Sudden Cardiac Death in Young Adults With Previous Hospital-Based Psychiatric Inpatient and Outpatient Treatment: A Nationwide Cohort Study From Denmark

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ABSTRACT

Introduction: Psychiatric patients have premature mortality compared to the general population. The incidence of sudden cardiac death (SCD) in psychiatric patients is unknown in a nationwide setting. The aim of this study was to compare nationwide SCD incidence rates in young individuals with and without previous psychiatric disease.

Method: Nationwide, retrospective cohort study including all deaths in people aged 18–35 years in 2000–2006 in Denmark. The unique Danish death certificates and autopsy reports were used to identify SCD cases. Psychiatric disease was defined as a previous psychiatric hospital contact and was identified using The Danish Psychiatric Central Research Register. All diagnoses in Danish registries are coded according to *ICD-8* or *ICD-10*. All hospital records were retrieved manually.

Results: Among 5,178 deaths, 395 were due to SCD and autopsies were performed on 262 (66%). In 77 SCD cases, a previous psychiatric hospital contact was identified. The SCD incidence rate in psychiatric patients was 14.8 (95% CI, 11.7–18.5) per 100,000 person-years versus 3.8 (95% CI, 3.4–4.3) per 100,000 person-years in individuals without psychiatric hospital contact (incidence rate ratio = 3.9; 95% CI, 3.0–5.0; $P < .01$). Incidence rates per 100,000 persons-years were the highest in patients with schizophrenia-spectrum disorders (38.9; 95% CI, 26.4–55.2) and substance-related disorders (31.6; 95% CI, 19.3–48.8). SCDs in psychiatric patients compared to nonpsychiatric patients were more often unexplained (65% vs 40%, $P = .02$), and cardiac symptoms were reported prior to death in 46% of psychiatric patients.

Conclusions: Patients with prior psychiatric hospital contact have a 4-fold increased risk of SCD. Since almost 50% had possible cardiac symptoms prior to death, cardiovascular risk monitoring and management in the mentally ill are essential.

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Extensive data from national registries in Nordic countries[1–5] have documented that patients with psychiatric disorders die prematurely compared to the general population. Women and men with severe mental disorders have a 15- and 20-year shorter life expectancy, respectively, and patients with bipolar disorders or schizophrenia are particularly vulnerable.[5–7] The shorter life expectancy is probably caused, in part, by unhealthy living, but other explanations, including medically induced malignant cardiac arrhythmias, have been proposed.[8] Medications known to prolong the heart rate–corrected QT interval have been associated with an increased risk of sudden cardiac death (SCD) in several studies.[9–11] In order to reduce the number of these deaths, psychiatric medications have been given considerable attention, and preventive strategies have been suggested.[12–14] Although nationwide registry-based studies have shown increased mortality in patients with psychiatric disorders,[1,2,5–7] nationwide data are lacking that determine whether these patients are also at an increased risk of SCD.

In the current study, we aimed at (1) comparing nationwide incidence rates and causes of SCD in individuals aged 18–35 years with and without previous contact with a psychiatric hospital and (2) characterizing symptoms, comorbidities, medications, and previously known medical history prior to SCD. We hypothesized that young adults with prior psychiatric hospital contact would be at increased risk for SCD and that cardiac symptoms prior to death would be present in a clinically relevant number of patients.

METHOD

Study Design

This was a nationwide register study, using data previously reported about all sudden deaths and SCD cases that occurred in individuals aged 1–35 years in Denmark from 2000 to 2006.[15] In brief, this study used all death certificates and all inpatient and outpatient activity in Danish hospitals and emergency rooms together with all medical records and autopsy reports in Denmark. For the current study, only deaths in young adults (18–35 years) were included, and history of contact with a psychiatric hospital was investigated as the hypothesized risk factor for SCD. Patients with previous psychiatric hospital contact included (1) hospitalized patients and (2) patients treated in hospital

Clinical Points

- Sudden cardiac death incidence rates in patients with and patients without previous psychiatric contact have never been compared in a nationwide sample.
- Patients with previous psychiatric contact had a 4-fold increased risk of sudden cardiac death. Deaths were more often unexplained after autopsy, suggesting primary arrhythmic death.
- Cardiac symptoms were common prior to death, highlighting the need for cardiovascular monitoring and management in the mentally ill.

outpatient clinics. Patients followed only in private practice were not included in this study since these patients are not identifiable in Danish registries.

The study was approved by the local ethics committee (H-KF-272484), the Danish Data Protection Agency (2011-41-5767), and the Danish National Board of Health (7-505-29-58/6).

