)	31	(27.7)	4,194	(52.3)	<.0001	SCZ, BD < No SMI
Place of death, n (%)								
Home	63	(33.9)	32	(28.6)	1,833	(22.9)	0.001	No SMI < SCZ
Hospital	46	(24.7)	41	(36.6)	2,378	(29.7)	0.093	-
Nursing home	54	(29.0)	26	(23.2)	3,051	(38.0)	0.000	SCZ, BD < no SMI
Other or unknown	23	(12.4)	13	(11.6)	758	(9.5)	0.309	-
Patients according to health care sector, n (%)								
GP or emergency room	164	(88.2)	109	(97.3)	6,313	(78.7)	<.0001	No SMI < SCZ, BD
Specialized somatic care	135	(72.6)	94	(83.9)	5,589	(69.7)	0.004	No SMI < BD
No health care use	9	(4.8)	1	(0.9)	986	(12.3)	<.0001	SCZ, BD < No SMI
Health care utilization per person-year, median (IQR)								
GP visits	3.7	(0.9-7.5)	7.3	(3.1-13.5)	1.7	(0.2-4.7)	<.0001	No SMI < SCZ < BD
Emergency room visits	0.2	(0.0-0.5)	0.2	(0.0-0.6)	0.0	(0.0-0.3)	<.0001	No SMI < SCZ, BD
Somatic admissions	0.0	(0.0-0.23)	0.2	(0.0-0.5)	0.0	(0.0-0.20)	<.0001	No SMI < SCZ < BD
Somatic outpatient visits	0.3	(0.0-1.2)	0.8	(0.2-2.1)	0.4	(0.0-1.3)	0.001	SCZ, No SMI < BD
Individuals with diagnosed CVD prior to CVD death								
Deaths, n	628		561		62,944			
Age at death, mean (SD)	78.9	(12.4)	77.1	(12.7)	84.3	(10.2)	<.0001	BD < SCZ < No SMI
Age 18-59 at death, n (%)	49	(7.8)	52	(9.3)	1,740	(2.8)	<.0001	No SMI < SCZ, BD
Age 60-79 at death, n (%)	237	(37.7)	236	(42.1)	13,824	(22.0)	<.0001	No SMI < SCZ, BD
Age ≥ 80 at death, n (%)	342	(54.5)	273	(48.7)	47,380	(75.3)	<.0001	SCZ, BD < No SMI
Place of death, n (%)								
Home	110	(17.5)	136	(24.2)	9,821	(15.6)	<.0001	SCZ, No SMI < BD
Hospital	173	(27.5)	176	(31.4)	21,825	(34.7)	0.000	SCZ < No SMI
Nursing home	319	(50.8)	228	(40.6)	29,006	(46.1)	0.002	BD < SCZ, No SMI
Other or unknown	26	(4.1)	21	(3.7)	2,292	(3.6)	0.797	-
Patients according to health care sector, n (%)								
GP or emergency room	607	(96.7)	556	(99.1)	61,966	(98.4)	0.001	SCZ < BD, No SMI
Specialized somatic care	601	(95.7)	552	(98.4)	61,189	(97.2)	0.017	SCZ < BD
No health care use	1	(0.2)	0	(0.0)	71	(0.1)	0.685	-
Health care utilization per person-year, median (IQR)								
GP visits	6.9	(3.1-13.6)	9.7	(5.5-16.0)	7.7	(4.1-13.2)	<.0001	SCZ < No SMI < BD
Emergency room visits	0.4	(0.1-1.0)	0.5	(0.2-1.1)	0.3	(0.1-0.7)	<.0001	NO SMI < SCZ < BD
Somatic admissions	0.5	(0.3-1.0)	0.6	(0.3-1.1)	0.5	(0.2-1.0)	<.0001	SCZ, No SMI < BD
Somatic outpatient visits	1.2	(0.5-2.5)	1.8	(0.8-3.6)	1.7	(0.7-3.4)	<.0001	SCZ < BD, No SMI

Abbreviations: CVD, Cardiovascular disease; SCZ, Schizophrenia; BD, Bipolar disorder; SMI, Severe mental illness; GP, General practitioner; SD, Standard Deviation; IQR, Interquartile range.

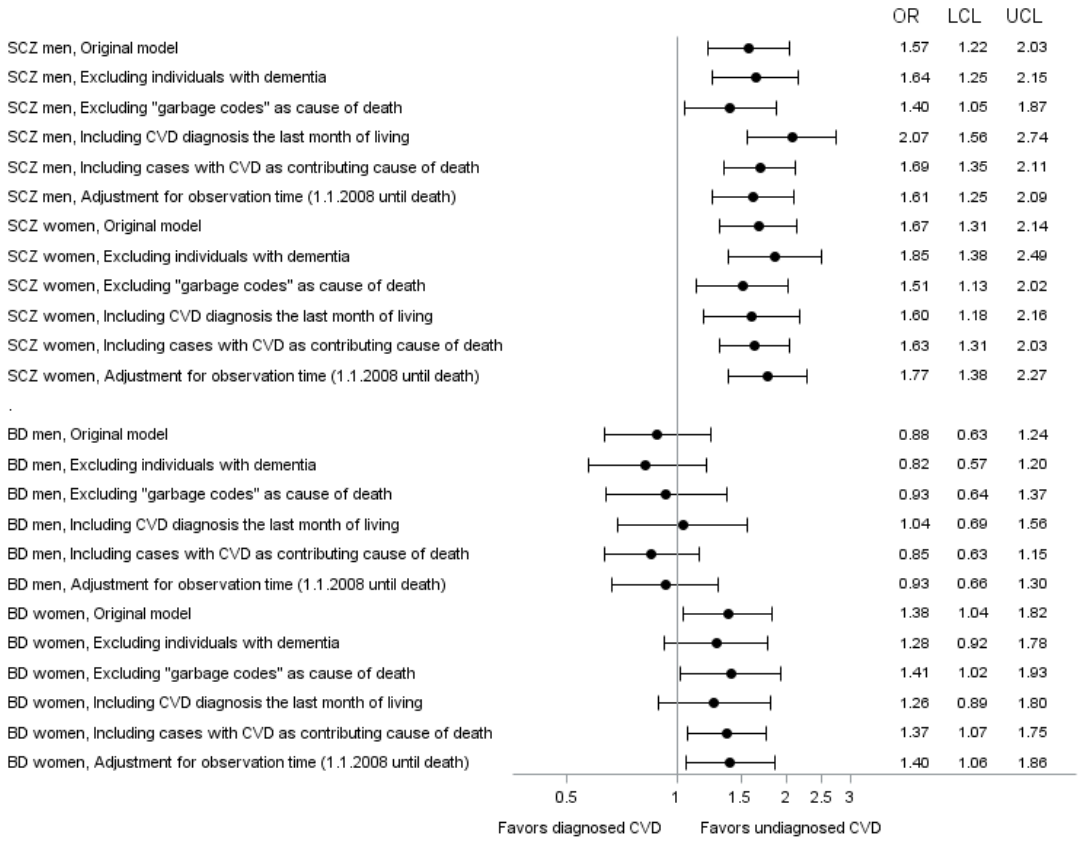


Figure S1. Results of sensitivity analyses. Adjusted Odds Ratios (OR) with 95% upper (UCL) and lower (UCL) Confidence Limits for not being diagnosed with cardiovascular disease (CVD) prior to cardiovascular death in individuals with schizophrenia (SCZ) or bipolar disorder (BD), according sex, patient group and differing inclusion criteria.

Paper III

Diagnostic tests and treatment procedures prior to cardiovascular death in individuals with severe mental illness

Running title: CVD prevention and treatment in SMI patients

Ina H. Heiberg[1]
Ragnar Nesvåg[2,3]
Lise Balteskard[1]
Jørgen G. Bramness[3,4]
Christina M. Hultman[5,6]
Øyvind Næss[7,8]
Ted Reichborn-Kjennerud[7,9]
Eivind Ystrom[9,10,11]
Bjarne K. Jacobsen[1,12,13]
Anne Høye[1,3,14]

[1]Center for Clinical Documentation and Evaluation (SKDE), Tromsø, Norway
[2]Norwegian Medical Association, Oslo, Norway
[3]Department of Clinical Medicine, UiT - The Arctic University of Norway, Tromsø, Norway
[4]Norwegian National Advisory Unit on Concurrent Substance Abuse and Mental Health Disorders, Innlandet Hospital Trust, Hamar, Norway
[5]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
[6]Icahn School of Medicine, Mt Sinai Hospital, New York, USA
[7]Institute of Clinical Medicine, University of Oslo, Oslo, Norway
[8]Institute of Health and Society, University of Oslo, Oslo, Norway
[9]Department of Mental Disorders, Norwegian Institute of Public Health, Oslo, Norway.
[10]PROMENTA research center, Department of Psychology, University of Oslo, Oslo, Norway.
[11]PharmacoEpidemiology and Drug Safety Research Group, School of Pharmacy, University of Oslo, Norway
[12]Department of Community Medicine, UiT - The Arctic University of Norway, Tromsø, Norway
[13] Centre for Sami Health Research, Department of Community Medicine, UiT - The Arctic University of Norway, Tromsø, Norway.
[14]Division of Mental Health and Substance Abuse, University Hospital of North Norway, Tromsø, Norway.

Contact information
Ina H. Heiberg
Center for Clinical Documentation and Evaluation (SKDE), postbox 6, 9038 Tromsø, Norway
Email: ina.heiberg@helse-nord.no
Telephone no. +47 45451195

Acknowledgments
This study was supported by a research grant from the Northern Norway Regional Health Authority (PFP1236-15).

Data availability statement
The data that support the findings of this study are available from the Norwegian Patient Registry, the Norwegian Directorate of Health (the KUHR database) and the Norwegian Cause of Death Registry. Restrictions apply to the availability of these data, which were used under license for this study. For information on how to access the data see https://www.helsedirektoratet.no/tema/statistikk-registre-og-rapporter/helsedata-og-helseregistre/norsk-pasientregister-npr/sok-om-data-fra-npr

Declaration of Interest
No conflicting interests to declare.

Abstract

Objective: To examine whether patients with schizophrenia (SCZ) or bipolar disorder (BD) had lower prevalence of diagnostic testing and treatment of cardiovascular disease (CVD) in primary or specialized health care.
Methods: A nationwide study of 72,385 individuals who died from CVD, of whom 814 and 673, respectively, were previously diagnosed with SCZ or BD. Log-binomial regression was applied to study the impact of SMI on uptake of diagnostic tests (e.g. blood pressure, glucose or HbA1c measurements, electrocardiography, echocardiography, coronary angiography, ultrasound of peripheral vessels) and invasive cardiovascular treatment (i.e. revascularization, arrhythmia treatment and vascular surgery).
Results: Patients with SCZ or BP had similar prevalence of cardio-metabolic diagnostic tests in primary care as patients without SMI, but patients with SCZ had lower prevalence of specialized CVD examinations (PR 0.78; 95% CI 0.73-0.85). Overall, subjects with SMI had lower prevalence of invasive cardiovascular treatment (PR 0.58 (95% CI 0.49-0.70) for SCZ and 0.78 (95% CI 0.66-0.92) for BD), but the prevalence of invasive cardiovascular treatment did not differ between those with and without SMI when CVD was diagnosed prior to death.
Conclusion: Access to specialized cardiovascular examinations and treatment are the main barriers to equality in cardiovascular treatment for those with SMI.

