Original research

Nationwide burden of sudden cardiac death among patients with a psychiatric disorder

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ABSTRACT

Background Patients with psychiatric disorders have increased all-cause mortality compared with the general population. Previous research has shown that there is a fourfold increased risk of sudden cardiac death (SCD) among the young.

Objective To investigate the incidence of SCD in patients with psychiatric disorders aged 18–90 years in the Danish population by systematically reviewing all deaths in 1 year.

Methods We examined all deaths in Denmark among residents aged 18–90 years in 2010 by reviewing death certificates and autopsy reports. All deaths were categorised as non-SCD or SCD based on the available information. Psychiatric disorder was defined according to International Classification of Diseases, 10th revision criteria or by redemption of a prescription for psychotropic medication within 1 year.

Results Of 4.3 million residents in 2010, we observed 45 703 deaths, of which 6002 were due to SCD. Overall, the incidence rate ratio of SCD was 1.79–6.45 times higher among patients with psychiatric disorders than in the general population and was age dependent ($p<0.001$ across all age groups). When adjusting for age, sex and comorbidities, psychiatric disorders were independently associated with SCD, with a HR of 2.31 (2.19 to 2.43, $p<0.001$), and HR was highest among patients with schizophrenic disorders, with a HR of 4.51 (3.95 to 5.16, $p<0.001$). Furthermore, 18-year-old patients with a psychiatric disorder had an expected 10-year excess loss of life. Patients aged 18–40 with a psychiatric disorder had 13% of excess life years lost caused by SCD.

Conclusion In this study, the rate of SCD in patients with psychiatric disorders is higher across all age groups than in the general population. Having a psychiatric disorder is independently associated with SCD. Patients with schizophrenic disease had the highest rates of SCD. Life expectancy for an 18-year old with a psychiatric disorder is estimated to be 10 years shorter in comparison with those without this disorder.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The risk of sudden cardiac death (SCD) is increased fourfold among young individuals (18–35 years) with a psychiatric disorder.

WHAT THIS STUDY ADDS

⇒ The increased risk for SCD extends across all age groups, from 18 to 90 years.
⇒ Patients with schizophrenia exhibit particularly high rates of SCD.
⇒ The life expectancy of an 18-year-old with a psychiatric disorder is reduced by approximately 10 years.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ There is a critical need for thorough monitoring of psychiatric patients, with a specific focus on cardiometabolic factors and regular ECG monitoring, to mitigate the heightened risk of SCD.

INTRODUCTION

Patients with psychiatric disorders have consistently been shown to die prematurely in comparison with the general population.[1] A patient with a severe psychiatric disorder is expected to have a life expectancy of 5–15 years shorter than that of the general population.[2]

The shorter lifespan is probably caused, in part, by physical comorbidities, such as diabetes mellitus and ischaemic heart disease.[3] In addition, some deaths are caused by malignant arrythmias due to prolongation of corrected QT (QTc), which is a known side effect of psychotropic medication.[4]

Sudden cardiac death (SCD) is defined as an unexpected and sudden death from a cardiovascular cause in a person with or without pre-existing heart disease. The incidence of SCD has been reported to occur at an annual rate of 0.8% in patients admitted to a psychiatric hospital, which is higher than in the general population, and studies have shown that the risk of SCD in psychiatric patients is three times higher than in the general population.[5]

In addition to the risk of QTc prolongation due to treatment with psychotropic medication, there is also a risk of metabolic syndrome due to lifestyle and side effects of medication, increasing the risk of cardiovascular disease.[6] It has previously been shown, that positive toxicology at autopsy was associated with SCD, with psychotropic drugs being most frequently involved.[7 8]

Patients diagnosed with schizophrenia or bipolar affective disorder have been shown to be at highest risk of SCD as well as all-cause mortality.[1 9] Previous research has highlighted cardiovascular disease as a primary cause of death among individuals with a psychiatric disorder. Autopsy studies have revealed that a significant proportion of patients

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with schizophrenia and apparently unexplained deaths had evidence of coronary atherosclerosis.[10] Furthermore, patients diagnosed with hereditary channelopathies, such as Brugada syndrome or long QT syndrome, are at increased risk of developing depression or anxiety.[11 12] Diabetes mellitus, a well-known comorbidity among patients with psychiatric disorders, as well as a risk factor for cardiovascular disease, is associated with a vastly higher incidence rate of SCD among the young compared with patients without diabetes.[13] Finally, it has previously been reported that the risk of SCD among individuals aged 18–35 years, with psychiatric disorders, is increased fourfold.[14] It is, however, largely unknown how psychiatric disease affects SCD risk in patients older than 35 years.