Danish Registries

All Danish citizens have a unique and personal civil registration number, which can be linked to national registries on an individual level. The Danish Psychiatric Central Research Register[16] contains information on all psychiatric hospitalizations since 1969. Since 1995, the registry has been part of the Danish National Patient Register,[17] which furthermore contains information on all inpatient and outpatient activities in Denmark since 1978. All diagnoses in the Danish registries are coded according to the corresponding *International Classification of Diseases*, using the 8th revision (*ICD-8*) until 1993 and the 10th revision (*ICD-10*) since 1994. All Danish registries used are run as a public enterprise under the Danish Ministry of Health (the Danish Government). The content, validity, and coverage of the Danish Psychiatric Central Research Register and the Danish National Patient Register have previously been described, and diagnoses have been validated.[17–21]

Identification of Sudden Cardiac Deaths

All death certificates were retrieved digitally and read independently by 2 physicians in order to identify deaths that were sudden and unexpected. Autopsy reports were read as described previously.[15] Moreover, toxicology screens are performed in unexplained adolescent and adult cases of sudden, unexpected death. In all SCD cases, illegal drugs were found in only trace amounts and all prescribed drugs were found in therapeutic concentrations. None of these deaths had a toxicology profile that the forensic pathologist concluded could explain their death. For further information regarding SCD identification, see Supplementary Methods at Psychiatrist.com.

Previous Psychiatric Hospital Contacts and Sudden Cardiac Death

Data collection: death certificates, registry entries, and hospital records. Sudden cardiac death cases in persons aged 18–35 years with a previous psychiatric hospital contact (irrespective of age and diagnosis) were identified with the use of the Danish Psychiatric Central Research Register (*ICD-8* 290–315 and *ICD-10* F00–F99). All involved psychiatric hospital departments and emergency rooms were contacted by letter, and all records were retrieved manually. A detailed analysis of the psychiatric clinic history was assessed by 2 psychiatrists (K.W. and A.F.-J.), using all available material, including the full hospital record, the death certificate, and autopsy report. In case of several psychiatric *ICD* diagnoses, 1 primary diagnosis was chosen based on clinical evaluation.

Definitions

Sudden death and sudden cardiac death. We defined *sudden death* as a sudden, natural unexpected death: in witnessed cases, as an acute change in cardiovascular status with time to death being < 1 hour and, in unwitnessed cases, as a person last seen alive and functioning normally < 24 hours before being found dead.

Sudden cardiac death in cases in which autopsies were performed was defined as a natural unexpected death of unknown or cardiac cause: in witnessed cases, as an acute change in cardiovascular status with time to death being < 1 hour and, in unwitnessed cases, as a person last seen alive and functioning normally < 24 hours before being found dead.[15]

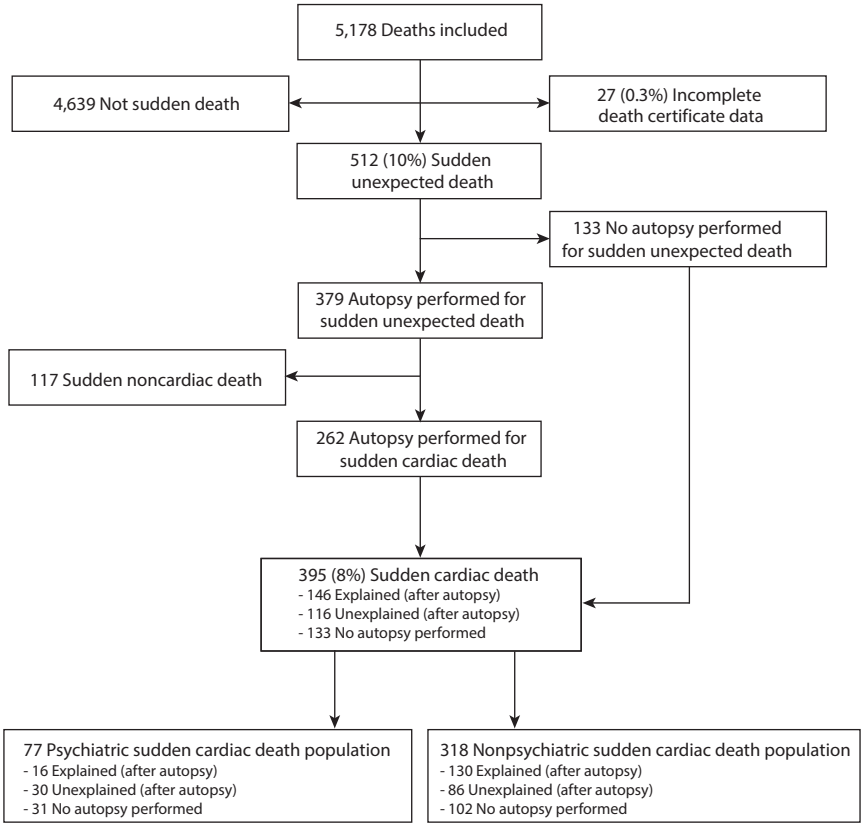
Sudden cardiac death verified by autopsy was subdivided into 2 groups: (1) explained SCD, in which a cardiac cause of death was established, and (2) sudden unexplained death, in which causes of death after autopsy remained unknown. In cases without autopsy, the same criteria were used in cases presumed to be of cardiac origin based on the circumstances relating to the death including all available information.