Keywords: Schizophrenia, Bipolar Disorder, Cardiovascular Diseases, Health Services

Significant Outcomes

- Patients with SCZ had lower prevalence of specialized CVD examinations, and patients with SCZ and BD lower prevalence of invasive cardiovascular treatment prior to cardiovascular death, implicating need of strengthened efforts to prevent, detect and treat CVD in these individuals.
- The prevalence of invasive cardiovascular treatment did not differ between those with and without SMI when CVD was diagnosed prior to death.
- Underutilization of specialized diagnostic tests rather than reduced access to primary care or disparate invasive treatment of acknowledged CVD may be the most important driver of disparities in the SMI population.

Limitations

- The level of screening/monitoring of CVD risk factors may be underestimated as we lacked precise information regarding the purpose and content of some common diagnostic tests included in broad batteries of biomarkers, some of which, but not all, measure CVD risk factors.
- The diagnostic quality has not been established for all causes of death and all disease categories.

Introduction

Equal access to health care for equal medical need is a core value in countries with universal health care. Although individuals with schizophrenia (SCZ) or bipolar disorder (BD) (henceforth referred to as severe mental illness, SMI) have higher prevalence of risk factors for cardiovascular disease (CVD)[1], and higher cardiovascular morbidity [2] and mortality [3, 4], inequalities in access to or uptake of health services for prevention and treatment of CVD have repeatedly been reported in these individuals [5-9]. Current guidelines for management of psychosis recommend regular assessments of smoking, diet, physical activity, weight, waist circumference, blood pressure, fasting blood glucose, glycated hemoglobin (HbA1c) and fasting lipids [10].

Meta-analyses mainly based on studies from the US, report inferior preventive care of CVD in individuals with SMI regarding metabolic monitoring [5, 6], blood pressure monitoring [5], hypertension treatment [7] and cardiovascular prescriptions [8], and also lower likelihood of invasive coronary procedures such as coronary angiography, percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) [9]. Lower likelihood of cardiovascular risk factor monitoring [11], cardiovascular prescriptions [12-16], and acute treatment of CVD [17-19] have also been reported in comparative studies from countries with universal health care, including the UK [11, 13, 16], Denmark [14, 17], Finland [12], Norway [15], Canada [19] and Taiwan [18]. Some recent studies, however, report similar access to treatment following acute myocardial infarction (MI) in patients with and without SMI [20, 21], and higher likelihood of statin prescribing [22] and revascularization [23] in younger individuals with SMI compared to controls.

A recent meta-analysis noted that it is unclear at what stage along the clinical pathway persons with SMI loose access to CVD prevention and care [24]. Earlier studies have reported both lower [11, 16, 25-27], similar [16, 25, 26, 28, 29] and higher [16, 28, 30] uptake of

CVD-related diagnostic tests in primary care among individuals with SMI. With the exception of post-MI treatment, there is also a scarcity of studies on uptake of specialized examinations and treatment for CVD among persons with SMI. Many previous studies have focused on prevention and treatment of CVD in relatively young persons with SMI, likely to be in an early and probably less severe phase of CVD [11, 27, 30, 31]. Although some studies found that older individuals with SMI are less likely to receive coronary revascularizations [23, 32, 33], CVD medications [22, 34, 35] and general medical outpatient services [22, 35], less is known whether the lower uptake of CVD-related diagnostic tests and cardiovascular treatment persists in the more severe phase of CVD, i.e. in the period prior to cardiovascular death. We recently documented that in a large group of 72,451 subjects who died of CVD, individuals with SCZ and women with BD were less likely to have CVD diagnosed before death [36]. In the current study, we investigate any differences in access to diagnostic tests and invasive treatment of CVD across health care levels. To our knowledge, there are no studies of the uptake of diagnostic tests and invasive treatment of CVD in individuals with SCZ or BD across health care sectors. Access to complete nationwide data from both primary and specialist health care up to nine years prior to cardiovascular death may help to pinpoint where along the clinical pathway disparities in cardiovascular care arise and identify individuals at particular risk of suboptimal treatment.

Aims of the study

In the present study we examined whether diagnoses of schizophrenia or bipolar disorder were associated with lower prevalence of diagnostic testing and treatment of cardiovascular disease prior to cardiovascular death, compared to patients without schizophrenia or bipolar disorder who died from cardiovascular disease. A secondary aim was to investigate if there was a difference between primary and specialist health care.

Material and methods

Study design and data sources

We conducted a national record-linkage study, including complete data on cardiovascular mortality and complete data on diagnoses and health care utilization in primary and specialized health care for all Norwegians who died from CVD during the years 2011-2016. We included mortality data from the Norwegian Cause of Death Registry (CDR), and diagnostic data and information on health care utilization during the years 2008-2016 from the Norwegian Patient Registry (NPR) and the Norwegian Directorate of Health's system for control and payment of health reimbursements in primary care (the KUHR database).

The CDR provides almost complete (98%) information on causes of death based on death certificates coded by the physician who examined the deceased [37], supplemented by autopsy data in approximately 8% of the cases. The NPR contains almost complete information about all specialized health care (i.e. government-owned hospitals and outpatient clinics, and private health clinics with governmental reimbursement). Due to technical problems when reporting data, about 15% of contacts with private somatic health clinics with governmental imbursement were missing in the study period [38, 39]. Data for substance abuse institutions was also missing for the year 2008. As contacts with private somatic health clinics and SUD treatment facilities constitute a minor proportion of all contacts (10%), and few patients (0.1%) used these services exclusively during the period, the problem of missing data is probably very minor.

The KUHR database contains administrative and clinical information on all contacts with general practitioners (GPs), including visits at their office or at home, telephone contacts, emergency room visits, as well as laboratory tests performed in primary and specialized health care. GPs are in contact with a large proportion of patients with SMI, and prescribe almost 70% of all antipsychotic drugs in Norway [40]. Reported episodes in the KUHR

database are considered to be almost 100% complete as GPs are funded mainly on a fee-for-service basis.

Diagnostic codes in the CDR and the NPR follow the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), while diagnostic codes for primary care contacts follow the International Classification of Primary Care, 2nd version (ICPC-2). Accurate linkage across registries was obtained using an encrypted personal identification number included in all registries.

Subject inclusion criteria and diagnostic and procedural categories

We identified all deceased residents of Norway aged 18 years or older with CVD (ICD-10 codes I00-I82) recorded as underlying cause of death in the death certificate in the years 2011-2016, and at least one registered primary or specialized somatic health care contact in the period 2008-2016, thus assuring at least three years of observation time in the NPR and the KUHR database prior to death. Individuals registered as having died abroad were excluded (N=132), as well as individuals with no health care contacts in the period (N=66, of whom none had SMI on the death certificate).

Patients were included in the SMI group if a diagnosis of SCZ (ICD-10 code F20 or ICPC-2 code P72) or BD (ICD-10 codes F30-F31 or ICPC-2 code P73) was recorded in the NPR or KUHR database during 2008-2016, or in the death certificate. Patients diagnosed with both SCZ and BD (N=94) were included in the SCZ group only. A diagnosis of CVD was considered present if ICD-10-codes I00-I82 or G45, or corresponding ICPC-2 diagnoses (codes K70-K71, K74-K80, K82-K84, K86-K87 and K89-K94) were recorded in the NPR or the KUHR database in the period from inclusion (January 1st, 2008) until death. Causes of death were sub-classified into ischemic heart disease (IHD, ICD-10 codes I20-I25), other forms of heart disease (ICD-10 codes I30-I52), cerebrovascular disease (ICD-10 codes I60-

I69) and other cardiovascular diseases. CVD diagnoses recorded in primary or specialized health care were classified into MI, congestive heart failure, cardiac arrhythmias, valvular disease, pulmonary circulation disorders, peripheral vascular disorders, cerebrovascular disease and hypertension according to coding algorithms used in established comorbidity indices [41, 42]. We including also cases identified through the corresponding ICPC-2 codes recorded in primary care (see list of specific diagnostic codes in Supporting Information, Table S1).

We used three composite measures of CVD-related procedures as main endpoints; (i) any CVD-related diagnostic test in primary care, (ii) any CVD-related diagnostic examination in specialized health care, and (iii) any invasive cardiovascular treatment procedure. CVD-related diagnostic test conducted in primary care included electrocardiography (ECG), 24-hour blood pressure measurement, total cholesterol test, blood glucose test and HbA1c test. Specific tests for diabetes (i.e. blood glucose and HbA1c) were included in the measure of CVD-related diagnostic tests as diabetes is a risk factor for CVD. CVD-related diagnostic examinations conducted in specialized health care included blood pressure measurements, ECG, echocardiography, coronary angiography, right-sided heart catheterization, invasive electrophysiological examination of the heart, ultrasound examination of blood vessels (conducted in medical departments), and Doppler pressure measurements. Information on ultrasound examination of blood vessels conducted in radiology departments was not available. Any invasive cardiovascular treatment included coronary revascularization (i.e. PCI and CABG), arrhythmia treatment (i.e. permanent transvenous cardiac pacemaker implant, cardioverter defibrillator implant, electroconversion of cardiac arrhythmia and transvenous ablation), heart valve replacement and vascular surgery (i.e. carotid surgery, aneurysm surgery and peripheral vessels surgery). Definitions of invasive procedures were in

accordance with definitions in the Norwegian Cardiovascular Disease Registry [43] and the Norwegian Registry for Vascular Surgery [44], supplemented with expired and newer codes.

Analysis and statistical methods

Since the outcomes are common, we applied log-binomial instead of logistic regression to study the association between presence of SMI and provision of diagnostic tests and treatment for CVD in primary or specialized somatic care prior to cardiovascular death [45]. The log-binomial model assumes a binary outcome, and estimate relative risk in prospective data and prevalence ratios (PRs) in cross-sectional data. When we examined uptake of diagnostic CVD-related test in primary care, the log-binomial model would not converge, we therefore used Poisson regression with robust error variance for estimation in this particular analysis [46].

Multivariable models were adjusted for sex and age at death (age groups 18-59, 60-69, 70-79, 80-89, and 90 and above). We also studied the impact of adding alcohol and substance abuse (see definitions in Table S1) and somatic comorbidities according to the Charlson's comorbidity index [47, 48] to the model, after excluding CVDs from the algorithm. However, this neither changed estimates nor improved model goodness-of-fit significantly. We therefore only report results from the simplest model, presented as adjusted PRs with 95 % confidence intervals (CI).

We conducted analyses for all subjects, and in sex-stratified subgroups, for the most common CVD-related diagnostic tests in primary care (i.e. ECG, 24-hour blood pressure measurement, blood glucose test and HbA1c tests) and the most common CVD-related diagnostic examinations in specialized care (i.e. echocardiography, coronary angiography and ultrasound of peripheral vessels). Finally, we conducted subgroup analyses of receipt of revascularization, in all subjects and among patients diagnosed with MI or other ischemic

heart diseases (ICD-10 codes I20, I23, I24, I25.1, I25.3-I25.9 or ICPC-2 codes K74 and K76), receipt of invasive arrhythmia therapy (all patients and among patients diagnosed with arrhythmia) (see definition in Table S1), and receipt of vascular surgery (all patients and among patients diagnosed with peripheral vascular disease) (see definition in Table S1) or carotid artery stenosis (ICD-10 code I65.2).