This study aims to examine SCD burden in patients with a psychiatric disorder, across age groups 18–90 years, for 1 year and compare this with the general population in Denmark.

METHODS

Study design

This 1-year nationwide cohort study includes all individuals aged 18–90 years in Denmark at the start of the study (1 January 2010) using national registers. All individuals were followed up from the start of the study to death, emigration or end of the study (31 December 2010), and all deaths were thoroughly adjudicated using autopsy reports, death certificates and information from national health registers.

The Danish healthcare system and Danish registers

All Danish residents are assigned a unique personal civil registration number, which can be linked to national registers on an individual level. For this study, we used several different registers: (1) The Danish National Patient Register, which holds information on previous medical history. Diagnoses can be retrieved from the Danish hospitals and emergency departments since 1977 (outpatient contacts since 1994), using International Classification of Diseases, 10th revision (ICD-10) diagnosis codes (ICD-10 from 1995 and onwards) for each visit. (2) The Danish Cause of Death Register, which holds information on the cause of death, in which immediate, contributory and underlying causes of death are recorded using ICD-10 codes. (3) The Danish National Prescription Register, which contains all claimed prescriptions since 1995.

Exposure and comorbidities

Psychiatric disorder was defined according to either (1) the presence of at least one psychiatric ICD-10 code (online supplemental table 1) within 10 years before the study start or (2) redemption of a prescription for psychotropic medication (online supplemental table 2) within 1 year before the study start. As ICD-10 codes are retrievable only from Danish hospitals or emergency departments, the inclusion of redemption of psychotropic medication is intended to work as a surrogate for milder forms of psychiatric disorders, as these patients might only seek treatment from their general practitioner, where the ICD-10 diagnosis is not available.

In order not to overstate psychiatric disorders, participants with acute intoxication diagnosis or dementia and no other F code diagnosis were regarded as non-exposed. The following medication: hypnotics for sleep, medication for dementia, parasympathomimetic agent or medication for smoking cessation were not included, as in a prior study.[15]

Information on comorbidities was obtained from discharge diagnoses issued up to 10 years prior to death. ICD codes used are available in the supplementary appendix (online supplemental table 3).

Outcomes

Death certificates and autopsy

The method of performing SCD adjudication has been described previously.[16] We used a nationwide approach with the extraction of comprehensive information from autopsy reports and nationwide health registries. In short, whenever a patient dies in Denmark, a death certificate is issued by a medical doctor, who, based on all available information, including medical records, determines the most likely immediate, contributory and underlying cause of death. Police involvement is mandatory whenever a person is found dead and/or death is sudden and unexpected. The police decide whether a medicolegal external examination should be performed. Information on the circumstances of death is often included in the supplementary information field and also in the absence of a medicolegal external examination, which makes Danish death certificates highly suitable for the identification of sudden death.[16]

All deaths in Denmark in 2010 were thoroughly and manually reviewed case by case to identify all cases of sudden death and from these, all SCD cases. All deceased with incomplete information on the death certificate were classified as non-SCD natural deaths. We followed European Society of Cardiology SCD criteria (where persons not seen alive and functioning normally within 24 hours are classified as non-SCD).[17]

SCD was categorised according to certainty of information.[18] SCD cases were assessed as SCD regardless of subgroup. The subgroups of SCD have been discussed elsewhere.[16] The definition and further grouping of SCD are available in the supplementary appendix.