By using the Danish Psychiatric Central Research Register, the sudden cardiac death population was divided into those with and those without previous psychiatric hospital contact defining our psychiatric SCD population and nonpsychiatric SCD population, respectively. Past history of contact with a psychiatric hospital, rather than past psychiatric diagnosis alone, was used as the defining variable because the aim was to identify patients with clinically significant psychiatric history and because we wanted to be able to verify the primary psychiatric diagnosis via a review of hospital records.

Cardiac symptoms and medications. We recorded all possible cardiac symptoms prior to death using death certificates and all psychiatric hospital records. Possible cardiac symptoms were defined as angina pectoris, dyspnea, dizziness, palpitations, syncope, seizures, and fatigue. All medications were recorded at the last visit at the psychiatric department, if seen within 1 year prior to death.

Psychiatric population in Denmark. We used the Danish Psychiatric Central Research Register to estimate the psychiatric background population in Denmark (denominator). Individuals aged 18–35 years in 2000–2006 with a prior hospital-based psychiatric inpatient and outpatient contact (irrespective of age and diagnosis) were

Figure 1. Flowchart of the Identification of All Sudden Cardiac Deaths in Individuals With Previous Psychiatric Disorders Aged 18–35 Years in Denmark in 2000–2006



considered to be at risk of SCD (*ICD-8* 290–315 and *ICD-10* F00–F99). Sudden cardiac death incidence rates for the most common psychiatric diseases were calculated including all individuals with the specific diagnosis irrespective of age (Supplementary eTable 1).

Statistical Analysis

All calculations and data analyses were performed using Stata, version 11.0 (StataCorp, College Station, Texas). Incidence rates were calculated using the age group population across the 7-year observation period as the denominator. Confidence intervals were calculated using Poisson distribution. Sensitivity analyses for incidence rates were carried out applying increasingly stringent criteria to the data in both cohorts (ie, requiring autopsies, autopsies with histology, or autopsies with histology and toxicology). Categorical data were compared using χ^2 test or Fisher exact test as appropriate. Medians were compared using Wilcoxon rank sum test. All tests were 2-sided, and α was set at .05.

RESULTS

Background Population and Death Certificates

In 2000–2006, the mean Danish population consisted of 5.38 million inhabitants, of whom 1.26 million were aged 18–35 years. The mean population with hospital-based psychiatric inpatient and outpatient treatment consisted of 74,499 individuals (6%), corresponding to 0.52 million psychiatric person-years; the nonpsychiatric population consisted of 1.18 million individuals, corresponding to 8.32 million nonpsychiatric person-years.

Sudden Cardiac Death

Of the 5,178 total deaths included, we identified 512 (10%) sudden unexpected death cases. Twenty-seven death certificates (< 1%) were excluded due to incomplete data (page 2 missing). There were 379 autopsies (74%) conducted on the sudden unexpected death cases, of which 117 (31%) were ascribed to noncardiac diseases, leaving 395 SCD cases (Figure 1).

Our psychiatric SCD population consisted of 77 individuals (20%); 318 individuals (80%) never had contact with a psychiatric hospital department (nonpsychiatric SCD population) (Figure 1).

Sudden Cardiac Death Population

Clinical characteristics. The SCD population had a median age of 30 years (interquartile range, 26–33); 67% (n = 265) were male, and 178 deaths (50%) were witnessed. Most often, deaths occurred when individuals were at home (n = 246, 64%), while they were awake and relaxed (n = 173, 51%), or when they were asleep (n = 114, 34%) (Table 1).