To test the consistency of study findings regarding the three main endpoints, we conducted sensitivity analyses to examine the impact of (i) excluding patients diagnosed with dementia, (ii) excluding patients aged 80 and above, (iii) excluding patients with the ambiguous affective disorder diagnosis (ICPC-2 code P75) from the BD group, (iv) including also cases with CVD as contributing cause of death, (v) adjusting for person-years of observation, and (vi) restricting analyses of uptake of invasive CVD treatment to those who survived their first CVD contact in the period on the results. We also examined the impact of excluding relevant CVD diagnoses registered only the last month of living in the subgroup analyses of revascularization, invasive arrhythmia therapy and vascular surgery.

Statistically significant results were defined at the conventional level (i.e. a two-tailed p-value < 0.05). Data management and analyses were conducted using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, N.C.).

Ethics

Data files contained unique, but encrypted, personal ID numbers when made available to the investigators. Legal basis and exemption from professional secrecy requirements for the use of personal health data in research was granted by the regional committee for medical and health research ethics (2014/72/REK nord).

Results

Characteristics of the study population

We included 72,385 residents of Norway aged 18 years and above who died due to CVD in the period 2011-2016, and who had utilized primary or specialized somatic care at least once in the period from January 1st, 2008 until death (Table 1). Of these, 814 (1.1%) were diagnosed with SCZ and 673 (0.9%) with BD. More than half (54%) of patients with SCZ and 45% of patients with BD had their SMI diagnosis recorded in primary care only, while 13% of SCZ patients and 28% of BD patients had their diagnosis recorded in specialized health care only. The remaining patients had their diagnosis recorded in at least two registries.

Patients with SMI had a younger age distribution and died at a mean age of 76 years, eight years younger than patients without SMI ($p < 0.0001$, Table 1). No differences in causes of cardiovascular death were noted between the three diagnostic groups, with IHD accounting for nearly 40% of all deaths in all groups. Patients with SMI had less diagnosed CVD prior to cardiovascular death for all CVD subtypes except pulmonary circulation disorder, in particular cardiac arrhythmias, hypertension and congestive heart failure. We found similar prevalence of diabetes and hyperlipidemia in patients with and without SMI, but more recorded alcohol and substance abuse and obesity among patients with SMI.

Patients with SCZ had less, and patients with BD more, GP visits, specialized somatic admissions and somatic outpatient visits, and patients with SMI more telephone contacts and emergency room visits compared to patients without SMI (Table 2). Regardless of frequency of contacts, contact type and level of health care, patients with SMI had fewer contacts with a recorded CVD diagnosis, and a shorter time span from first CVD-examination in the observation period until cardiovascular death. Seventeen percent of patients with SCZ and 11% of patients with BD had their CVD diagnosis first recorded when they died. In patients without SMI, this was the situation in 8% (Table 1).

Receipt of CVD-related diagnostic tests prior to cardiovascular death

About four out of five patients with and without SMI underwent some kind of CVD-related diagnostic test in primary care prior to cardiovascular death, where patients with BD had slightly higher prevalence than others. About 44% of patients with SCZ and 54-55% of patients with BD or no SMI received some kind of CVD-related diagnostic examination in specialized health care (Table 2).

Adjusted analyses showed that patients with SCZ and BD had similar prevalence of any CVD-related diagnostic test in primary care prior to cardiovascular death as patients without SMI (Figure 1). Patients with BD also had similar prevalence of specialized diagnostic tests as patients without SMI, while patients with SCZ had lower prevalence of specialized diagnostic CVD examinations (PR 0.78; 95% CI 0.73-0.85) (Table 3).

Patients with SCZ had similar prevalence of ECG and diabetes tests in primary care, but lower prevalence of 24 hour blood pressure measurement (PR 0.39; 95% CI 0.28-0.55), compared to patients without SMI. Patients with BD had higher prevalence of blood glucose testing (PR 1.13; 95% CI 1.07-1.19) and HbA1c testing (PR 1.12; 95% CI 1.03-1.21, but similar prevalence of ECG and 24h blood pressure measurement in primary care (Table 3). Sex-stratified analyses showed the same overall pattern as in the main analysis regarding CVD-related diagnostic tests in primary care (Table 3).

Patients with SCZ had significantly lower uptake of specialized diagnostic tests, such as echocardiography (PR 0.77; 95% CI 0.70-0.84), coronary angiography (PR 0.66; 95% CI 0.55-0.79) and ultrasound of peripheral vessels (PR 0.44; 95% CI 0.32-0.61), compared to patients without SMI (Table 3). Patients with BD also had reduced uptake of echocardiography (PR 0.90; 95% CI 0.82-0.98) and coronary angiography (PR 0.81; 95% CI 0.67-0.96), but similar uptake of ultrasound of peripheral vessels. Sex-stratified analyses showed the same overall pattern (Table 3).

Receipt of invasive cardiovascular procedures prior to death

Twelve percent of patients with SCZ and 16% of patients with BD underwent some kind of invasive cardiovascular treatment procedure prior to cardiovascular death, compared to 19% among patients without SMI. Adjusted for sex and age at death, patients with SCZ who died from CVD had 42% lower prevalence (PR 0.58; 95% CI 0.48-0.70) and patients with BD 21% lower prevalence (PR 0.79; 95% CI 0.67-0.94) of any invasive cardiovascular treatment prior to cardiovascular death (Figure 1).

Adjusted subgroup analyses according to type of invasive treatment procedure showed 35% lower prevalence (PR 0.65; 95% CI 0.50-0.84) of revascularization in patients with SCZ who died due to CVD, but similar prevalence of revascularization in patients with SCZ who were diagnosed with IHD prior to death, compared to patients without SMI (Table 4). We found 31% lower prevalence (PR 0.69; 95% CI 0.51-0.92) of any invasive arrhythmia treatment in patients with SCZ who died due to CVD, but similar prevalence in patients with SCZ who were diagnosed with arrhythmia prior to death. Patients with BD had similar prevalence of revascularization and arrhythmia therapy as patients without SMI both among those who died of CVD and the subset diagnosed with IHD or arrhythmia, respectively. Analyses of receipt of vascular surgery in patients who died from CVD showed 57% (PR 0.43; 95% CI 0.28-0.68) and 63% (PR 0.37; 95% CI 0.22-0.62) lower prevalence in patients with SCZ and BD, respectively, compared to patients without SMI. Patients with BD diagnosed with peripheral vascular or carotid artery stenosis prior to death also had lower prevalence of vascular surgery (PR 0.50; 95% CI 0.31-0.82), compared to patients without SMI (Table 4).

Results of sensitivity analyses

Sensitivity analyses that investigated the impact of (i) excluding patients diagnosed with dementia, (ii) excluding patients aged 80 and above, (iii) excluding patients with the ambiguous affective disorder diagnosis (ICPC-2 code P75) from the BD group, (iv) including also cases with CVD as contributing cause of death, (v) adjusting for person-years of observation and (vi) restricting analyses of invasive CVD treatment to those who survived their first CVD encounter in the period gave essentially the same estimates for PR as the original analysis (Figure S1 in Supporting Information). Excluding relevant CVD diagnoses registered only the last month of life in the subgroup analyses of revascularization, invasive arrhythmia therapy and vascular surgery had no impact on results.

Discussion

In this nationwide registry study we found that compared to patients without SMI, subjects with a diagnosis of SCZ had similar prevalence of CVD-related diagnostic tests in primary care, but lower uptake of specialized diagnostic CVD examinations and invasive CVD treatment. The lower prevalence of CVD examinations was particularly pronounced for lengthy procedures or those that require physical contact with the patient (such as 24-hour blood pressure measurement, echocardiograms, coronary angiography and ultrasound of peripheral vessels). Patients with BD had similar prevalence of diagnostic CVD examinations in primary and specialized somatic care as patients without SMI, but lower prevalence of invasive CVD treatment. Patients with SCZ or BD with acknowledged CVD had similar uptake of invasive cardiovascular treatment as those without SCZ or BD. Patients with SMI also had fewer contacts with a recorded CVD diagnosis both in primary and specialized somatic care, and a shorter time span from first CVD-diagnosis in the observation period until cardiovascular death.

Comparisons with other studies

We are not aware of other studies examining uptake of CVD-related diagnostic tests in a sample of deceased patients with and without SMI, but our findings show similarities with other studies on adjacent topics. A previous Norwegian primary care study found similar likelihood of ECG, and higher frequency of HbA1c testing, in individuals with SCZ aged 25-60 years, compared to controls with similar somatic comorbidity [30]. We found similar likelihood of both procedures in patients with and without SCZ, but congruent results when restricting the analysis to the same age groups, possibly implying increased health care seeking or increased awareness of elevated cardiovascular risk in younger patients with SCZ.

A lower prevalence of 24-hour blood pressure measurement in patients with SCZ in primary care is in accordance with earlier findings regarding blood pressure measurement in general among persons with SCZ [11, 16, 49], and a similar prevalence of blood pressure measurement found in individuals with BD is compatible with some [25, 28, 50], but not all [26] studies in the wider SMI population. The similar (SCZ) or higher (BD) prevalence of diabetes testing in primary care, compared to patients without SMI, also resembles earlier findings in the SMI population [26, 28, 51, 52]. An interprofessional primary care practice with mandate to care for persons with barriers to health care reported similar levels of blood pressure measurement and higher levels of diabetes screening in patients with SMI than in age- and sex-matched controls [50], implicating that tailor-made treatment for this group may improve uptake.

Our results indicated a decreased prevalence of coronary angiography prior to cardiovascular death in patients with SCZ and BD, which is in accordance with earlier studies in patients with SCZ [9, 18, 33, 53-55], BD [18], psychosis [19] or mental illness in general [9, 56-59], particularly in older age groups [33, 56]. Our findings are also compatible with a study reporting lower likelihood of preventive interventions during somatic hospitalization among patients with SMI [60]. Little is known about receipt of echocardiography and ultrasound of peripheral vessels in patients with and without SMI, but patients with mental illness have been reported to have lower likelihood of left ventricular ejection fraction assessment, in which echocardiography is a common examination method [61].

We found lower prevalence of invasive cardiovascular procedures in patients with SCZ or BD, in accordance with previous studies of receipt of cardiovascular surgery in patients with and without SMI [55, 62]. There were lower (SCZ) or similar (BD) prevalence of revascularization in patients who died due to CVD, but similar uptake of revascularization in patients with and without SCZ or BD who were diagnosed with IHD prior to death. The

latter finding is in contrast to earlier findings in various populations [9, 18, 23, 53-55, 63, 64], but consistent with a nationwide Swedish study [20], and also a recent Danish study showing no difference in post-MI treatment in patients with and without SCZ who had undergone coronary angiography, as well as studies showing similar likelihood of revascularization in patients with IHD and BD [63] or mood disorders [23]. The finding of similar prevalence of revascularization in patients with SMI also diagnosed with IHD is also compatible with a study in the general Norwegian population demonstrating that lower revascularization rates among patients with low education were explained by differences in receipt of coronary angiography [65].

With the exception of revascularization, receipt of invasive cardiovascular treatment in persons with SMI appears to be little described in the literature [66]. However, an Israeli study found a 50% reduced likelihood of cardiac pacemaker implantation in patients with schizophrenia [55] and a US study found a reduced likelihood of receiving major surgery, including vascular surgery, among persons with SMI, particularly in those with SCZ [62]. These findings are in line with ours in the sample of those who died from CVD.

Barriers to care

Our study indicates that the differences in receipt of CVD prevention and treatment among persons with particularly SCZ may be driven by underdiagnosis of CVD and underutilization of specialized diagnostic tests rather than reduced access to primary care and disparate invasive treatment of acknowledged CVD.

