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# Epidemiological studies of suicide in patients with psychiatric illness



Johan Reutfors

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Clinical Epidemiology Unit, Department of Medicine, Solna  
Karolinska Institutet, Stockholm, Sweden

# **EPIDEMIOLOGICAL STUDIES OF SUICIDE IN PATIENTS WITH PSYCHIATRIC ILLNESS**

Johan Reutfors



**Karolinska  
Institutet**

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Front cover by Lena Reutfors. With inspiration from a haiku poem  
by Tomas Tranströmer in the collection of poems *Den stora gåtan*:

*Stor och långsam vind  
från havets bibliotek.  
Här får jag vila.*

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## ABSTRACT

A link between suicide and psychiatric illness is well recognized. However, knowledge is limited as to what characterizes suicide in different mental disorders. The overall aim of the work described in this thesis was to increase the understanding of suicide in psychiatric illness.

**Study I:** In this population-based case-control study, all suicide cases 18 years and older in Sweden from 1991 to 2003 (14,501 men and 6,174 women) were individually matched to ten controls from the general population. Of male and female suicide victims, 23% and 31%, respectively, had been hospitalized with a mental disorder in the year before the suicide. The highest suicide risk during hospitalization and in the year following discharge was found in patients with mood disorder [odds ratio (OR) 55 (95% CI 47–65) for men and OR 86 (95% CI 70–107) for women] with the risk peaking in the first week following discharge [OR 177 (95% CI 78–401) for men and OR 268 (95% CI 85–846) for women]. Compared to that for mood disorder, the suicide risks for schizophrenia spectrum disorder and alcohol use disorder were about half and were more constant over time.

**Study II:** Seasonal patterns among suicides committed by individuals aged 18 years and older in Sweden from 1992 to 2003 (9,902 men and 4,128 women) were assessed in relation to their history of psychiatric inpatient diagnosis in the five years before the suicide. We found an increased incidence of suicide in spring and early summer. The seasonal variation was more evident in suicide victims with a psychiatric illness than in those without such a diagnosis. The seasonal variation was found in most of the eight diagnostic groups studied.

**Studies III and IV:** These population-based case-control studies focused on suicide among patients diagnosed with schizophrenia in Stockholm County from 1984 to 2000. Data from 84 patients who died by suicide within five years from the diagnosis were compared with 84 matched controls from the same study population. We found that higher educational attainment, age  $\geq 30$  years at onset of symptoms, and a history of a suicide attempt were associated with an increased risk of suicide. Gender did not significantly affect the suicide risk, nor did substance use disorder or a family history of mental disorder or suicide. A diagnostic re-assessment according to DSM-IV criteria of the cases and controls showed that a mood disorder diagnosis increased the risk of suicide more than three-fold. We conclude that certain risk factors for suicide in schizophrenia may differ from those found in the general population and other mental disorders. The identification of mood disorder is important for suicide risk assessment in patients with schizophrenia.

*Keywords:* suicide, mental disorder, mood disorder, depression, bipolar disorder, alcohol use disorder, schizophrenia, sex differences, trend, seasonality, method of suicide, epidemiology, case-control study

## LIST OF PUBLICATIONS

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## LIST OF ABBREVIATIONS

CI	Confidence Interval
DSM	Diagnostic and Statistical Manual of Mental Disorders
ICD	International Statistical Classification of Diseases and Related Health Problems
OR	Odds Ratio
PAF	Population Attributable Fraction
RR	Relative Risk
SMR	Standardized Mortality Ratio
WHO	World Health Organization





# 1 INTRODUCTION

## 1.1 OCCURRENCE OF SUICIDE

Suicide is an important public health problem, estimated to cause the death of about one million people per year in the world. This corresponds to an annual mortality rate of 16 deaths per 100,000 people (WHO, 2010). Suicide accounts for about 1.5% of all deaths and is the tenth leading cause of death globally (Hawton and van Heeringen, 2009). In the majority of cases, a death by suicide has a profound negative impact emotionally, socially and economically on friends and family of the suicide victim.

Suicide rates vary considerably between different countries. The countries with the highest suicide rates according to recent WHO statistics are Lithuania, Russia, and Belarus, which all have suicide rates higher than 60 per 100,000 men and 10 per 100,000 women. Low rates of suicide are reported from southern Europe, several predominantly Muslim countries and some Latin American countries (Bertolote, 2009; Hawton and van Heeringen, 2009).