Table 1. Clinical Characteristics and Comparisons Between the Psychiatric Sudden Cardiac Death Population and the Nonpsychiatric Sudden Cardiac Death Population Aged 18–35 Years in Denmark, 2000–2006

Characteristic	All SCD (n = 395)[a]	Psychiatric SCD Population (n = 77)[a]	Nonpsychiatric SCD Population (n = 318)[a]	*P* Value[b]
Age, median (IQR), y	30 (26–33)	31 (28–33)	30 (26–33)	.11
External examinations	325 (82)	64 (83)	261 (82)	.83
Male distribution	265 (67)	60 (78)	205 (64)	< .05
Witnessed deaths	n/n = 178/356 (50)	n/n = 20/69 (29)	n/n = 158/283 (56)	< .01
SCD from autopsy	262 (66)	46 (60)	216 (68)	.17
Sudden unexplained death	116 (44)	30 (65)	86 (40)	.02
Explained SCD	146 (56)	16 (35)	130 (60)	
	n = 395	n = 77	n = 318	
Previous medical history other than psychiatric disease				
Asthma	30 (8)	8 (10)	22 (7)	.30
Epilepsy	26 (7)	9 (12)	17 (5)	< .05
Ischemic heart disease	10 (3)	0 (0)	10 (3)	.12
Other heart diseases	65 (16)	8 (10)	57 (18)	.11
Diabetes	24 (6)	6 (8)	18 (6)	.48
Hypertension	18 (5)	1 (1)	17 (5)	.13
Other	44 (11)	12 (16)	32 (10)	.17
	n = 382	n = 73	n = 309	
Place of death				
At home	246 (64)	54 (74)	192 (62)	.06
Institution	14 (4)	6 (8)	8 (3)	.02
Public place	60 (16)	2 (3)	58 (19)	< .01
At hospital				
Death during hospitalization	31 (8)	8 (11)	23 (7)	.32
Death in emergency room	22 (6)	3 (4)	19 (6)	.78
	n = 339	n = 65	n = 274	
Activity at death				
Sleeping	114 (34)	34 (52)	80 (29)	< .01
Awake and relaxed	173 (51)	30 (46)	143 (52)	.38
Moderate to high intensity sport	26 (8)	0 (0)	26 (10)	< .05
At work	12 (4)	1 (2)	11 (4)	.33
Other	14 (4)	0 (0)	14 (5)	.10

[a]Values are shown as n (%) unless otherwise noted.
[b]*P* value for differences between psychiatric SCD population and the nonpsychiatric SCD population.
Abbreviations: IQR = interquartile range, SCD = sudden cardiac death.

Schizophrenia and substance-related mental and behavioral disorders were the most common diagnoses in the psychiatric SCD population (Table 2). Compared to the nonpsychiatric SCD population, the psychiatric SCD population was more often male (60/77 [78%] vs 205/318 [64%], $P < .05$), their death was more often unwitnessed (49/69 [71%] vs 125/283 [44%], $P < .01$), and their death was more often unexplained (30/46 [65%] vs 86/216 [40%], $P = .02$) (Table 1).

Cause of death. An autopsy was conducted in 46 (60%) of 77 psychiatric SCD cases. After review of all autopsy reports, 16 deaths (34%) were caused by a structural heart disease, whereas 30 deaths (65%) remained unexplained. The distribution of different structural heart diseases (Figure 2) did not differ between the psychiatric and nonpsychiatric SCD population ($P = .14$).

Incidence rates and incidence rate ratios. The overall SCD incidence rate was 4.5 (95% CI, 4.0–5.0) per 100,000 person-years. The incidence rate of SCD in the psychiatric SCD population was 14.8 (95% CI, 11.7–18.5) per 100,000 psychiatric person-years compared to 3.8 (95% CI, 3.4–4.3) per 100,000 person-years in the nonpsychiatric SCD population (Table 3) (incidence rate ratio, 3.9; 95% CI, 3.0–5.0; $P < .01$) . In men and woman, the SCD incidence rate ratio was 5.3 (95% CI, 3.9–7.1; $P < .01$) and 2.1 (95% CI, 1.2–3.6; $P < .01$), respectively.

Incidence rates per 100,000 persons-years were 38.9 (96% CI, 26.4–55.2) for patients with schizophrenia-spectrum disorders, 31.6 (95% CI, 19.3–48.8) for patients with substance-related disorders, and 6.9 (95% CI, 4.5–10.1) for those with other psychiatric diagnoses (Supplementary eTable 1).