Explanations for lower uptake of specialized diagnostic tests in persons with SMI are multifactorial, and may differ between individuals with SCZ and BD. Disease-related factors such as limited and disorganized self-care capacity, poor communications skills, self-stigma, depression and social isolation, particularly in those with SCZ, may lead to delayed

presentation or diagnosis, and missed referrals. Earlier studies suggest that especially older patients with SMI may have reduced health care seeking regarding CVD [35]. Increased pain tolerance [67] and increased risk of silent CVD [68] have been reported in individuals with SCZ, possibly affecting timely health care seeking. Due to increased early cardiovascular mortality [69, 70], individuals with SMI may die at ages when health care providers not usually suspect CVD. Prevailing risk prediction algorithms for CVD also have been shown to underestimate the risk of CVD in individuals with SCZ [71]. Furthermore, shared genetic risk factors for both SCZ and CVD [72, 73] may imply a more malign course of CVD, with shorter time to recognize symptoms. Also, users of antipsychotic medication are at higher risk of adverse cardiac effects such as arrhythmias, deviations in blood pressure, heart failure, myocarditis and cardiomyopathy [74, 75], possibly leading to sudden cardiac death [76-78].

Provider-level explanations put forward include time constraints, complexity of care and misattribution of physical symptoms to mental illness [79-81]. Discomfort with or stigmatizing attitudes towards patients with SMI among health care providers have been reported [82], particularly regarding SCZ [83, 84], and may unintendedly influence medical decision-making. In a study of quality of somatic treatment among older persons with SCZ, higher adequacy of somatic treatment was associated with lower rates of depression, fewer positive symptoms, more negative symptoms, and, surprisingly, fewer medical care visits [85]. Increased rates of GP visits, including increased rates of emergency room visits, as observed in the SMI group in our study, could thus be a signal of unmet medical needs. In another study of providers' decision making, a history of SCZ was found to negatively affect primary care provider's expectations of treatment adherence and ability to understand educational materials [86]. In spite of younger age, people with SMI have more comorbidities, including higher rates of smoking, obesity and substance use disorder [87], higher risk for postoperative complications [88, 89] and mortality following cardiac treatment

[20]. Disparities in invasive CVD treatment may thus reflect clinicians' uncertainty and judgments about treatment risks and compliance with postoperative care. Lack of consent, or lack of capacity to give informed consent, may also be an issue, as noted in a recent study investigating decisions about cardiac examination and treatment, where patients with SCZ tended to be more likely to decline both examination and treatment post MI [90].

Finally, mismatch between patients' health care needs and the fragmented organization of health care may be an important barrier to equitable somatic health care [91]. The current health care system relies on the individuals' ability to initiate contact with health care providers. Navigating between psychiatric, primary and specialized somatic health care systems may constitute a particular challenge to those with SMI, reinforced by potentially unclear responsibilities as to who is responsible for physical health monitoring among persons with SMI [92]. Both patients with SMI and mental health staff point to a fragmented health system when asked about opportunities for improved prevention and treatment for physical problems among persons with SMI [91, 93].

It may seem as a paradox that people with BD who died from CVD died at the same age as patients with SCZ, and much younger than subjects without SMI, despite higher overall health care utilization, and generally higher education and lower impairment, than persons with SCZ [1]. We can only speculate what the reasons for this might be. Comorbid alcohol use disorder, which was more prevalent in individuals with BD, was associated with lower prevalence of specialized somatic examination and treatment, and may be part of the explanation. Higher somatic comorbidity, also observed in those with BD, including conditions that complicate invasive cardiovascular treatment may be another explanation. Individuals with BD have, as examples, increased risk of chronic obstructive pulmonary disease, and women with BD a higher prevalence of renal failure [94], which may complicate invasive cardiac therapy.

Strengths and limitations

The strengths of the study include the nationwide sample with complete diagnostic data from both primary and specialized health care during a maximum nine-year period. Inclusion of everyone who died of CVD made it possible to study the utilization of CVD-related health care services in persons with assumed similar severity of CVD with and without a history of SCZ or BD. We also had the possibility to assess the impact of somatic comorbidity and alcohol and drug use on uptake of diagnostic tests and treatment. Our extensive sensitivity analyses strengthen our conclusions and our results seem solid. However, some limitations need mentioning.

Firstly, although we examined a wide range of procedures, we lacked information on some types of diagnostics and treatment of CVD, such as pharmacological prevention and treatment of CVD, procedures conducted at radiology departments (such as computed tomographic angiography and ultrasound of peripheral vessels), and prehospital procedures during transportation to hospital (such as ECG or thrombolysis), which reduced the scope and precision in the measurement of performed diagnostic tests and treatment. We also lacked precise information regarding the purpose and content of some diagnostic blood tests. A large volume of blood tests both in primary and specialized somatic care were taken as part of broad batteries of biomarkers, some of which, but not all, measure risk factors for diabetes and CVD (such as cholesterol). We did not know the specific indication for taking these tests, hence did not include them in our measure of CVD-related diagnostic tests. The level of screening/monitoring of CVD risk factors may thus be underestimated in all patients, but probably more in patients without SMI as patients with SMI should also be monitored for adverse effects of psychopharmacological medications. Also, very common procedures, such as blood pressure measurements or ECG, may be underreported in administrative data, but it is unlikely that this differ systematically between patients with and without SMI.

Secondly, we lacked information on severity of CVD (such as ST-segment elevation MI and extent of coronary disease). Equal severity of CVD could, however, be approximated by the fact that they all died from the same causes of death. Previous studies have reported similar severity of MI among patients with SCZ [20], and similar [20] or higher [63] severity of MI among patients with BD, implicating possibility of underestimated disparities in access to invasive cardiovascular treatments among those with BD. We also lacked information on time since symptom onset and travel time to hospital, which may have impacted treatment options differentially in those with and without SMI.

Thirdly, we lacked information on the socioeconomic status of the patients before their prodromal phase (e.g. their parents' educational attainment). The results found here could thus be due to social stratification in treatment utilization.

Fourthly, the validity of registry diagnoses is unknown for some disease categories. Previous studies have found high agreement between clinical diagnoses of SMI and research based diagnosis [95], and valid information regarding stroke [96] and intracranial hemorrhage [96] in the NPR. Studies from other Nordic countries have found high diagnostic accuracy of cardiovascular diagnoses in general [97, 98], atrial fibrillation and flutter [99] and intracerebral hemorrhage [100], but questionable validity of heart failure [101] and peripheral arterial disease diagnoses [102]. Diagnoses in the KUHR database has not been validated, but diagnoses have been found to be valid in general practice registries in other countries, particularly for chronic diseases [103]. The KUHR database include limited information regarding comorbidity, however, since most claims only have one recorded diagnosis, but our long follow-up time probably outweighs this limitation. The registered cause of death was not validated by autopsy for the large majority of patients. Still, the CDR is found to provide high quality information on causes of death [104]. A Norwegian study from 2011 reported very good agreement between mortality statistics and autopsy findings for both coronary heart

disease and stroke in the CDR [105], while an earlier Norwegian study investigating the impact of autopsies on mortality statistics, found substantial (17%) underreporting of cardiovascular deaths, particularly in the young and old, and in women [106]. Autopsies are, however, not made at random, and findings from such studies may therefore not be transferable to other cases. The most common error in mortality statistics is that immediate or intermediate causes of death are registered as the underlying cause of death [107]. Patients with high co-morbidity, such as patients with BD, could be underrepresented in our sample due to competing causes of death. We found, however, only eleven patients with a SMI diagnosis recorded as underlying cause of death and CVD as contributing cause of death, and very few with a substance use disorder recorded as underlying cause of death. Also, we found similar results when we included all deaths with CVD as underlying or contributing cause of death, as shown in the sensitivity analysis. We lacked data on sudden death (ICD-10 code R98), which may imply underreported cardiovascular deaths. However, only 2% of underlying causes of death in Norway in the years 2011-2016 were assigned to unknown or unspecified causes (R96–R99) [108]. Studies have reported longer postmortem time before discovery in individuals with SCZ compared to others [109], possibly affecting the reliability of cause of death codes in individuals with SCZ.

Finally, external validity may be limited to individuals with severe CVD in countries with publicly funded and readily available health services for both somatic and mental disorders.

Clinical implications

In this nationwide study, we found lower prevalence of cardiovascular examinations and interventions prior to cardiovascular death in patients with SCZ and BD, in spite of high levels of primary and somatic health care use. Vulnerable individuals may thus not receive medically indicated cardiovascular treatment. In patients with diagnosed CVD, however, we found similar prevalence of invasive cardiovascular treatment among those with and without SMI.

In conclusion, these results suggest that underdiagnosis and underutilization of specialized cardiovascular examinations, rather than poor access to primary care or restraints due to contraindications or perceived noncompliance with postoperative care, are the main obstacles to achieve more equal access to cardiovascular health care. Existing risk prediction algorithms has been shown to underestimate cardiovascular risk in patients with SMI. Hence, the health care disparities shown in our study require a proactive and tailored approach for correct diagnosis and treatment of cardiovascular diseases, underlined by the fact that cardiovascular disease in these patients may have a more malignant disease course, with shorter time to recognize symptoms.

References

1. Rødevand, L., et al., *Cardiovascular risk remain high in schizophrenia with modest improvements in bipolar disorder during past decade.* Acta Psychiatr Scand, 2019. **139**(4): p. 348-360.
2. Correll, C.U., et al., *Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls.* World Psychiatry, 2017. **16**(2): p. 163-180.
3. Fan, Z., et al., *Schizophrenia and the risk of cardiovascular diseases: a meta-analysis of thirteen cohort studies.* J Psychiatr Res, 2013. **47**(11): p. 1549-56.
4. Prieto, M.L., et al., *Risk of myocardial infarction and stroke in bipolar disorder: a systematic review and exploratory meta-analysis.* Acta Psychiatr Scand, 2014. **130**(5): p. 342-53.
5. Lord, O., D. Malone, and A.J. Mitchell, *Receipt of preventive medical care and medical screening for patients with mental illness: a comparative analysis.* Gen Hosp Psychiatry, 2010. **32**(5): p. 519-43.
6. Mitchell, A.J., et al., *Guideline concordant monitoring of metabolic risk in people treated with antipsychotic medication: systematic review and meta-analysis of screening practices.* Psychol Med, 2012. **42**(1): p. 125-47.
7. Ayerbe, L., et al., *Hypertension risk and clinical care in patients with bipolar disorder or schizophrenia; a systematic review and meta-analysis.* J Affect Disord, 2018. **225**: p. 665-670.
8. Mitchell, A.J., O. Lord, and D. Malone, *Differences in the prescribing of medication for physical disorders in individuals with v. without mental illness: meta-analysis.* Br J Psychiatry, 2012. **201**(6): p. 435-43.
9. Mitchell, A.J. and D. Lawrence, *Revascularisation and mortality rates following acute coronary syndromes in people with severe mental illness: comparative meta-analysis.* Br J Psychiatry, 2011. **198**(6): p. 434-41.
10. Kuipers, E., et al., *Management of psychosis and schizophrenia in adults: summary of updated NICE guidance.* BMJ, 2014. **348**: p. g1173.
11. Roberts, L., et al., *Physical health care of patients with schizophrenia in primary care: a comparative study.* Fam Pract, 2007. **24**(1): p. 34-40.
12. Lahti, M., et al., *Cardiovascular morbidity, mortality and pharmacotherapy in patients with schizophrenia.* Psychol Med, 2012. **42**(11): p. 2275-85.
13. Smith, D.J., et al., *Multimorbidity in bipolar disorder and undertreatment of cardiovascular disease: a cross sectional study.* BMC Med, 2013. **11**: p. 263.
14. Laursen, T.M., et al., *Cardiovascular drug use and mortality in patients with schizophrenia or bipolar disorder: a Danish population-based study.* Psychol Med, 2014. **44**(8): p. 1625-37.
15. Skrede, S., et al., *Incident users of antipsychotic agents and future use of cholesterol-lowering drugs: an observational, pharmacoepidemiologic study.* J Clin Psychiatry, 2015. **76**(1): p. e111-6.
16. Woodhead, C., et al., *Cardiovascular disease treatment among patients with severe mental illness: a data linkage study between primary and secondary care.* Br J Gen Pract, 2016. **66**(647): p. e374-81.
17. Laursen, T.M. and M. Nordentoft, *Heart disease treatment and mortality in schizophrenia and bipolar disorder - changes in the Danish population between 1994 and 2006.* J Psychiatr Res, 2011. **45**(1): p. 29-35.
18. Wu, S.I., et al., *Diagnostic procedures, revascularization, and inpatient mortality after acute myocardial infarction in patients with schizophrenia and bipolar disorder.* Psychosom Med, 2013. **75**(1): p. 52-9.
19. Kisely, S., L.A. Campbell, and Y. Wang, *Treatment of ischaemic heart disease and stroke in individuals with psychosis under universal healthcare.* Br J Psychiatry, 2009. **195**(6): p. 545-50.