Toxicology had been performed in instances where the circumstances regarding death implied that toxicology might have been the cause. The autopsy rate was 7% in this study. Further examination of the data showed that only 15 individuals with a psychiatric diagnosis had a toxicological screening, showing primarily traces of alcohol in under three individuals, otherwise there were no results, or signs of overdosage.

Statistical methods

Baseline characteristics are presented as median (first quartile, third quartile) for continuous variables, and categorical variables as count (%). Incidence rates were calculated by dividing the number of SCDs by total person-time at risk along 95% Poisson CIs. Hazard ratios (HRs) were obtained using multivariable Cox proportional hazards models, with adjustment for sex, cardiovascular disease, arrhythmic disease, heart failure, ischaemic heart disease, peripheral artery disease, cerebrovascular disease, diabetes, and age used as the primary time scale.

The impact of psychiatric disorders on all-cause mortality and SCD is illustrated by calculating life-years lost due to SCD and excess life-years lost compared with the general population before the age of 90 years.[19] These analyses are performed using the R package *lillies*.[20] In short, the life expectancy at a given age is calculated as the area under the survival curve for different exposure groups with an artificial maximum of 90 years imposed. Excess life-years lost are the difference in life expectancy for these exposure groups. Further, life-years lost, and excess life-years lost were analysed to determine the specific causes of death—that is, of the excess years lost for patients with psychiatric disorders, how many excess life-years were due, for example, to SCD. For these analyses, outcomes were categorised

Table 1 Baseline characteristics showing the proportion of people with comorbidities, aged 18–90 years, in the general population (n=3 550 449) and in patients with a psychiatric disorder (n=732 288) in Denmark in 2010, who are included as the study population

Characteristics	General population n=3 550 449	Psychiatric disorder: n=732 288
Age (years)	47 (34, 62)	51 (37, 65)
Male sex	1 813 745 (51%)	297 622 (41%)
Cerebral disease	82 481 (2.3%)	52 557 (7.2%)
Diabetes	96 193 (2.7%)	19 463 (2.7%)
Heart failure	39 754 (1.1%)	41 104 (5.6%)
Arrhythmic disease	109 727 (3.1%)	41 802 (5.7%)
Ischaemic heart disease	148 686 (4.2%)	59 479 (8.1%)
Peripheral artery disease	50 203 (1.4%)	23 791 (3.2%)
Other cardiovascular disease	407 324 (11%)	148 486 (20%)
Resultsare shown as median (IQR) or n (%).		

into (1) SCD, (2) non-SCD natural death, and (3) non-natural deaths (accidents, suicides, overdoses due to drugs and alcohol, violent deaths, etc).

The main analysis was carried out on all SCD categories as one group (definite, probable and possible). Additionally, a sensitivity analysis was performed using only the category of definite SCD, and all other categories as non-SCD natural deaths.

Information about natural/non-natural deaths was obtained from the Danish Death Certificate.

In all Cox models adjustment for age was carried out using age as the primary time scale.

All analyses were performed using R version 4.2.1 (R Core Team, 2021).

Ethics

This study complies with the Declaration of Helsinki and was approved by the Danish Data Protection Agency (2015-41-4510) and the Danish Patient Safety Authority (3-3013-2262/1). Patient consent was not required for this study.[16]

RESULTS

Background and population

On 1 January 2010, the population of Denmark was 5.5 million inhabitants, of whom 4.3 million were aged 18 to 90 years. Of the 4.3 million inhabitants, 732 288 fulfilled the definition for a psychiatric disorder. Patients with psychiatric disorders were older, more often female and more disposed to comorbidities, such as cardiovascular disease, heart failure, arrythmias, and ischaemic heart disease (table 1).

Outcomes and incidence of SCD

During a 1-year follow-up, 45 703 deaths were recorded, with 6002 due to SCD. Among these, 3683 SCD cases were in the general population and 2319 among patients with a psychiatric disorder. Of 4 241 439 person years of follow-up, 3 521 435 were in the general population and 720 004 in those with psychiatric disorders. Patients with psychiatric disorders had a 1.79–6.45 times higher incidence rate ratio (IRR), of SCD, depending on the age group compared with the general population. While it was 3.53 times higher across the cohorts without taking age groups into account (95% CI 3.42 to 3.64, p<0.001).