In Sweden, suicide rates are close to the average in the European Union. In 2007, 1,443 suicides, corresponding to 18.9 suicides per 100,000 inhabitants, were registered in Sweden (NASP, 2009). This number includes both definite (certain) suicides and undetermined deaths (uncertain suicides). Differing practices in ascertaining suicides as well as in reporting or lack of reporting probably explain some of the international differences in suicide rates (Bertolote, 2009; Hawton and van Heeringen, 2009).

Suicide rates are higher in males in most countries, with male-to-female ratios for suicide between two and four to one (Hawton and van Heeringen, 2009). In Sweden in 2007, 1019 suicides were committed by men and 424 by women giving a male-to-female ratio of 2.4:1 (NASP, 2009). The corresponding suicide rates were 27 per 100,000 men and 11 per 100,000 women.

The international suicide statistics show that suicide rates increase with age. Thus, the global suicide rate in 2000 in 15–24 year olds was 22 per 100,000 men and 5 per 100,000 women whereas in the age group of 75 and older, the suicide rate was 50 per 100,000 men and 16 per 100,000 women (WHO, 2010). Nevertheless, in Sweden, the suicide rate was highest in the 45–64 year age group with 34 per 100,000 men and 14 per 100,000 in women, while in the 65 years and older they were 30 per 100,000 men and 11 per 100,000 women (NASP, 2009).

## 1.2 TRENDS IN SUICIDE

A study of 47 countries between 1965 and 1999 found varying trends in different countries (Levi et al., 2003). In the European Union, suicide mortality declined by 11% in men and 29% in women from 1980–84 to 1995–98. During the same time period, Swedish suicide rates decreased by 26% for both men and women. In the last decade, the overall decline in suicide rates has continued in Sweden, although the decreasing trend has become slower and may have ceased in younger women (NASP, 2009; Kosidou et al., 2010).

### **1.3 SEASONALITY OF SUICIDE**

Suicide rates vary by season with a peak in spring or summer according to studies from countries in both the northern and southern hemispheres (Chew and McCleary, 1995; Petridou et al., 2002). Investigations near the equator, however, have found a lower or absent seasonality effect in suicide incidence (Chew and McCleary, 1995; Heerlein et al., 2006; Parker et al., 2001). The suicide seasonality appears to differ by sex, since several studies have found that for women, in addition to a peak in spring and early summer, there is also a second and smaller peak in the fall (Hakko et al., 1998; Mearns et al., 1981). Suicide seasonality has been found to be more evident in suicides committed by violent methods (Maes et al., 1993). It has also been found that suicide seasonality is higher in the countryside and that the suicide seasonality may have decreased in recent years – the disappearing traditional rural society has been suggested as the cause (Ajdacic-Gross et al., 2005). However, only few studies have investigated how suicide seasonality is related to psychiatric illness and those studies have been limited by small samples (Bradvik and Berglund, 2002; Kim et al., 2004), by a lack of information about specified psychiatric diagnoses (Rocchi et al., 2007; Yip et al., 2006) or only one investigated diagnosis (Postolache et al., 2010).

### **1.4 PSYCHIATRIC ILLNESS AND SUICIDE**

An important predisposing factor for most suicides is the presence of psychiatric illness. A common method for a psychiatric assessment of a suicide victim is the psychological autopsy. This method usually includes interviews with relatives of the deceased as well as the gathering of data from medical records of the deceased. Such studies have found that about 90% of suicide victims suffered from a psychiatric illness at the time of suicide (Arsenault-Lapierre et al., 2004; Conwell et al., 1996; Henriksson et al., 1993; Waern et al., 2002). These diagnoses were, however, retrospectively assessed, which means that not all of these suicide victims had been given a psychiatric diagnosis and received psychiatric treatment before their death. Nevertheless, a large proportion of suicide victims had been in contact with health care services not long before the suicide. A review of studies that have investigated the degree to which suicide victims had been in contact with psychiatric services found that on average 19% had had such a contact within one month before the suicide, 32% had been in contact during the year before the suicide, and 53% had had a lifetime contact with mental health services prior to the suicide (Luoma et al., 2002). A contact with primary health care was even more common in close proximity to the suicide: 45% of suicide victims had been in contact with primary care providers within one month of suicide.