20. Bodén, R., et al., *Higher mortality after myocardial infarction in patients with severe mental illness: a nationwide cohort study.* J Intern Med, 2015. **277**(6): p. 727-36.
21. Jakobsen, L., et al., *Severe Mental Illness and Clinical Outcome After Primary Percutaneous Coronary Intervention.* Am J Cardiol, 2017. **120**(4): p. 550-555.
22. Blackburn, R., et al., *Statin prescribing for prevention of cardiovascular disease amongst people with severe mental illness: Cohort study in UK primary care.* Schizophr Res, 2018. **192**: p. 219-225.
23. Manderbacka, K., et al., *How does a history of psychiatric hospital care influence access to coronary care: a cohort study.* BMJ Open, 2012. **2**(2): p. e000831.
24. Ayerbe, L., et al., *Disparities in the management of cardiovascular risk factors in patients with psychiatric disorders: a systematic review and meta-analysis.* Psychol Med, 2018. **48**(16): p. 2693-2701.
25. Hippisley-Cox, J., et al., *Inequalities in the primary care of patients with coronary heart disease and serious mental health problems: a cross-sectional study.* Heart, 2007. **93**(10): p. 1256-62.
26. Osborn, D.P., et al., *Inequalities in the provision of cardiovascular screening to people with severe mental illnesses in primary care: cohort study in the United Kingdom THIN Primary Care Database 2000-2007.* Schizophr Res, 2011. **129**(2-3): p. 104-10.
27. Hardy, S., P. Hinks, and R. Gray, *Screening for cardiovascular risk in patients with severe mental illness in primary care: a comparison with patients with diabetes.* J Ment Health, 2013. **22**(1): p. 42-50.
28. Whyte, S., et al., *Quality of diabetes care in patients with schizophrenia and bipolar disorder: cross-sectional study.* Diabet Med, 2007. **24**(12): p. 1442-8.
29. Rathmann, W., et al., *Diabetes treatment in people with type 2 diabetes and schizophrenia: Retrospective primary care database analyses.* Prim Care Diabetes, 2016. **10**(1): p. 36-40.
30. Hetlevik, O., M. Solheim, and S. Gjesdal, *Use of GP services by patients with schizophrenia: a national cross-sectional register-based study.* BMC Health Serv Res, 2015. **15**: p. 66.
31. Himelhoch, S., et al., *Care and management of cardiovascular risk factors among individuals with schizophrenia and type 2 diabetes who smoke.* Gen Hosp Psychiatry, 2009. **31**(1): p. 30-2.
32. Druss, B.G., *Cardiovascular procedures in patients with mental disorders.* Jama, 2000. **283**(24): p. 3198-9.
33. Young, J.K. and D.A. Foster, *Cardiovascular procedures in patients with mental disorders.* Jama, 2000. **283**(24): p. 3198; author reply 3198-9.
34. Brink, M., et al., *Physical Health, Medication, and Healthcare Utilization among 70-Year-Old People with Schizophrenia: A Nationwide Danish Register Study.* Am J Geriatr Psychiatry, 2017. **25**(5): p. 500-509.
35. Swildens, W., et al., *Somatic Care with a Psychotic Disorder. Lower Somatic Health Care Utilization of Patients with a Psychotic Disorder Compared to Other Patient Groups and to Controls Without a Psychiatric Diagnosis.* Adm Policy Ment Health, 2016. **43**(5): p. 650-62.
36. Heiberg, I.H., et al., *Undiagnosed cardiovascular disease prior to cardiovascular death in individuals with severe mental illness.* Acta Psychiatr Scand, 2019. **139**(6): p. 558-571.
37. Pedersen, A.G. and C.L. Ellingsen, *Data quality in the Causes of Death Registry.* Tidsskr Nor Laegeforen, 2015. **135**(8): p. 768-70.
38. Helsedirektoratet [The Norwegian Directorate of Health]. *Aktivitetsdata for avtalespesialister 2009 [Data on activities by specialists in private practice 2009]*. 2010; Available from: https://helsedirektoratet.no/Lists/Publikasjoner/Attachments/504/Aktivitetsdata-for-avtalespesialister-2009-IS-1818.pdf.
39. Lützen, J., A.S. Fuglset, and I. Dahlstrøm, *Aktivitetsdata for avtalespesialister 2015 [Data on activities by specialists in private practice 2015]*. 2015, Helsedirektoratet [The Norwegian Directorate of Health]: Oslo.

40. Kjosavik, S.R., S. Ruths, and S. Hunskaar, *Psychotropic drug use in the Norwegian general population in 2005: data from the Norwegian Prescription Database.* Pharmacoepidemiol Drug Saf, 2009. **18**(7): p. 572-8.
41. Elixhauser, A., et al., *Comorbidity measures for use with administrative data.* Med Care, 1998. **36**(1): p. 8-27.
42. Quan, H., et al., *Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data.* Med Care, 2005. **43**(11): p. 1130-9.
43. Kvåle R, et al., *Hjerte- og karregisteret • Rapport for 2012–2016*. 2018, Folkehelseinstituttet [The Norwegian Institute of Public Health]: Oslo, Norway.
44. Hovland, S., R. Seifert, and S. Rotevatn, *Årsrapport for 2016 med plan for forbedringstiltak*. 2017, Norsk Register for Invasiv Kardiologi [Norwegian Register of Invasive Cardiology] (NORIC),: Bergen, Norway.
45. Barros, A.J. and V.N. Hirakata, *Alternatives for logistic regression in cross-sectional studies: an empirical comparison of models that directly estimate the prevalence ratio.* BMC Med Res Methodol, 2003. **3**: p. 21.
46. Zou, G., *A modified poisson regression approach to prospective studies with binary data.* Am J Epidemiol, 2004. **159**(7): p. 702-706.
47. Charlson, M.E., et al., *A new method of classifying prognostic comorbidity in longitudinal studies: development and validation.* J Chronic Dis, 1987. **40**(5): p. 373-83.
48. Quan, H., et al., *Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries.* Am J Epidemiol, 2011. **173**(6): p. 676-82.
49. Jørgensen, M., et al., *Quality and Predictors of Diabetes Care Among Patients With Schizophrenia: A Danish Nationwide Study.* Psychiatr Serv, 2018. **69**(2): p. 179-185.
50. Ritchie, S. and L. Muldoon, *Cardiovascular preventive care for patients with serious mental illness.* Can Fam Physician, 2017. **63**(11): p. e483-e487.
51. Woodhead, C., et al., *Patterns of physical co-/multi-morbidity among patients with serious mental illness: a London borough-based cross-sectional study.* BMC Fam Pract, 2014. **15**: p. 117.
52. Gal, G., H. Munitz, and I. Levav, *Health Care and Mortality among Persons with Severe Mental Illness.* Can J Psychiatry, 2017. **62**(4): p. 259-267.
53. Bresee, L.C., et al., *Utilization of general and specialized cardiac care by people with schizophrenia.* Psychiatr Serv, 2012. **63**(3): p. 237-42.
54. Kurdyak, P., et al., *High mortality and low access to care following incident acute myocardial infarction in individuals with schizophrenia.* Schizophr Res, 2012. **142**(1-3): p. 52-7.
55. Gal, G., H. Munitz, and I. Levav, *Health care disparities among persons with comorbid schizophrenia and cardiovascular disease: a case-control epidemiological study.* Epidemiol Psychiatr Sci, 2016. **25**(6): p. 541-547.
56. Druss, B.G., et al., *Mental disorders and use of cardiovascular procedures after myocardial infarction.* Jama, 2000. **283**(4): p. 506-11.
57. Petersen, L.A., et al., *Process of care and outcome after acute myocardial infarction for patients with mental illness in the VA health care system: are there disparities?* Health Serv Res, 2003. **38**(1 Pt 1): p. 41-63.
58. Kisely, S., et al., *Inequitable access for mentally ill patients to some medically necessary procedures.* Cmaj, 2007. **176**(6): p. 779-84.
59. Li, Y., et al., *Mental illness, access to hospitals with invasive cardiac services, and receipt of cardiac procedures by Medicare acute myocardial infarction patients.* Health Serv Res, 2013. **48**(3): p. 1076-95.
60. Briskman, I., et al., *Impact of co-morbid mental illness on the diagnosis and management of patients hospitalized for medical conditions in a general hospital.* Int J Psychiatry Med, 2012. **43**(4): p. 339-48.