Sensitivity Analysis

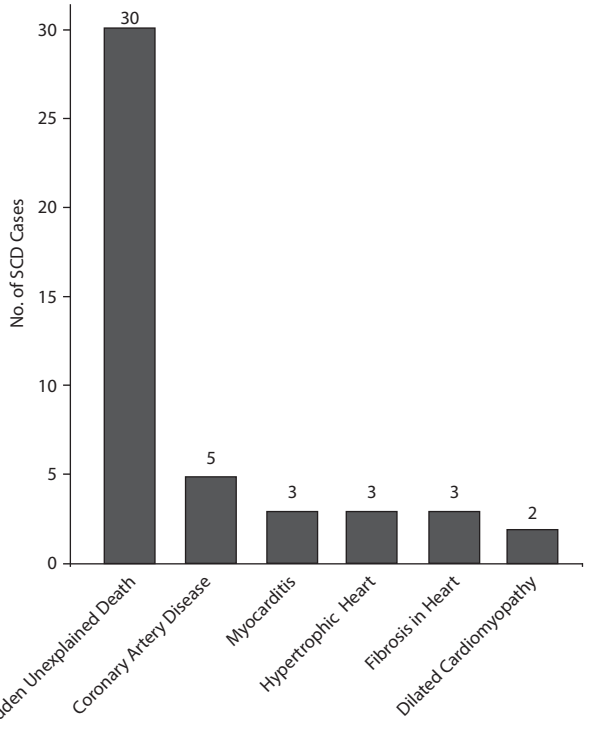
At each level of the sensitivity analysis, the psychiatric SCD population had significantly elevated SCD incidence rates compared to the nonpsychiatric SCD population (Table 3). Incidence rate ratios were 3.4 (95% CI, 2.4–4.7; $P < .01$) in SCD cases verified by autopsy and 6.4 (95% CI, 4.3–9.5; $P < .01$) in cases verified by autopsy with histology followed by toxicology screening.

Possible cardiac symptoms and medications prior to death. Altogether, 35 patients (46%) of the psychiatric cohort had possible cardiac symptoms within 1 year prior to death. Symptoms included angina (n = 13, 17%), palpitations (n = 9, 12%), and dyspnea (n = 8, 10%) (Supplementary eTable 2). In patients seen within 1 year prior to death,

Table 2. Distribution of Primary Psychiatric Diagnoses and Substance Use Disorder as a Comorbid Condition in the Psychiatric Sudden Cardiac Death (SCD) Population

ICD-10 Diagnosis	Crude n	Proportion in Psychiatric SCD Population (n = 77), %
Schizophrenia, schizotypal and delusional disorders (F20–F29)	31	40.2
Mental and behavioral disorders due to psychoactive substance use (F10–F19)		
Primary diagnosis	20	26.0
Secondary diagnosis	47	61.0
Neurotic, stress-related and somatoform disorders (F40–F48)	7	9.1
Disorders of adult personality and behavior (F60–F69)	7	9.1
Behavioral syndromes associated with physiological disturbances and physical factors (F50–F59)	4	5.2
Mood (affective) disorders (F30–F39)	3	3.9
Behavioral and emotional disorders with onset usually occurring in childhood and adolescence (F90–F98)	2	2.6
Organic, including symptomatic, mental disorders (F00–F09)	1	1.3
Mental retardation (F70–F79)	1	1.3
Disorders of psychological development (F80–F89)	1	1.3

Figure 2. Causes of Sudden Cardiac Death (SCD) in Persons Aged 18–35 Years in Denmark in 2000–2006: Distribution of the Causes of Death According to Autopsies of 46 Cases of Sudden Cardiac Death in Persons With a Previous Psychiatric Hospital Contact



the most commonly used medications were antipsychotic agents (51%) and benzodiazepines (35%) (Table 4). Only 12 electrocardiograms (ECGs) were available prior to death, and none of the ECGs had a QT interval above 460 ms.

DISCUSSION

In this Danish population-based study of people aged 18–35 years, we report a significantly increased incidence rate ratio of SCD of 3.9 (95% CI, 3.0–5.0; $P < .01$) in patients with psychiatric disorders and previous hospital-based inpatient or outpatient psychiatric contact compared to the nonpsychiatric SCD population. The significantly elevated incidence rate ratio remained significant in males and females and when applying increasingly stringent criteria for the assignment of SCD. Moreover, this increased mortality was to some extent driven by very high SCD incidence rates in patients with schizophrenia-spectrum disorders and substance use–related disorders.