SCD incidence rate and incidence rate ratios were higher in all age groups, although attenuated in the oldest groups (figure 1, table 2 and online supplemental figure 2).

Multivariable adjustment

In a multivariable Cox proportional hazards model where age was used as the underlying time scale and, with adjustment for, sex, heart failure, arrhythmic disease, peripheral artery disease, ischaemic heart disease, cerebrovascular disease, diabetes and other cardiovascular disease, we found that psychiatric disorders were independently associated with SCD, HR=2.31 (95% CI 2.19 to 2.43, p<0.001)(online supplemental table 4). For patients with depressive disorders the HR was 2.10 (95% CI 1.92 to 2.30, p<0.001), whereas it was 2.93 (95% CI 2.36 to 3.62, p<0.001) for patients with bipolar disorder. However, patients with schizophrenic disorder had the highest SCD rates HR=4.51 (95% CI 3.95 to 5.17, p<0.001) (online supplemental table 5).

Accounting for relevant comorbidities, HR for patients with SCD and psychiatric disorder was 2.08 (95% CI 1.74 to 2.49, p<0.001)(online supplemental table 6).

To differentiate further between ICD-10 code diagnosis and psychotropic medication the same adjustment was made regarding diagnosis versus medication yielding a HR=3.23 (95% CI 3.03 to 3.44, p<0.001) for ICD-10 diagnosis and HR=1.73 (95% CI 1.62 to 1.85, p<0.001) for medication (online supplemental table 7).

Furthermore, psychiatric disorders were significantly associated with non-SCD mortality when adjusted for the aforementioned comorbidities with a HR of 2.81 (95% CI 2.75 to 2.86, p<0.001) (online supplemental table 8).

Excess life-years lost due to SCD

The probabilities of survival and death from the three different causes for people with psychiatric disorders and the general population is shown in figure 2. An 18-year-old with a psychiatric disorder could on average expect to reach an age of 68 years compared with 78 years for the general population in this study (online supplemental figure 1). This difference diminishes with age, a 70-year-old has an expectancy of 80 years versus 84 years in the general population. Up to an age of around 40 years, SCD explains around 13% of the excess loss of life years and around 17% of the loss due to natural deaths (figure 3).

DISCUSSION

This nationwide cohort study shows that there is an association between psychiatric disorders and the risk of SCD in people aged 18–90 years.

We report an increase in the incidence of SCD among the patients with psychiatric disorders across all age groups. We also find that psychiatric disorder, when adjusting for comorbidities, independently is significantly associated with SCD. Furthermore, we show that the young with a psychiatric disorder alone have a life expectancy that is 10 years shorter than that of the general population, in accordance with prior findings,[2 21] and specifically, with 13% of excess loss of life-years being due to SCD. To our knowledge, this has not been reported previously.

It has previously been reported that patients aged 18–35 years admitted with a psychiatric disorder have a fourfold increased incidence of SCD.[14] These findings are similar to our study, with risk being between 2–6-fold higher depending on the age group and 3.53-fold higher overall.

The incidence rate ratio is highest in people aged <50 years and decreases with age. This phenomenon could be explained by depletion of people susceptible to SCD with psychiatric disorders, as well as the age-dependent increase in SCD rate in the general population due to competing causes.