Mood disorders are the most common psychiatric disorders in completed suicides. In a review of studies using psychological autopsies, the most common diagnoses were mood disorder (30%), substance misuse (18%), schizophrenia (14%) and personality disorder (13%) (Bertolote et al., 2004). A similar review confirmed that the two most common diagnoses were mood disorders (43%), and substance use disorder (26%) (Arsenault-Lapierre et al., 2004).

In an often cited meta-analysis, the standardized mortality rate (SMR) for suicide was estimated for a number of specific mental disorders (Harris and Barraclough, 1997). The SMR was calculated as the ratio of observed number of suicides in patients with a mental disorder to the expected number of suicides in a general population with a similar age and sex distribution. The highest SMR was found in anorexia nervosa with

a 23 times greater risk of suicide. The results for the other major psychiatric disorders were: major depression SMR 20, unspecified mood disorders SMR 16, bipolar disorder SMR 15, bulimia SMR 13, dysthymia SMR 12, obsessive compulsive disorder SMR 12, schizophrenia SMR 8, and personality disorder SMR 7, unspecified substance use-disorder SMR 6, and alcohol use disorder SMR 6.

#### **1.4.1 Suicide in mood disorder**

As also mentioned above, a meta-analysis found the highest suicide risks among the mood disorders in major depression, followed by unspecified mood disorders, bipolar disorder, and dysthymia (Harris and Barraclough, 1997). A Swedish study of inpatient-treated psychiatric disorder between the years 1973 to 1995 found the SMR for suicide to be 15 for males and 22 for females with bipolar disorder. In unipolar disorder, the SMR for suicide was 21 for males and 27 for females (Ösby et al., 2001). SMRs were higher for young patients at an early stage after the first diagnosis. The lifetime suicide rate was estimated in a meta-analysis at 6% for mood disorder (Inskip et al., 1998). Another meta-analysis found that 2–12% of those with major depressive episode die by suicide (Bostwick and Pankratz, 2000) and 10–15% of those with bipolar disorder (Hawton and van Heeringen, 2009).

Risk factors that have been established for suicide in mood disorder in high quality studies are suicide attempt, male sex, being single or living alone, being an inpatient, high levels of hopelessness (Coryell and Young, 2005; Hawton and van Heeringen, 2009), and loss of job (Hoyer et al., 2009). However, risk factors may be associated with differing suicide risks over time. A prospective study of a mixed population of patients with different mood disorders with regard to this issue showed that diminished concentration, global insomnia, moderate alcohol abuse, and severe loss of interest or pleasure (anhedonia) predicted suicide within one year from the start of the study (Fawcett et al., 1990). Three other factors were associated with suicide after one year: severe hopelessness, suicidal ideation, and history of previous suicide attempts.

In mood disorder, it is also found that measurable neurobiological disturbances such as serotonin dysfunction and hypothalamic-pituitary axis hyperactivity may be predictive of subsequent suicide (Hawton and van Heeringen, 2009). It has been shown that a low level of the serotonin metabolite 5-HIAA in the cerebrospinal fluid may predict suicide after a suicide attempt (Nordström et al., 1994). A pathological dexamethasone suppression test has also been shown to predict suicide in suicide attempters with mood disorder (Jokinen et al., 2007).

#### **1.4.2 Suicide in schizophrenia and other psychotic disorders**

In schizophrenia, suicide is the specific cause of death that is most elevated compared to the general population. According to a recent meta-analysis, the suicide rate in schizophrenia is 12 times higher than in the general population (Saha et al., 2007). This rate is higher in young patients and shortly after the schizophrenia diagnosis (Alaraisanen et al., 2009; Ösby et al., 2000). The lifetime suicide mortality in schizophrenia has been estimated by a meta-analysis to be approximately 5% (Palmer et al., 2005).

A meta-analysis of risk factors for suicide in schizophrenia demonstrated that previous depressive disorder, hopelessness, history of a suicide attempt, and poor adherence to treatment have been repeatedly found to be associated with a higher suicide risk

(Hawton et al., 2005). Other factors which have been found to be risk factors for suicide in populations without schizophrenia have shown ambiguous results. These include male gender, higher educational attainment, substance use disorders, family history of suicide (Hawton et al., 2005), and age of onset (Carlborg et al., 2010). Psychotic symptoms such as delusions, hallucinations and negative symptoms appear not to be clearly associated with the suicide risk (Hawton et al., 2005).