61. Rathore, S.S., et al., *Mental disorders, quality of care, and outcomes among older patients hospitalized with heart failure: an analysis of the national heart failure project.* Arch Gen Psychiatry, 2008. **65**(12): p. 1402-8.
62. Copeland, L.A., et al., *Serious mental illnesses associated with receipt of surgery in retrospective analysis of patients in the Veterans Health Administration.* BMC Surg, 2015. **15**: p. 74.
63. Schulman-Marcus, J., et al., *Comparison of Trends in Incidence, Revascularization, and In-Hospital Mortality in ST-Elevation Myocardial Infarction in Patients With Versus Without Severe Mental Illness.* Am J Cardiol, 2016. **117**(9): p. 1405-10.
64. Laursen, T.M., et al., *Somatic hospital contacts, invasive cardiac procedures, and mortality from heart disease in patients with severe mental disorder.* Arch Gen Psychiatry, 2009. **66**(7): p. 713-20.
65. Sulo, E., et al., *Coronary angiography and myocardial revascularization following the first acute myocardial infarction in Norway during 2001-2009: Analyzing time trends and educational inequalities using data from the CVDNOR project.* Int J Cardiol, 2016. **212**: p. 122-8.
66. Copeland, L.A., et al., *Postoperative complications in the seriously mentally ill: a systematic review of the literature.* Ann Surg, 2008. **248**(1): p. 31-8.
67. Stubbs, B., et al., *Decreased pain sensitivity among people with schizophrenia: a meta-analysis of experimental pain induction studies.* Pain, 2015. **156**(11): p. 2121-31.
68. Nielsen, J., et al., *Unrecognised myocardial infarction in patients with schizophrenia.* Acta Neuropsychiatr, 2015. **27**(2): p. 106-12.
69. Chung, K.H., et al., *Risk factors for early circulatory mortality in patients with schizophrenia.* Psychiatry Res, 2018. **267**: p. 7-11.
70. Goldstein, B.I., et al., *Excessive and premature new-onset cardiovascular disease among adults with bipolar disorder in the US NESARC cohort.* J Clin Psychiatry, 2015. **76**(2): p. 163-9.
71. McLean, G., et al., *Standard cardiovascular disease risk algorithms underestimate the risk of cardiovascular disease in schizophrenia: evidence from a national primary care database.* Schizophr Res, 2014. **159**(1): p. 176-81.
72. Andreassen, O.A., et al., *Improved detection of common variants associated with schizophrenia by leveraging pleiotropy with cardiovascular-disease risk factors.* Am J Hum Genet, 2013. **92**(2): p. 197-209.
73. So, H.C., et al., *Exploring shared genetic bases and causal relationships of schizophrenia and bipolar disorder with 28 cardiovascular and metabolic traits.* Psychol Med, 2018: p. 1-13.
74. Honkola, J., et al., *Psychotropic medications and the risk of sudden cardiac death during an acute coronary event.* Eur Heart J, 2012. **33**(6): p. 745-51.
75. Li, K.J., A.P. Greenstein, and L.E. Delisi, *Sudden death in schizophrenia.* Curr Opin Psychiatry, 2018. **31**(3): p. 169-175.
76. Ray, W.A., et al., *Atypical antipsychotic drugs and the risk of sudden cardiac death.* N Engl J Med, 2009. **360**(3): p. 225-35.
77. Ifteni, P., et al., *Sudden unexpected death in schizophrenia: autopsy findings in psychiatric inpatients.* Schizophr Res, 2014. **155**(1-3): p. 72-6.
78. Khan, A.A., et al., *Clozapine and incidence of myocarditis and sudden death - Long term Australian experience.* Int J Cardiol, 2017. **238**: p. 136-139.
79. Graber, M.A., et al., *Effect of a patient's psychiatric history on physicians' estimation of probability of disease.* J Gen Intern Med, 2000. **15**(3): p. 204-6.
80. Shefer, G., et al., *Diagnostic overshadowing and other challenges involved in the diagnostic process of patients with mental illness who present in emergency departments with physical symptoms--a qualitative study.* PLoS One, 2014. **9**(11): p. e111682.
81. Atzema, C.L., M.J. Schull, and J.V. Tu, *The effect of a charted history of depression on emergency department triage and outcomes in patients with acute myocardial infarction.* Cmaj, 2011. **183**(6): p. 663-9.

82. Vistorte, A.O.R., et al., *Stigmatizing attitudes of primary care professionals towards people with mental disorders: A systematic review.* Int J Psychiatry Med, 2018. **53**(4): p. 317-338.
83. Mittal, D., et al., *Healthcare providers' attitudes toward persons with schizophrenia.* Psychiatr Rehabil J, 2014. **37**(4): p. 297-303.
84. Noblett, J.E., R. Lawrence, and J.G. Smith, *The attitudes of general hospital doctors toward patients with comorbid mental illness.* Int J Psychiatry Med, 2015. **50**(4): p. 370-82.
85. Vahia, I.V., et al., *Adequacy of medical treatment among older persons with schizophrenia.* Psychiatr Serv, 2008. **59**(8): p. 853-9.
86. Sullivan, G., et al., *Influence of schizophrenia diagnosis on providers' practice decisions.* J Clin Psychiatry, 2015. **76**(8): p. 1068-74; quiz 1074.
87. Garcia-Portilla, M.P., et al., *Impact of substance use on the physical health of patients with bipolar disorder.* Acta Psychiatr Scand, 2010. **121**(6): p. 437-45.
88. Brunner, S., et al., *Patients under Psychiatric Medication Undergoing Cardiac Surgery Have a Higher Risk for Adverse Events.* Thorac Cardiovasc Surg, 2016. **64**(7): p. 575-580.
89. Beck, C.A., et al., *Alcohol and drug use disorders among patients with myocardial infarction: associations with disparities in care and mortality.* PLoS One, 2013. **8**(9): p. e66551.
90. Attar, R., et al., *Treatment following myocardial infarction in patients with schizophrenia.* PLoS One, 2017. **12**(12): p. e0189289.
91. Brämberg, E.B., et al., *Access to primary and specialized somatic health care for persons with severe mental illness: a qualitative study of perceived barriers and facilitators in Swedish health care.* BMC Fam Pract, 2018. **19**(1): p. 12.
92. De Hert, M., et al., *Physical illness in patients with severe mental disorders. II. Barriers to care, monitoring and treatment guidelines, plus recommendations at the system and individual level.* World Psychiatry, 2011. **10**(2): p. 138-51.
93. Blanner Kristiansen, C., et al., *Promoting physical health in severe mental illness: patient and staff perspective.* Acta Psychiatr Scand, 2015. **132**(6): p. 470-8.
94. Castro, V.M., et al., *Stratifying Risk for Renal Insufficiency Among Lithium-Treated Patients: An Electronic Health Record Study.* Neuropsychopharmacology, 2016. **41**(4): p. 1138-43.
95. Nesvåg, R., et al., *The quality of severe mental disorder diagnoses in a national health registry as compared to research diagnoses based on structured interview.* BMC Psychiatry, 2017. **17**(1): p. 93.
96. Varmdal, T., et al., *Comparison of the validity of stroke diagnoses in a medical quality register and an administrative health register.* Scand J Public Health, 2016. **44**(2): p. 143-9.
97. Sundbøll, J., et al., *Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study.* BMJ Open, 2016. **6**(11): p. e012832.
98. Pajunen, P., et al., *The validity of the Finnish Hospital Discharge Register and Causes of Death Register data on coronary heart disease.* Eur J Cardiovasc Prev Rehabil, 2005. **12**(2): p. 132-7.
99. Rix, T.A., et al., *Validity of the diagnoses atrial fibrillation and atrial flutter in a Danish patient registry.* Scand Cardiovasc J, 2012. **46**(3): p. 149-53.
100. Hald, S.M., et al., *Intracerebral hemorrhage: positive predictive value of diagnosis codes in two nationwide Danish registries.* Clin Epidemiol, 2018. **10**: p. 941-948.
101. Delekta, J., et al., *The validity of the diagnosis of heart failure (I50.0-I50.9) in the Danish National Patient Register.* Dan Med J, 2018. **65**(4).
102. Lasota, A.N., et al., *Validity of Peripheral Arterial Disease Diagnoses in the Danish National Patient Registry.* Eur J Vasc Endovasc Surg, 2017. **53**(5): p. 679-685.
103. Khan, N.F., S.E. Harrison, and P.W. Rose, *Validity of diagnostic coding within the General Practice Research Database: a systematic review.* Br J Gen Pract, 2010. **60**(572): p. e128-36.
104. Phillips, D.E., et al., *A composite metric for assessing data on mortality and causes of death: the vital statistics performance index.* Popul Health Metr, 2014. **12**: p. 14.
105. Gulsvik, A.K., et al., *Diagnostic validity of fatal cerebral strokes and coronary deaths in mortality statistics: an autopsy study.* Eur J Epidemiol, 2011. **26**(3): p. 221-8.

106. Alfsen, G.C. and J. Mæhlen, *Obduksjonens betydning for registrering av dødsårsak [The value of autopsies for determining the cause of death].* Tidsskr Nor Laegeforen, 2012. **132**(2): p. 147-51.
107. Eriksson, A., et al., *Accuracy of death certificates of cardiovascular disease in a community intervention in Sweden.* Scand J Public Health, 2013. **41**(8): p. 883-9.
108. Folkehelseinstituttet [Norwegian Institute of Public Health]. *Dødsårsaker, nøkkeltall (LHF) – per 100 000, standardisert [Causes of death, key figures (LHF) - per 100,000, standardized]*. 2018 January 15, 2019]; Available from: http://www.norgeshelsa.no/norgeshelsa/.
109. Nilsson, L.L. and B. Logdberg, *Dead and forgotten--postmortem time before discovery as indicator of social isolation and inadequate mental healthcare in schizophrenia.* Schizophr Res, 2008. **102**(1-3): p. 337-9.

Tables and figures

Tables

Table 1. Descriptive characteristics of individuals with or without schizophrenia or bipolar disorder who died due to cardiovascular disease at ages 18 and above.

Table 2. Health care utilization prior to cardiovascular death in patients with or without schizophrenia or bipolar disorder who died due to cardiovascular disease at ages 18 and above.

Table 3. Adjusted Prevalence Ratios (PR) with 95% Confidence Intervals (CI) for receipt of diagnostic CVD tests prior to cardiovascular death in individuals with schizophrenia (SCZ) or bipolar disorder (BD), according to sex, patient group and type of procedure.

Table 4. Adjusted Prevalence Ratios (PR) with 95% Confidence Intervals (CI) for receipt of invasive cardiovascular treatment prior to cardiovascular death in individuals with schizophrenia (SCZ) or bipolar disorder (BD), according to patient group, inclusion criteria and type of procedure.

Figure

Figure 1. Adjusted Prevalence Ratios (PR) with 95% lower (LCL) and upper (UCL) Confidence Limits for receipt of diagnostic CVD tests or invasive cardiovascular treatment prior to cardiovascular death in individuals with schizophrenia (SCZ) or bipolar disorder (BD), according to patient group and type of procedure.

Tables

Table 1. Descriptive characteristics of individuals with or without schizophrenia or bipolar disorder who died due to cardiovascular disease at ages 18 and above.