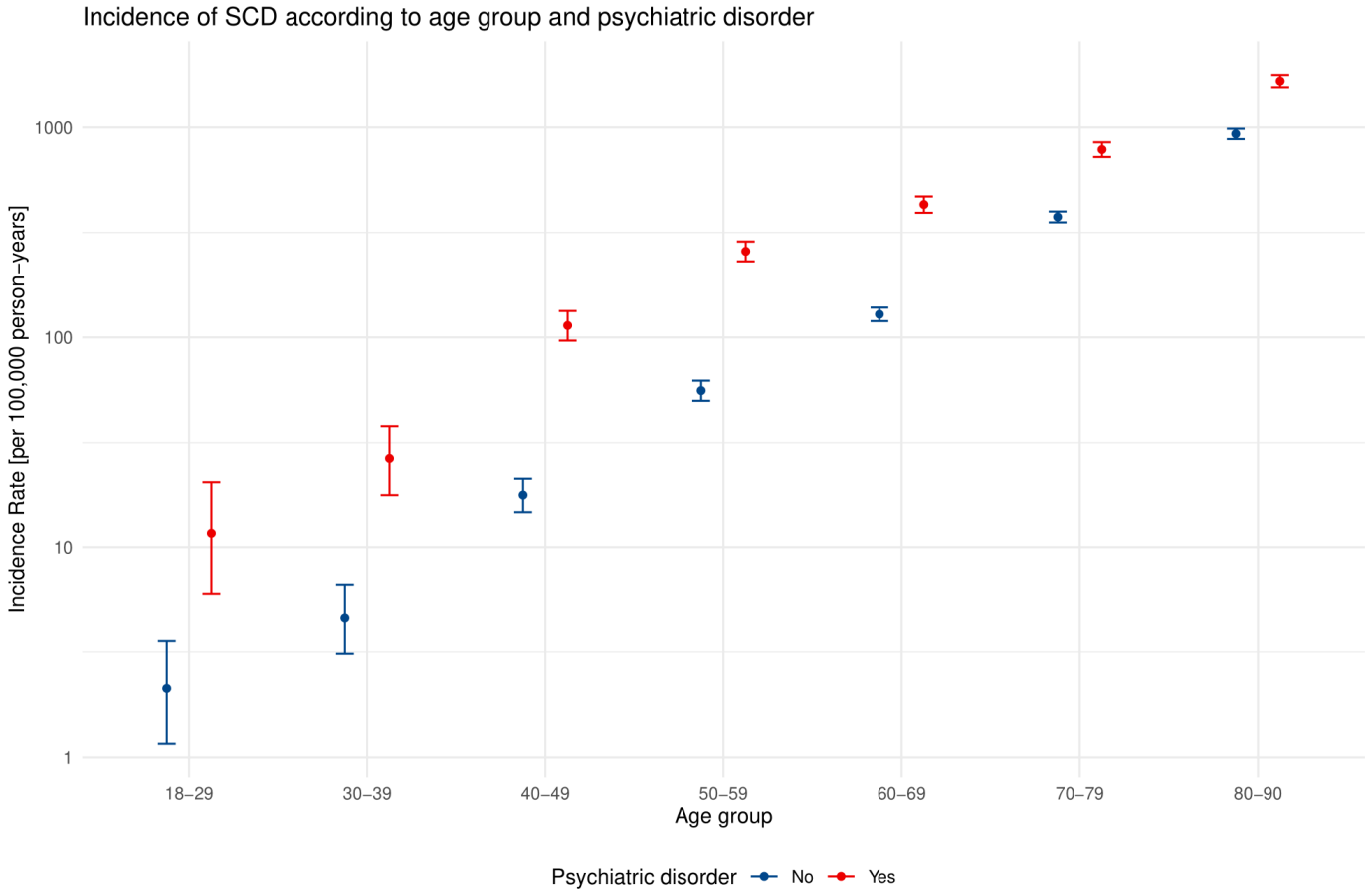

Figure 1 Incidence rate per 100 000 person-years, for sudden cardiac death in the study population comparing people with (red) and without (blue) a psychiatric disorder stratified by age groups. (Logarithimic scale showing the incidence rate per 100 000 person-years on the y-axis. Age groups on the x-axis.)

The higher prevalence of comorbidities in people with a psychiatric disorder emphasises the complexity in terms of mental health and cardiovascular death. A patient with a psychiatric disorder is more disposed to have an unhealthy lifestyle, with unhealthy food habits, smoking, alcohol or substance abuse, and low adherence to exercise as well as obesity, a known side effect of tricyclic antidepressant or antipsychotic agents. All these factors independently can lead to the development of conditions such as hypertension, atherosclerosis and ischaemic heart disease.