Relatively little knowledge exists about suicide in different types of psychotic disorders. A higher suicide mortality has been reported in schizoaffective disorder than in schizophrenia for men but not for women (Laursen et al., 2007). Suicidal behavior has been found to be higher in schizoaffective disorder by some investigators (Radomsky et al., 1999; Walsh et al., 2001) but not by all (Fenton et al., 1997). A similar overall mortality has been reported in schizoaffective disorder as in schizophrenia (Capasso et al., 2008).

### **1.4.3 Suicide in substance use disorder**

Of substance use disorders, alcoholism is the most prevalent one. In psychological autopsy studies, alcoholism is present in 25–50% of those who died by suicide (Sher, 2005) and alcohol has been found in the blood of 33–69% of suicide completers (Sher, 2006a). High alcohol consumption has been found to be correlated with high suicide rates on national levels, but the causal relationship needs further study (Sher, 2006a).

The life-time suicide rate in alcoholism has been estimated to be 2–3.4% (Murphy and Wetzel, 1990). Although this is lower than for the other major psychiatric disorders predisposing to suicide, the high prevalence of alcohol use-disorder makes it an important factor contributing to many suicides. It also appears that the suicide risk in alcoholism is low but more chronic than in some other disorders, which means that suicide in alcoholism often does not occur early in the course of the substance abuse. According to one study, abuse had been ongoing for almost 20 years when the suicide occurred (Murphy and Wetzel, 1990).

The suicide risk is raised both during alcohol intoxication and in the abstinence phase, although the risk is much higher during intoxication (Sher, 2006a). Risk factors for suicide which have been identified in alcoholism are loss of a close personal relationship, including separation, divorce, widowhood, male sex, higher age, living alone, unemployment, a recent increase in alcohol consumption, previous treatment for alcoholism, family history of alcoholism, and history of co-morbid substance use disorder, previous suicidal communication and suicidal behavior (Murphy, 2000; Sher, 2006b). Affective disorder, especially major depression, has been found to co-exist in the majority of suicide victims with alcoholism (Sher, 2006a).

There is much less knowledge about suicide risk factors in substance use disorders other than alcoholism, but it has been suggested that also among these, recent loss and an affective disorder increase the suicide risk (Murphy, 2000). A meta-analysis found the following SMRs in different substance use disorders: opiate dependence SMR 14, cannabis abuse SMR 4, sedatives SMR 20 and sedatives combined with other drugs SMR 44 (Harris and Barraclough, 1997).

#### **1.4.4 Suicide in personality disorder**

A review of psychological autopsy studies found that estimates of the prevalence of personality disorder among suicide completers range between 0–57% (Isometsa, 2001). The divergent results are likely to reflect differences in research methodology. As most research in this field has focused on borderline personality disorder, little is known about suicide in relation to other personality disorders.

The results from studies of patients with borderline personality disorder who had received moderate to extensive mental health care gave a suicide rate of about 8% (Linehan et al., 2000). In a study of patients in Sweden with a long-term disabling mental disorder, a diagnosis of borderline personality disorder was the strongest predictor of suicide (Tidemalm et al., 2005).

In borderline personality disorder, the suicide risk is greater among those with comorbid substance use disorder, depression or other personality disorder (Isometsa et al., 1996; McGirr et al., 2007). Other risk factors identified in personality disorder are discharge from a psychiatric inpatient unit, previous suicidal ideation and suicide attempts, a history of antisocial behavior, and higher education (Linehan et al., 2000). Gender, age and marital status did not predict suicide in borderline personality disorder (Linehan et al., 2000).

### **1.5 PSYCHIATRIC HOSPITALIZATION AND SUICIDE**

A case-control study of suicide cases in Denmark 1981–1997 showed that 37% of men and 57% of women had a life-time history of psychiatric inpatient treatment (Qin and Nordentoft, 2005). Such a psychiatric history was associated with an adjusted suicide risk of 10.4 (95% CI 9.9–10.9) for men and 19.8 (95% CI 18.7–20.9) for women. In a study of suicide and mental disorders that had required hospitalization, 44.6% (95% CI 43.6–45.5) of all suicides were attributable to mental illness that had required psychiatric inpatient treatment (Mortensen et al., 2000).