Increased Mortality

Previous studies in patients with psychiatric disorders have shown an excess of comorbidities.[22] These include obesity, hypertension, dyslipidemia, insulin resistance, and other behavioral factors, such as smoking and physical inactivity.[23] The association between these risk factors and cardiovascular diseases is well known, but when using standardized mortality ratios, investigators in the Nordic countries have shown an increased cardiovascular risk in patients with psychiatric disease even after controlling for these risk factors.[1,2,5,6,24] These studies have been conducted with the use of registries, such as the Danish Psychiatric Central Research Register,[16] the Danish National Patient Register,[17] and the Danish Register of Causes of Death.[25] However, Nordic registries do not contain autopsy data from forensic pathology departments and they do not allow identification of deaths that are sudden and unexpected. Hence, previous nationwide studies were unable to report incidence rates or causes of SCD in psychiatric patients, but these data are needed to improve risk stratification and reduce mortality in the future.[14,26]

Comparing our results to other studies is complicated by different study designs and age groups. Osby et al[1] reported cardiovascular death as the most common natural cause of death in patients with bipolar and unipolar disorders. They calculated standardized mortality ratios of 1.9 and 2.6 in males and females with bipolar disorders and 1.5 and 1.7 in males and females with unipolar disorders.[1] Similar standardized mortality ratios for cardiovascular death have

Table 3. Incidence Rates and Sensitivity Analysis: Sudden Cardiac Death per 100,000 Person-Years by Sex

Annual Incidence Rate (denominator)	All, Incidence Rate (95% CI)	Men, Incidence Rate (95% CI)	Women, Incidence Rate (95% CI)	*P* Value[a]
Sudden cardiac death (general population)	4.5 (4.0–5.0)	5.9 (5.2–6.7)	3.0 (2.5–3.5)	<.01
Sudden cardiac death (no PPHC)	3.8 (3.4–4.3)	4.8 (4.2–5.5)	2.8 (2.3–3.3)	<.01
Sudden cardiac death (PPHC)	14.8 (11.7–18.5)	25.7 (19.6–33.0)	5.9 (3.4–9.5)	<.01
Autopsy performed in sudden cardiac death cases only (no PPHC)	2.6 (2.3–3.0)	3.2 (2.7–3-8)	2.0 (1.6–2.4)	<.01
With histology	2.3 (2.0–2.7)	2.9 (2.4–3.4)	1.7 (1.4–2.2)	<.01
With toxicology	1.2 (0.9–1.5)	1.4 (1.1–1.9)	0.9 (0.6–1.3)	<.05
With histology and toxicology	1.1 (0.9–1.4)	1.3 (1.0–1.7)	0.9 (0.6–1.2)	<.05
Autopsy performed in sudden cardiac death cases only (PPHC)	8.8 (6.5–11.8)	15.4 (10.8–21.3)	3.5 (1.7–6.4)	<.01
With histology	8.1 (5.8–10.9)	14.1 (9.7–19.8)	3.1 (1.4–5.9)	<.01
With toxicology	7.5 (5.3–10.2)	12.8 (8.6–18.3)	3.1 (1.4–5.9)	<.01
With histology and toxicology	7.1 (5.0–9.8)	12.4 (8.3–17.8)	2.8 (1.2–5.5)	<.01

[a]*P* value for differences in incidences rates between men and women.
Abbreviation: PPHC = previous psychiatric hospital contact.

Table 4. Medications Used by Patients (n = 43) With Psychiatric Contact Within 1 Year Prior to Sudden Cardiac Death

Medication	n (%)
Any antipsychotic agent	22 (51)
First-generation antipsychotic	13 (30)
Second-generation antipsychotic	19 (44)
Benzodiazepine	15 (35)
Antidepressant	9 (21)
Methadone	4 (9)
Other	6 (14)
No known medication	4 (9)
No. of medications	
1	11 (26)
2	9 (21)
>2	12 (28)

been reported in patients with schizophrenia and other major psychiatric disorders.[2,5] Notably, the increased cardiovascular risk has also been associated with antipsychotics and antidepressants.[8–11,27,28]

Cause of Death

We found that deaths upon autopsy remained unexplained in 65% of the cases in the psychiatric SCD population, which is much higher than previously reported.[29] This finding is of interest, as some psychotropic drugs, including methadone and antipsychotics, delay cardiac repolarization. This effect can prolong the QT interval with an increasing risk of primary arrhythmias, such as torsades de pointes ventricular tachycardia (TdP-VT).[30] This has led to concern about these medications,[9,10,13,30] and preventive strategies have been suggested to reduce medication-induced arrhythmias.[11,14] However, TdP-VT has never been identified in epidemiologic studies of sudden death in antipsychotic users.[31] To the best of our knowledge, this is the first study reporting that young patients treated for psychiatric disorders have more unexplained deaths after autopsy that are most likely due to arrhythmias compared to patients without psychiatric disorders. Notably, only 12 ECGs were available prior to death, and none of the ECGs had a QT interval above 460 ms.