There was a higher prevalence of cardiovascular disease among patients with psychiatric disorders in our cohort. A broad range of psychiatric diagnoses are associated with a higher burden of comorbidities, reported to be 1.4–2.0 times higher among patients with psychiatric disorders than among the general population.[22] Something that holds true in this study as well.

Table 2 Incidence rate ratios (IRR) for sudden cardiac death between study population with psychiatric disorders and general population without psychiatric disorders. Stratified by age groups

Age group	IRR	95% CI	P value
18–29 years	5.49	2.54 to 11.87	<0.001
30–39 years	5.70	3.41 to 9.54	<0.001
40–49 years	6.45	5.07 to 8.19	<0.001
50–59 years	4.60	3.95 to 5.36	<0.001
60–69 years	3.33	2.97 to 3.74	<0.001
70–79 years	2.09	1.89 to 2.31	<0.001
80–90 years	1.79	1.64 to 1.96	<0.001

Furthermore, after adjusting for comorbidities, psychiatric disorder remained associated with SCD. This suggests that comorbidities, such as cardiovascular disease, are not the only mediators contributing to the higher risk of SCD, but that psychiatric disorder is an independent risk factor. The effect varies, with patients who have schizophrenic disorders being more vulnerable than patients with depressive disorders. It should be noted that the adjusted HR for non-SCD deaths was also significantly associated with psychiatric disorder. The associations might be due to the previously mentioned unhealthy lifestyle, substance abuse, greater burden of comorbidities and non-sufficient diagnostics in patients with psychiatric disorders, as they are less likely to seek medical attention, despite symptoms.[23]

It has previously been reported, that patients with severe psychiatric disorders might be less likely to access or pursue medical care for their symptoms, and that they might receive inadequate care when they do seek help.[22] Patients with schizophrenia are reported to be 50% less likely to receive revascularisation for myocardial infarction.[24] Furthermore, patients with schizophrenia and depressive disorder have been shown to have an increased risk of SCD, due to higher burdens of cardiovascular comorbidities and risk factors, as well as poorer resuscitation.[25] The incidence of non-ischaemic cardiomyopathy is also higher among patients with schizophrenia, while the risk of ventricular tachycardia/ventricular fibrillation, independently of