Several studies have demonstrated that the period following discharge from psychiatric hospitalization is associated with an increased suicide risk. Among the relatively few studies that have investigated the post-discharge suicide risk by psychiatric diagnosis, a cohort study from the UK showed the highest risk for suicide within the first month from discharge for depression in men but for neuroses in women (Goldacre et al., 1993). Another cohort study from Hong Kong failed to identify any significant risk difference between the diagnoses following discharge with substance abuse, schizophrenia, mood disorder, neurotic disorder, or ‘other diagnoses’ (Ho, 2003). In a case control study using Danish registers, the highest risk following discharge was associated with a mood disorder diagnosis (Qin and Nordentoft, 2005). Suicide risks in substance use disorder declined more slowly than for affective or schizophrenia spectrum disorders.

During the time period of the present study, psychiatric hospital beds in Sweden have been reduced by more than 50% as in many other comparable countries (Priebe et al., 2005). The question of how this relates to suicide rates and suicide prevention has been addressed by only a few studies. An investigation in Scotland studied the suicide rate during the 28 days after discharge from psychiatric hospitals between 1968 and 1992, during which time psychiatric beds for adults were reduced by 60% (Geddes and Juszczak, 1995). They found a decrease in suicide rate for males and an increase for

females. In Finland, the number of post discharge suicides did not increase between 1985 and 2001 (Pirkola et al., 2007). Similar results have been found in Sweden for 1987–2004 (Ljung, 2007) and in Denmark for 1981–1997 (Qin and Nordentoft, 2005).

## **1.6 SOCIOECONOMIC AND DEMOGRAPHIC RISK FACTORS FOR SUICIDE**

A considerable number of social, demographic, and economic risk factors for suicide have been identified in the general population. These include unemployment, low education, singleness, low income, and retirement (Agerbo, 2007; Qin et al., 2003). Adverse life events associated with higher suicide risk are interpersonal conflicts, economic problems, major losses or other acute psychosocial crises (Plutchik, 2000). Studies of ethnicity have found that immigrants have higher suicide rates in several European countries (Lindert et al., 2008). A Swedish study reported an almost doubled risk of suicide amongst those born abroad, but also that the country of origin is important (Johansson et al., 1997a). Compared to people born in Sweden, an elevated suicide risk was found in immigrants from Finland (RR 1.9, 95% CI 1.8–2.1) and Eastern European countries (RR 1.7, 95% CI 1.4–2.1), while a lower suicide risk was found in immigrants from Southern Europe (RR 0.5, 95% CI 0.4–0.6) and outside Europe (RR 0.8, 95% CI 0.6–1.0) (Johansson et al., 1997b). In the US, suicide rates are lower among citizens of Hispanic and African origin than in those of Caucasian origin (McKenzie et al., 2003).

However, most of the above-mentioned risk factors also affect the risk for psychiatric illness and thereby interact with the risk for suicide. A study that estimated the contribution of both psychiatric illness and socio-economic factors to suicide risk found that the effect of socioeconomic variables decreased after adjustment for history of psychiatric illness (Mortensen et al., 2000). The highest attributable risk was found for psychiatric illness that had required hospitalization: 44.6% (95% CI 43.6–45.5) whereas the attributable risk associated with unemployment was 3.0% (95% CI 1.4–6.6) and with being single 10.3% (6.1–16.9).

Moreover, data suggest that not all of the above-mentioned socioeconomic and demographic risk factors are relevant for psychiatric patients. In fact, it has been shown that suicide risk was instead higher among patients who had received psychiatric inpatient treatment and who had a higher income, higher education, were employed and married (Agerbo, 2007). However, little research has addressed the question of how suicide risk patterns differ between mental disorders.

## **1.7 FAMILIAL RISK FACTORS FOR SUICIDE**

Studies of families, twins and adopted offspring have demonstrated a genetic component influencing the risk of suicide. It has been suggested that the familial increase in suicide risk is linked to a familial disposition to psychiatric illness or a factor related to impulsivity and aggressiveness (Bondy et al., 2006). It has been shown that a family history of suicide increases the risk at least two-fold, and that this increase is not associated with the pattern of mental disorders in the family (Qin et al., 2002). Concordance rates of suicide are higher among monozygotic twins than among dizygotic twins (Bondy et al., 2006).