	SCZ		BD		No SMI	
Demographic characteristics						
Persons, n	814		673		70,898	
Men, n (%)	384	(47.2)	291	(43.2)	32,962	(46.5)
Age at death, mean (SD)	76.0	(14.6)	75.6	(13.4)	83.5	(11.3)
Age 18-59 at death, n (%)	122	(15.0)	83	(12.3)	3,065	(4.3)
Age 60-69 at death, n (%)	145	(17.8)	129	(19.2)	5,423	(7.6)
Age 70-79 at death, n (%)	153	(18.8)	157	(23.3)	10,844	(15.3)
Age 80-89 at death, n (%)	237	(29.1)	201	(29.9)	27,481	(38.8)
Age 90 and above at death, n (%)	157	(19.3)	103	(15.3)	24,085	(34.0)
Causes of death						
I20-I25 Ischemic heart disease, n (%)	327	(40.2)	252	(37.4)	25,806	(36.4)
I30-I52 Other forms of heart disease, n (%)	223	(27.4)	169	(25.1)	20,420	(28.8)
I60-I69 Cerebrovascular disease, n (%)	184	(22.6)	167	(24.8)	16,514	(23.3)
Other cardiovascular diseases, n (%)	80	(9.8)	85	(12.6)	8,158	(11.5)
Time from CVD diagnosis until death						
First CVD at date of death, n (%)	139	(17.1)	76	(11.3)	5,562	(7.8)
First CVD ≤ 30 days before death, n (%)	186	(22.9)	114	(16.9)	7957	(11.2)
Years from 1. CVD diagnosis until death, median (25/75 percentile)	4.3	(2.4-6.0)	4.2	(2.7-6.2)	4.8	(3.2-6.5)
Diagnoses, n (%)						
Cardiovascular disease	698	(85.7)	610	(90.6)	66,351	(93.6)
Hypertension	390	(47.9)	384	(57.1)	43,341	(61.1)
Cardiac arrhythmia	298	(36.6)	262	(38.9)	35,492	(50.1)
Congestive heart failure	333	(40.9)	257	(38.2)	34,186	(48.2)
Myocardial infarction	238	(29.2)	183	(27.2)	24,278	(34.2)
Cerebrovascular disease †	295	(36.2)	275	(40.9)	29,986	(42.3)
Valvular disease	114	(14.0)	116	(17.2)	16,367	(23.1)
Peripheral vascular disorder	95	(11.7)	101	(15.0)	14,242	(20.1)
Pulmonary circulation disorder	58	(7.1)	62	(9.2)	5,043	(7.1)
Hyperlipidemia	73	(9.0)	84	(12.5)	7,525	(10.6)
Diabetes	186	(22.9)	156	(23.2)	14,726	(20.8)
Obesity	36	(4.4)	51	(7.6)	1489	(2.1)
Alcohol abuse	46	(5.7)	90	(13.4)	2,283	(3.2)
Drug abuse	37	(4.5)	64	(9.5)	728	(1.0)
Modified CCI, mean (SD)	1.60	(2.0)	1.65	(2.1)	1.67	(2.2)
No CC groups, n (%)	341	(41.9)	250	(37.1)	28232	(39.8)
≥ 2 CC groups, n (%)	219	(26.9)	165	(24.5)	18,010	(25.4)

Abbrevations: SCZ, Schizophrenia; BD, Bipolar disorder; SMI, Severe mental illness; SD, Standard Deviation
† ICD-10 codes I60-I69, G45-G46 or H340, or ICPC-2 codes K89-K91. Based on data from the Norwegian Patient Registry (2008-2016), the Norwegian Directorate of Health's system for control and payment of health reimbursements in primary care (2008-2016) and the Norwegian Cause of Death Registry (2011-2016).
Data sources: The Norwegian Patient Registry (2008-2016), the Norwegian Directorate of Health's system for control and payment of health reimbursements in primary care (2008-2016) and the Norwegian Cause of Death Registry (2011-2016).

Table 2. Health care utilization prior to cardiovascular death in patients with or without schizophrenia or bipolar disorder who died due to cardiovascular disease at ages 18 and above.

	SCZ		BD		No SMI	
Primary care utilization per person-year, median (25/75 percentile)						
Contacts in primary care	12.9	(6.5-22.9)	15.8	(9.3-26.2)	11.4	(11.4-5.9)
No. of contacts according to type, median (25/75 percentile)						
GP visits	5.9	(2.6-12.0)	9.3	(5.1-15.4)	7.0	(3.4-12.4)
Emergency room visits	0.4	(0.2-0.9)	0.5	(0.2-1.1)	0.4	(0.2-0.7)
GP telephone contacts	4.6	(2.0-9.2)	4.9	(2.2-9.5)	2.8	(1.1-6.0)
No. of contacts according to diagnoses, median (25/75 percentile)						
Psychiatric symptoms/diagnoses	3.3	(1.2-7.3)	4.7	(1.7-9.8)	0.2	(0.0-1.2)
General symptoms/diagnoses	1.3	(0.4-3.4)	1.5	(0.5-3.5)	1.0	(0.3-1.2)
CVD symptoms/diagnoses	1.1	(0.1-3.8)	1.5	(0.2-4.3)	2.8	(0.7-7.5)
Other somatic symptoms/diagnoses	1.6	(0.5-4.0)	2.3	(1.0-5.0)	2.1	(0.7-4.4)
No. of patients with procedure, n (%)						
Any CVD-related diagnostic test	621	(76.3)	566	(84.1)	56,202	(79.3)
Electrocardiography (ECG)	410	(50.4)	382	(56.8)	38,736	(54.6)
24h blood pressure measurement	31	(3.8)	57	(8.5)	5,702	(8.0)
Glucose measurement	492	(60.4)	464	(68.9)	43,605	(61.5)
HbA1c measurement	325	(39.9)	308	(45.8)	28,371	(40.0)
Specialized somatic care utilization per person-year, median (25/75 percentile)						
No. of contacts according to type, median (25/75 percentile)						
Somatic admissions	0.5	(0.2-0.9)	0.6	(0.3-1.2)	0.5	(0.2-1.0)
Somatic emergency admissions	0.4	(0.2-0.8)	0.5	(0.2-1.0)	0.5	(0.2-0.8)
Days in somatic hospital	2.1	(0.9-4.8)	3.0	(1.0-6.4)	2.6	(0.9-5.4)
Somatic outpatient visits	1.0	(0.3-2.2)	1.7	(0.7-3.3)	1.6	(0.6-3.2)
No. of contacts according to diagnoses, median (25/75 percentile)						
Admissions with a CVD diagnosis	0.3	(0.0-0.6)	0.3	(0.1-0.7)	0.4	(0.1-0.7)
Outpatient visits with a CVD diagnosis	0.0	(0.0-0.3)	0.0	(0.0-0.4)	0.1	(0.0-0.5)
No. of patients with procedure, n (%)						
Any diagnostic CVD examination	359	(44.1)	366	(54.4)	38,907	(54.9)
Echocardiography	277	(34.0)	272	(40.4)	30,389	(42.9)
Coronary angiography	97	(11.9)	98	(14.6)	10,026	(14.1)
Ultrasound of peripheral vessels	34	(4.2)	73	(10.8)	6,516	(9.2)
Any invasive CVD procedure	98	(12.0)	109	(16.2)	13,217	(18.6)
Revascularization	54	(6.6)	54	(8.0)	5,684	(8.0)
Arrhythmia treatment	42	(5.2)	44	(6.5)	5,378	(7.6)
Vascular surgery	19	(2.3)	14	(2.1)	3,693	(5.2)

Abbrevations: SCZ, Schizophrenia; BD, Bipolar disorder; SMI, Severe mental illness; GP, General practitioner; CVD, Cardiovascular disease. Based on data from the Norwegian Patient Registry (2008-2016), the Norwegian Directorate of Health's system for control and payment of health reimbursements in primary care (2008-2016) and the Norwegian Cause of Death Registry (2011-2016).
Data sources: The Norwegian Patient Registry (2008-2016), the Norwegian Directorate of Health's system for control and payment of health reimbursements in primary care (2008-2016) and the Norwegian Cause of Death Registry (2011-2016).

Table 3. Adjusted Prevalence Ratios (PR) with 95% Confidence Intervals (CI) for receipt of diagnostic CVD tests prior to cardiovascular death in individuals with schizophrenia (SCZ) or bipolar disorder (BD), according to patient group, sex and type of procedure.

	All patients			Men			Women	
	PR †‡	95% CI	N	PR †‡	95% CI	n	PR †‡	95% CI
Diagnostic tests in primary care								
Electrocardiography (ECG)								
Schizophrenia	0.95	(0.89-1.02)	194	0.93	(0.84-1.03)	216	0.97	(0.88-1.06)
Bipolar disorder	1.06	(0.99-1.13)	173	1.05	(0.96-1.16)	212	1.06	(0.97-1.16)
24h Blood pressure measurement								
Schizophrenia	**0.39**	(0.28-0.55)	14	**0.34**	(0.20-0.56)	17	**0.45**	(0.28-0.72)
Bipolar disorder	0.83	(0.65-1.07)	30	0.89	(0.63-1.26)	28	0.77	(0.54-1.10)
Glucose test								
Schizophrenia	1.00	(0.95-1.06)	228	1.00	(0.92-1.08)	264	1.00	(0.93-1.08)
Bipolar disorder	**1.13**	(1.07-1.19)	210	**1.17**	(1.09-1.26)	257	1.09	(1.02-1.17)
Glycated hemoglobin (HbA1c) test								
Schizophrenia	0.99	(0.91-1.07)	163	1.00	(0.89-1.12)	162	0.97	(0.86-1.10)
Bipolar disorder	**1.12**	(1.03-1.21)	149	**1.16**	(1.04-1.30)	162	1.07	(0.95-1.20)
Diagnostic tests in specialized health care								
Echocardiography								
Schizophrenia	**0.77**	(0.70-0.84)	138	**0.74**	(0.65-0.85)	139	**0.79**	(0.69-0.91)
Bipolar disorder	**0.90**	(0.82-0.98)	136	0.93	(0.82-1.05)	137	**0.84**	(0.74-0.96)
Coronary angiography								
Schizophrenia	**0.66**	(0.55-0.79)	58	**0.61**	(0.48-0.77)	39	**0.72**	(0.54-0.97)
Bipolar disorder	**0.81**	(0.67-0.96)	66	0.93	(0.75-1.15)	32	**0.64**	(0.46-0.89)
Ultrasound of peripheral vessels								
Schizophrenia	**0.44**	(0.32-0.61)	19	**0.46**	(0.30-0.72)	15	**0.41**	(0.25-0.67)
Bipolar disorder	1.09	(0.88-1.36)	35	1.04	(0.76-1.42)	39	1.12	(0.83-1.51)

Abbrevations: PR, Prevalence Ratio; CI, Confidence Interval; n, no. of patients with procedure

† Adjusted for sex, age at death, alcohol and drug use disorder and somatic comorbidity

‡ Bold figures: Significant association at p-value <0.05

Data sources: The Norwegian Patient Registry (2008-2016), the Norwegian Directorate of Health's system for control and payment of health reimbursements in primary care (2008-2016) and the Norwegian Cause of Death Registry (2011-2016).

Table 4. Adjusted Prevalence Ratios (PR) with 95% Confidence Intervals (CI) for receipt of invasive cardiovascular treatment prior to cardiovascular death in individuals with schizophrenia (SCZ) or bipolar disorder (BD), according to patient group, inclusion criteria and type of procedure.

	Patients	Patients with procedure	PR †‡	95% CI
PCI or CABG				
Patients with CVD as underlying cause of death				
Schizophrenia	814	54	**0.65**	(0.50-0.84)
Bipolar disorder	673	54	0.79	(0.61-1.01)
Patients with diagnosed IHD prior to death				
Schizophrenia	327	54	0.82	(0.65-1.03)
Bipolar disorder	272	54	0.94	(0.75-1.18)
Arrhythmia therapy				
Patients with CVD as underlying cause of death				
Schizophrenia	814	42	**0.69**	(0.51-0.92)
Bipolar disorder	673	44	0.87	(0.65-1.15)
Patients with diagnosed arrhythmia prior to death				
Schizophrenia	298	42	0.86	(0.65-1.14)
Bipolar disorder	262	44	0.97	(0.74-1.27)
Peripheral vascular surgery				
Patients with CVD as underlying cause of death				
Schizophrenia	814	19	**0.43**	(0.28-0.68)
Bipolar disorder	673	14	**0.37**	(0.22-0.62)
Patients with diagnosed peripheral vascular disease prior to death				
Schizophrenia	101	19	0.73	(0.49-1.09)
Bipolar disorder	103	14	**0.50**	(0.31-0.82)

Abbrevations: PR, Prevalence Ratio; CI, Confidence Interval; PCI, Percutaneous coronary intervention; CABG, Coronary artery bypass surgery; CVD, Cardiovascular disease; IHD, Ischemic heart disease.
† Adjusted for sex, age at death, alcohol and drug use disorder and somatic comorbidity
‡ Bold figures: Significant association at p-value <0.05.
Data sources: The Norwegian Patient Registry (2008-2016), the Norwegian Directorate of Health's system for control and payment of health reimbursements in primary care (2008-2016) and the Norwegian Cause of Death Registry (2011-2016).