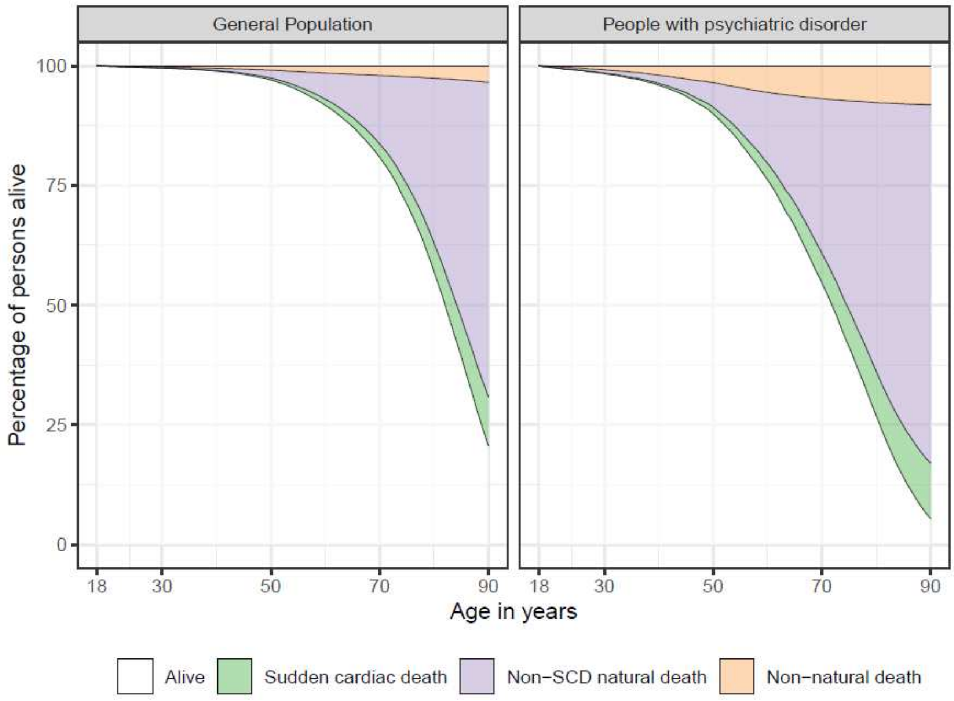

Figure 2 Probabilities of survival and death from different causes from age 18 and upward among people with (right) or without (left) psychiatric disorder. SCD, sudden cardiac death.

cardiovascular disease, is increased among patients with depressive mental disorder.[25]

In addition to mental illness itself, treatment with psychotropic medication might mediate cardiometabolic outcomes such as weight gain, and type 2 diabetes. There are also varying degrees of cardiac conduction delay, causing a prolonged QTc interval, which might predispose to torsades-de-pointes, causing sudden death. Although the QTc interval alone cannot identify the risk of SCD in patients treated with antipsychotic drugs, psychiatric medication still warrants considerable attention, and several preventive measures have been proposed to reduce the number of deaths (smoking cessation, reducing alcohol

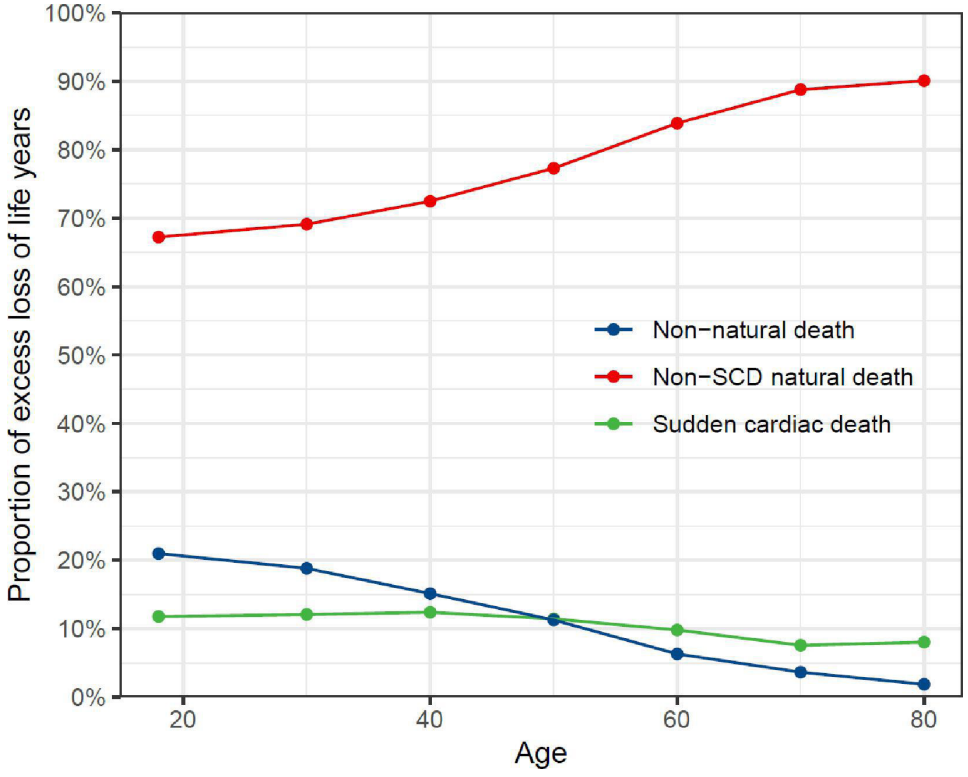

Figure 3 Proportion of excess loss of life-years according to age in patients with a psychiatric disorder. SCD, sudden cardiac death.

intake, optimising cardiovascular health and increasing social support).[25 26]