## 1.8 ATTEMPTED SUICIDE

A history of a suicide attempt is a prominent predictor for completed suicide. At least 40% of suicide victims have previously attempted suicide (Hawton and van Heeringen, 2009), and individuals with a history of suicide attempts have, overall, an increased suicide risk nearly 40 times that of the general population (Harris and Barraclough, 1997). Repetition of a suicide attempt further increases the suicide risk, and more so in women than in men (Zahl and Hawton, 2004).

Other characteristics which increase the risk of subsequent suicide are a higher severity of the suicide attempt (high suicide intent) and the use of a violent method in the suicide attempt (Harriss et al., 2005; Holley et al., 1998). Swedish researchers have recently shed more light on how the method used in a suicide attempt affects the risk of a subsequent completed suicide. Of 48,649 suicide attempters during 1973–1982, 12% died by suicide during the period up to 2003. The worst prognosis was found for hanging and similar methods: 54% of men and 57% of women who had attempted suicide by this method later died by suicide, the majority within a year. The majority died by the same method as they had used in the previous suicide attempt (Runeson et al., 2010). The same researchers have also shown that the type of psychiatric disorder influences the risk of completed suicide. Following a suicide attempt, the highest short-term suicide risk was found in mood disorder and schizophrenia. Schizophrenia was the diagnosis with the strongest association with completed suicide (Tidemalm et al., 2008).

## 1.9 METHODS OF SUICIDE

Factors that affect the choice of suicide method include the availability of and accessibility to a particular method (Huisman et al., 2010). Gender also affects the choice of method in that men are known to commit suicide by violent methods more often than women (Hawton and van Heeringen, 2009; Kposowa and McElvain, 2006). In a study of 16 countries in the European Union, the most common suicide methods among males were hanging (54.3%) and the use of firearms (9.7%). In females, the most common methods were hanging (35.6%) followed by poisoning by drugs (24.7%) (Värnik et al., 2008). In many countries of Asia and Latin America, poisoning by pesticide is a preferred method of suicide, whereas in the USA, the use of firearms is the predominant method among both men (60.6%) and women (35.7 %) (Ajdacic-Gross et al., 2008). In Sweden, the most common suicide methods in men are hanging (37.5%) and poisoning (27.4%) and in women poisoning (45.8%) and hanging (19.3%) (NASP, 2009).

Another factor that may influence the choice of suicide method is the type of psychopathology. Among suicide victims with schizophrenia, several studies have found an overrepresentation of violent suicide methods (Hunt et al., 2006). A cross-sectional study from the Netherlands of 505 suicide victims with various diagnoses found that psychotic disorder was associated with suicide by jumping and that substance use disorder was associated with poisoning. Depressive disorder was not associated with any particular method (Huisman et al., 2010). A similar study from Taiwan confirmed that suicide by jumping was associated with more severe psychopathology. This study of the four diagnostic categories bipolar disorder, major depression, schizophrenia, and neurotic disorder found that hanging was the predominant method in all categories (Chen et al., 2009). A prospective study of



patients with mood disorder found that, among patients with major depression, 68% committed suicide by violent methods and 13% by poisoning with psychopharmacological drugs (Isometsa et al., 1994a). A higher proportion of bipolar patients were found to commit suicide by psychopharmacological drugs (35%) (Isometsa et al., 1994b). In alcohol intoxication, more lethal means of suicide have been shown to be used (Sher, 2006a).

## **1.10 RESEARCH APPROACHES IN SUICIDOLOGY**

One of the most challenging tasks in psychiatric clinical practice is the prevention of suicide. Therefore, an important goal is to identify individuals who are at risk for suicide and to offer them treatment. However, to increase the possibility of identifying the individuals at high risk of suicide, more knowledge is needed concerning how suicide is related to different psychiatric illnesses and about patterns of suicide risk in different mental disorders. Such studies can help to better understand the etiology of suicide and thereby provide data to enhance the assessment of suicide risk.

As is evident from the introductory review in this thesis, suicide is a complex phenomenon with many interacting determinants. Qualitative as well as quantitative methods are valuable to increase the knowledge of suicide (Goldney, 2002). However, to identify and assess the importance of risk factors for suicide, quantitative studies with control groups are needed. Furthermore, to justify the drawing of generalized conclusions, studies in this field should be population-based. In Sweden, the various population-based health registers enable epidemiological studies of suicide in large well-defined populations.