Figure 1

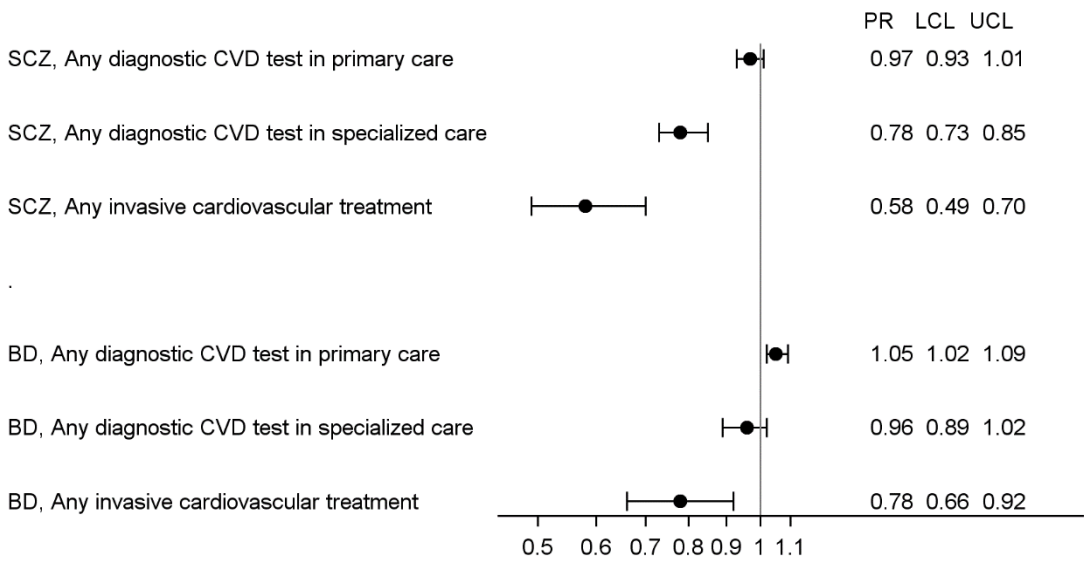


Figure 1. Adjusted Prevalence Ratios (PR) with 95% lower (LCL) and upper (UCL) Confidence Limits for receipt of diagnostic CVD tests or invasive cardiovascular treatment prior to cardiovascular death in individuals with schizophrenia (SCZ) or bipolar disorder (BD), according to patient group and type of procedure.
Data sources: The Norwegian Patient Registry (2008-2016), the Norwegian Directorate of Health's system for control and payment of health reimbursements in primary care (2008-2016) and the Norwegian Cause of Death Registry (2011-2016).

Supporting information

Table S1 Definitions of patient groups

Figure S1 Results of sensitivity analyses. Adjusted Prevalence Ratios (PR) with 95% lower (LCL) and upper (UCL) Confidence Limits for receipt of diagnostic CVD tests or invasive cardiovascular treatment prior to cardiovascular death in individuals with schizophrenia (SCZ) or bipolar disorder (BD), according to patient group, health care sector and type of procedure.

Table S1 Definitions of patient groups

Patient group	ICD-10 codes	ICPC-2 codes
Congestive Heart Failure	I43, I50, I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, P29.0	K71, K77
Cardiac arrhythmias	I47-I49, I44.1-I44.3, I45.6, I45.9, R00.0-R00.1, R00.8, T82.1, Z45.0, Z95.0	K05, K78-K80
Valvular disease	I05-I08, I34-I39, A52.0, I09.1, I09.8, Q23.0-Q23.3, Z95.2-Z95.4	K83
Pulmonary circulation disorders	I26-I27, I28.0, I28.8-I28.9	K82, K93
Peripheral vascular disorders	I70-I71, I73.1, I73.8-I73.9, I77.1, I79.0, I79.2, K55.1, K55.8-K55.9, Z95.8, Z95.9	K92
Hypertension, uncomplicated	I10	K86
Hypertension, complicated	I11-I13, I15	K87
Paralysis	G81-G82, G04.1, G11.4, G80.1-G80.2, G83.0-G83.4, G83.9	-
Other neurological disorders	G10-G13, G20-G22, G32, G35-G37, G40-G41, R56, G25.4-G25.5, G31.2, G31.8-G31.9, G93.1, G93.4, R47.0	N07, N86-N88
Chronic pulmonary disease	J40-J47, J60-J67, I27.8-I27.9, J68.4, J70.1, J70.3	K82, R79, R95-R96
Diabetes, uncomplicated	E10.0-E10.1, E10.9-E11.1, E11.9-E12.1, E12.9-E13.1, E13.9-E14.1, E14.9	T90
Diabetes, complicated	E10.2-E10.8, E11.2-E11.8, E12.2-E12.8, E13.2-E13.8, E14.2-E14.8	T89
Hypothyroidism	E00-E03, E890	T86
Renal failure	N18-N19, I12.0, I13.1, N25.0, Z49.0-Z49.2, Z94.0, Z99.2	-
Liver disease	B18, I85, K70, K72-K74, I86.4, I98.2, K71.1, K71.3-K71.5, K71.7, K76.0, K76.2-K76.9, Z94.4	D97
Peptic ulcer disease excluding bleeding	K25.7, K25.9, K26.7, K26.9, K27.7, K27.9, K28.7, K28.9	D85-D86
AIDS/HIV	B20-B22, B24	B90
Lymphoma	C81-C85, C88, C96, C90.0, C90.2	B72, B74
Metastatic cancer	C77-C80	-
Solid tumor without metastasis	C0-C1, C6, C20-C26, C30-C34, C37-C41, C43, C45-C58, C70-C76, C97	D74-D75, D77, L71, N74, R84-R85, T71, U75-U77, W72, X75-X77, Y77-Y78
Rheumatoid arthritis/collagen vascular diseases	M05-M06, M08, M30, M32-M35, M45, L94.0-L94.1, L94.3, M12.0, M12.3, M31.0-M31.3, M46.1, M46.8-M46.9	L88
Coagulopathy	D65-D68, D69.1, D69.3-D69.6	-
Obesity	E66	T82-T83
Weight loss	E40-E46, R64, R63.4	T08
Fluid and electrolyte disorders	E86-E87, E22.2	T11
Blood loss anemia	D50.0	-
Deficiency anemia	D51-D53, D50.8-D50.9	B80-B81
Alcohol abuse	F10, E52, T51, G62.1, I42.6, K29.2, K70.0, K70.3, K70.9, Z50.2, Z71.4, Z72.1	P15, P16
Drug abuse	F11-F16, F18-F19, Z71.5, Z72.2	P18-P19
Lipidemia	E78	T93
Dementia	F00-F03, G30, F05.1, G31.1	P70

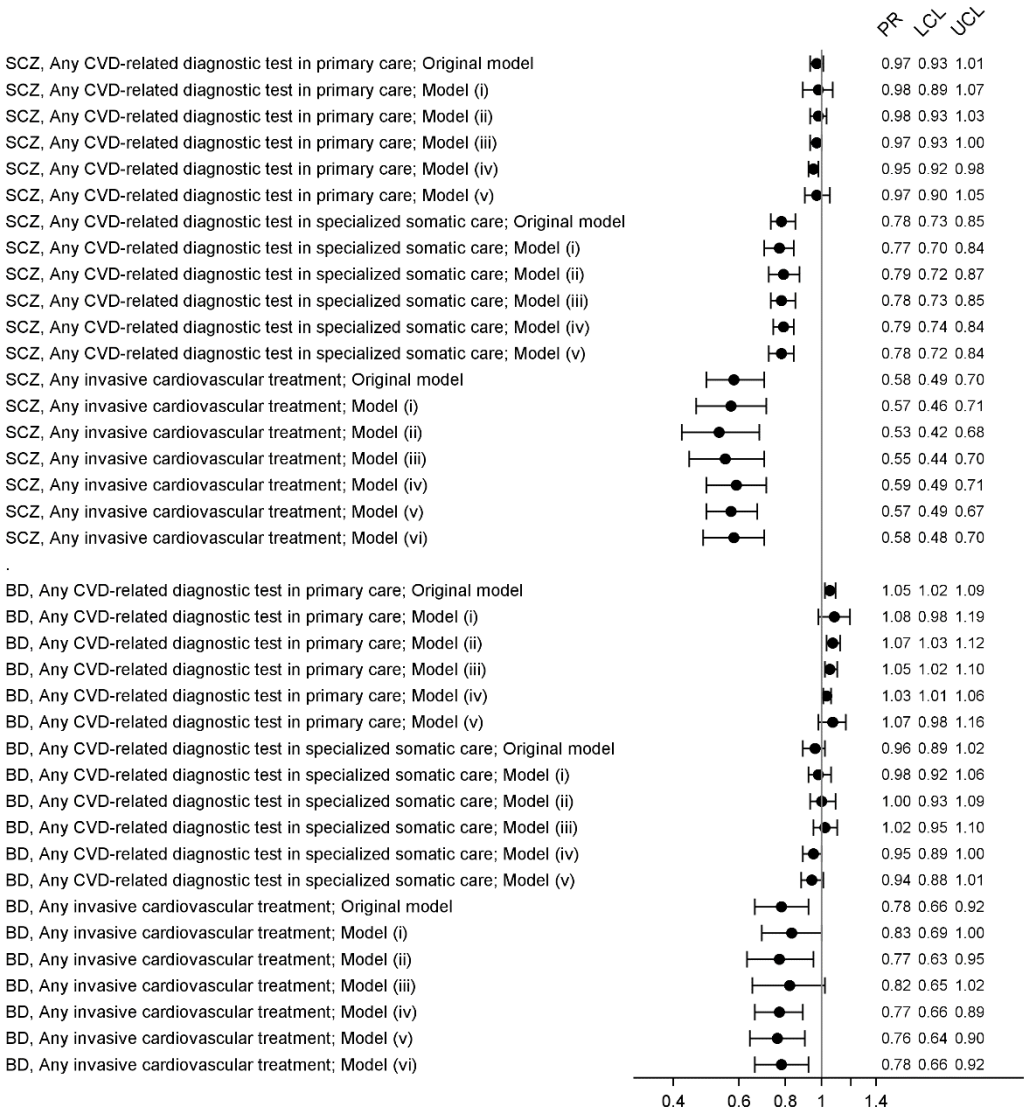


Figure S1 Results of sensitivity analyses. Adjusted Prevalence Ratios (PR) with 95% lower (LCL) and upper (UCL) Confidence Limits for receipt of diagnostic CVD tests or invasive cardiovascular treatment prior to cardiovascular death in individuals with schizophrenia (SCZ) or bipolar disorder (BD), according to patient group, health care sector and type of procedure. Data sources: The Norwegian Patient Registry (2008-2016), the Norwegian Directorate of Health's system for control and payment of health reimbursements in primary care (2008-2016) and the Norwegian Cause of Death Registry (2011-2016).

Model (i): Excluding patients diagnosed with dementia
Model (ii): Excluding patients aged 80 and above
Model (iii): Excluding patients with the ambiguous affective disorder diagnosis (ICPC-2 code P75) from the BD group
Model (iv): Including also cases with CVD as contributing cause of death
Model (v): Adjusting for person-years of observation
Model (vi): Excluding persons who died at their first CVD encounter in the period