It should also be noted that across age groups there is a disproportion in the number of women among patients with psychiatric disorders in our cohort (60% vs 49% in general population). Women, in general, are reported to more often suffer from depression and anxiety disorders than men, which could explain the sex disproportionality.[27] Furthermore, women might be more aware of symptoms and signs of psychiatric disorders, and more motivated to seek out their general practitioner or the healthcare system for assessment.[28] Nevertheless, previous findings indicate that male symptoms of depression might be different than the typically expected symptoms as men are more likely to overwork, indulge in substance abuse or exert aggressive type of behaviour, which might suggest that depression among men can go unrecognised.[29]

The causes of an increase in SCD among patients with psychiatric disorders, is most likely to be multifactorial, as these patients have a higher prevalence of cardiac comorbidities, and are at risk of adverse side effects due to psychotropic medication. Furthermore, a lifestyle with social isolation might contribute to unwitnessed cardiac arrest, reducing the odds of resuscitation.[25]

Treatment with psychotropic medication might act as a mediator for cardiometabolic outcomes, as well as cardiac conduction delay, and there are findings indicating genetic variants present with a vulnerability for psychotropic medication inducing a QTc-interval prolongation.[30]

Limitations

As this is an observational study, limitations are inherent, and causality cannot be inferred. We rely on register-based data such as ICD codes for diagnosis, and ATC codes for medications, which might under-represent or misrepresent true disease status. Thus, psychiatric disorder in this study represents diagnosis by ICD-10 code or redeemed prescriptions and does not necessarily include all instances of psychiatric illness. The classification of psychiatric disorder or common causes of death in Denmark might be comparable to that of other Western European and North American countries; however, there will be greater variations across the world. The follow-up took place in 2010, and it is therefore difficult to assess whether the data hold true today, as treatments and outcomes might have changed. The possibility cannot be excluded that the risk of SCD related to mental illness has decreased in clinical practice since 2010 as mental health services during the past decade have increasingly focused on reducing metabolic risk factors, such as body mass index, smoking and alcohol and substance use, as well as side effects of psychotropic medication, including arrythmia, weight gain, cholesterol, lipids, blood sugar, etc. Extrapolation of the findings from this study to countries with different demographics and healthcare systems should be done with caution.

CONCLUSION

In this study patients with psychiatric disorders, in comparison with the general population, had an increased rate of SCD across all age groups. Patients with schizophrenic disorders were shown have the highest rates of SCD.

These associations were independent of other comorbidities. Furthermore, in this study, life expectancy for an 18-year-old with a psychiatric disorder is expected to be 10 years shorter, with 13% of excess life-years lost due to SCD. These results highlight the importance of thoroughly following up patients with a psychiatric disorder, focusing on cardiometabolic factors and ECG monitoring, to treat risk factors associated with SCD, in order to prevent premature death.

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Contributors JM drafted the manuscript. All authors contributed to the conception, and design of the study, as well as acquisition, analysis and interpretation of data. All authors contributed to the final text and approved it. JT-H is the guarantor of this study.

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Competing interests LVKe has within the preceding three years been a consultant for Teva and Lundbeck. LVKø has received speaker's honorarium from AstraZeneca, Boehringer, Novartis and Novo Nordisk. JT-H is a consultant for Johnson and Johnson, Microport, Boston, Cytokinetics and Leo Pharma, and has received funding from John and Birthe Family foundation. The remaining authors declare no conflicts of interests.

Patient and public involvement This is a retrospective observational study. In this study, data was extracted from the Danish National Patient Register which holds information on previous medical history, the Danish Cause of Death Register which holds information on the cause of death and the Danish National Prescription Register which contains all claimed prescriptions since 1995. There was no direct patient or public involvement in the design, recruitment, or conduct of the study.

Patient consent for publication Not applicable.

Ethics approval This study complies with the Declaration of Helsinki and was approved by the Danish Data Protection Agency (2015-41-4510) and the Danish Patient Safety Authority (3-3013-2262/1). Patient consent was not required for this study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. Data from participants is pseudonymised and is accessible from Danish Nationwide registers for authorised staff/researchers.

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