Previous Medical History

We found that 87% of psychiatric SCD cases had a substance abuse history. This prevalence is substantially higher than previously reported in patients with schizophrenia (26%) and bipolar disorders (21%).[22] However, this difference is caused by the various data sources that we had access to, including medical records, autopsy reports, and death certificates. Including only patients hospitalized for primary substance abuse/addiction would drop the frequency to 26%, which is closer to prior studies (data not shown). Importantly, in this study, all illegal drugs were found in trace amounts only and all prescribed drugs were found in therapeutic concentrations upon autopsy. Therefore, none of these deaths could be explained by the toxicology profile.

Overall, we found few differences regarding known medical conditions between the psychiatric and nonpsychiatric SCD population. Epilepsy was overrepresented in the psychiatric SCD population, a finding consistent with prior data suggesting that epilepsy is associated with an increased risk of sudden unexplained death.[32]

Study Limitations

Study limitations mainly include the retrospective design, although this feature allowed us to examine a large, nationwide and representative population. In witnessed cases, it was easy to extract information on whether the person was seen alive < 24 hours prior to death, but it was difficult to assess more precise time limits in unwitnessed cases. Due to a reduced social network, psychiatric patients will probably less likely be found within 24 hours. Therefore, SCD incidence rates are probably conservative. Furthermore, as shown in the sensitivity analysis, incomplete data, including lack of autopsy, histopathology, and/or toxicology, add some uncertainty to the SCD incidence estimates. Only 12 ECGs were available prior to death. Hence, we could not evaluate acquired or long QT syndrome or other primary arrhythmogenic disorders for the entire psychiatric SCD population.

Only patients with previous hospital contact were included, and the background psychiatric population was estimated using the Danish Psychiatric Central Research Register. The proportion of psychiatric patients followed only in private practice is not available, but it is expected that most patients with severe psychiatric illness are hospitalized at some point in life. Disease-specific incidence rates were

calculated, including all individuals previously having the specific diagnosis irrespective of age. Hence, the background populations can be considered the largest possible groups, and incidence rates are conservative.

Cardiac symptoms were reported using hospital medical records and death certificates as judged by the physician. We cannot exclude that symptoms were misinterpreted or underreported. Previous medical history was reported in patients only if they were seen within 1 year prior to death, exact medication taken prior to death was not available, and detailed information on background risk factors for SCD was not available. Hence, we were unable to adjust for confounders and risk factors for SCD, including cardiovascular illness,[29] which may be higher in the psychiatric group.[33,34] However, the aim of this study was not to identify specific medications or medical disorders that may increase the risk of SCD in patients with psychiatric disorders. Rather, we aimed to assess incidence rates of SCD, causes of SCD, and cardiac symptoms prior to SCD in patients with and without previous psychiatric inpatient or outpatient contact and to investigate the frequency of possible cardiac symptoms prior to death, which could guide education and intervention strategies. Thus, despite the limitations discussed above, this is the first study assessing the risk of SCD in psychiatric and nonpsychiatric populations in a large and nationwide sample, which augmented database information with autopsy and clinical chart information, providing representative information on this topic that is difficult to study prospectively.

CONCLUSION

This is the first nationwide study reporting incidence rates and autopsy findings in a psychiatric SCD population aged 18–35 years, finding an incidence rate ratio for SCD of 3.9 for the psychiatric versus nonpsychiatric cohort. The increased incidence rates of SCD was largely driven by schizophrenia-spectrum and substance-related disorders. In the psychiatric SCD population, deaths were more often unexplained than in the nonpsychiatric SCD population, and almost half of the psychiatric SCD population had possible cardiac symptoms prior to death that could have been addressed. This latter finding highlights the need for cardiovascular monitoring and management in the mentally ill.[35] Patients treated with drugs that have the potential to prolong the QT interval who present with cardiac symptoms should always have a clinical examination, including an ECG. To generate future strategies to prevent SCD in psychiatric patients, the contribution of specific medications to an increased SCD risk should be investigated.

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Drug names: methadone (Methadose, Dolophine, and others).

Author contributions: Drs Risgaard and Waagstein contributed equally to the manuscript. Dr Risgaard has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr Risgaard contributed to the conception and design of the study, the data analysis, the data acquisition, the data interpretation, the manuscript drafting, and the critical revision of the manuscript. Dr Waagstein contributed to the data analysis, the data interpretation, the data acquisition, the manuscript drafting, and the critical revision of the manuscript. Dr Winkel contributed to the conception and design of the study, the data analysis, the data acquisition, the data interpretation, the manuscript drafting, and the critical revision of the manuscript. Dr Jabbari contributed to the data interpretation, the manuscript drafting, and the critical revision of the manuscript. Mr Lynge contributed to the data interpretation, the manuscript drafting, and the critical revision of the manuscript. Dr Glinge contributed to the data interpretation, the manuscript drafting, and the critical revision of the manuscript. Dr Albert contributed to the data interpretation, the manuscript drafting, and the critical revision of the manuscript. Dr Correll contributed to the data interpretation, the manuscript drafting, and the critical revision of the manuscript. Dr Haunsø contributed to the data interpretation, the manuscript drafting, the critical revision of the manuscript, and funding. Dr Fink-Jensen contributed to, the supervision, the data acquisition, the data analysis, the data interpretation, the manuscript drafting, and the critical revision of the manuscript. Dr Tfelt-Hansen contributed to the conception and design of the study, the supervision, the data acquisition, the data analysis, the data interpretation, the manuscript drafting, and the critical revision of the manuscript.

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Sudden Cardiac Death in Young Adults With Previous Hospital-Based Psychiatric Inpatient and Outpatient Treatment: A Nationwide Cohort Study From Denmark

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List of Supplementary Material for the article

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This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplemental methods:

Identification of sudden cardiac death through review of death certificates

In case of disagreement, a consensus was reached after re-evaluating the circumstances surrounding the death, including a review of the previous medical history, which was taken into account in every single case. Danish death certificates can only be issued by a medical doctor and are informative and highly suitable to identify sudden unexpected deaths, as they have a supplemental information field *(see supp. Data, Winkel et. al* [15]*)*. This field is mandatory in all medico-legal external examinations (external examinations), including cases in which it is decided not to conduct an autopsy. In cases where citizens or patients are found dead and/or the death is sudden and unexpected, external examinations are mandatory by Danish law.

Conduct of autopsies

In Denmark, there are three forensic departments conducting around 1500 autopsies per year. A forensic autopsy is to be performed when an external examination concludes that the mode of death cannot be established. All *forensic autopsies* are supervised by another forensic pathologist and follow a protocol in which all organs are systematically examined. *Hospital autopsies* are also performed in local pathology departments throughout the country. These autopsies can be requested by a physician and the relatives when – after external examination – it is decided not to perform a *forensic autopsy*.

eTable 1: Annual sudden cardiac death incidence rates and incidence rate ratios per 100,000 psychiatric person-years compared to the general population grouped by the most common psychiatric diseases

Diagnostic groups	Background population[a]	No.	SCD incidence rates (95% CI)	SCD Incidence rate ratios (95% CI)[b]	P-value
Schizophrenia, schizotypal and delusional disorders (F20-F29)	79,686	31	38.9 (26.4-55.2)	10.2 (6.8-14.7)	<0.01
Mental and behavioural disorders due to psychoactive substance use (F10-F19)	63,239	20	31.6 (19.3-48.8)	8.3 (5.0-13.0)	<0.01
Other psychiatric diagnoses	378,574	26	6.9 (4.5-10.1)	1.8 (1.2-2.7)	<0.01

[a]The disease specific background population (denominator) was calculated including all individuals previously having the specific diagnosis irrespective of age; [b]Indicates ratios in incidence rates between the psychiatric SCD population and the non-psychiatric SCD population according to diagnostic groups.

eTable 2: Possible cardiac symptoms and previous known abuse within one year prior to sudden cardiac death in patients with psychiatric contact

Reported possible cardiac symptoms (%)	n = 77
Any cardiac symptom	35 (46)
Angina	13 (17)
Palpitations	9 (12)
Dyspnoea	8 (10)
Seizures	8 (10)
Syncope	6 (8)
Dizziness	4 (5)
Unspecific	7 (9)
Previously known substance abuse according to medical records or death certificate	n = 77
Any known abuse	62 (83)
Polydrug abuse	38 (49)
Alcohol	10 (13)
Cannabis	2 (3)
Opioids	1 (1)
Unknown type	11 (14)