## **2 AIMS**

The overall objective of this thesis was to increase the understanding of suicide in psychiatric illness.

The specific aims were the following:

- To estimate suicide risk during hospitalization and in the year following discharge for patients with psychiatric illness (Study I)
- To assess suicide seasonality patterns with regard to the history of psychiatric illness among suicide victims (Study II)
- To identify risk factors for suicide in schizophrenia (Studies III and IV)

## **3 METHODS**

### **3.1 DEFINITION OF SUICIDE**

The word suicide comes from the Latin word *suicidium*, from *sui caedere*, "to kill oneself".

By suicide, we understand that

- there was a death;
- the death was achieved by the individual who died;
- the death was intentional;
- there was an active or passive agent (eg, it was the commission or omission of an act that resulted in the death) (Maris, 2002).

In the first study in this thesis, both certain (definite) suicides and uncertain suicides (undetermined deaths) according to ICD-9 and ICD-10 were defined as suicides. The same codes were used to define suicide attempts. In papers II, III, and IV, however, only certain suicides were studied.

In the second paper, suicide methods were defined as violent and non-violent according to the commonly used convention that all intentionally self-inflicted poisonings by different substances were regarded as non-violent. The other defined methods of intentional self-harm were regarded as violent.

### **3.2 DEFINITION OF DIAGNOSTIC CATEGORIES**

In the first paper, broad psychiatric diagnostic categories were defined as shown in Table 1. We first defined the category of mental disorder as comprising all mental disorders except organic mental disorders. Then three major diagnostic groups were defined: mood disorders, schizophrenia spectrum disorders, which in this study included all non-organic psychosis diagnoses, and alcohol use disorder.

Table 2 shows the eight more narrow diagnostic groups that were defined for the second paper to explore their relationship with suicide seasonality. They were: depression; neurotic disorder (including stress-related, or somatoform disorder); schizophrenia (including schizoaffective disorder); other non-organic psychotic disorder; personality disorder; alcohol use disorder; other substance use disorder; other mental disorder.

In the third paper, schizophrenia was defined as schizophrenia or schizoaffective disorder (code 295 in ICD-8 and ICD-9; codes F20 and F25 in ICD-10). Schizophreniform disorder as defined by DSM-IV is usually included under 'other schizophrenia' (code F20.8) in ICD-10. In the fourth paper, schizophrenia, schizoaffective disorder and schizophreniform disorder as defined above were together termed schizophrenia spectrum disorder.

Table 1. Diagnostic categories classified according to WHO ICD-9 (1991–1996) and ICD-10 (1997–2003) used in Study I.

<b>Diagnostic group</b>	<b>ICD-9</b>	<b>ICD-10</b>
Any mental disorder (except dementia)	291–292, 295–315	F10–F99
Mood disorder <sup>a</sup>	296 (except 296X), 300E, 311	F30–F33
Schizophrenia spectrum disorder	295, 297, 298	F20, F22–F25, F28–F29
Alcohol use disorder	291, 303, 305A	F10
Suicide attempt <sup>b</sup>	E950–E959, E980–E989	X60–X84, Y10–Y34
Certain suicide	E950–E959	X60–X 84
Uncertain suicide / undetermined death	E980–E989	Y10–Y34

<sup>a</sup> Including bipolar disorder defined as codes 296A, 296C, 296D, 296E according to ICD-9 and F30–F31 according to ICD-10.

<sup>b</sup> Prior to 1991, the codes E950–E959 according to ICD-8 were applied.

Table 2. Diagnostic categories classified according to WHO ICD-9 (1991 – 1996) and ICD-10 (1997 – 2003) used in Study II.

<b>Diagnostic group</b>	<b>ICD-9</b>	<b>ICD-10</b>
Depression	298A, 300E, 311	F32–F33
Neurotic, stress-related, or somatoform disorder	300 (except 300E), 306, 307W, 308, 309	F40–F48
Schizophrenia	295	F20, F25
Other psychotic disorder	297–299 (except 298A)	F21–F24, F26–F29
Personality disorder	301	F60–F69
Alcohol use disorder	291, 303, 305A	F10
Other substance use disorder	292, 304, 305X	F11–F19
Other mental disorder	290, 293, 294, 296A, 296C–E, 296W, 296X, 302, 305B, 307A–H, 307X, 310, 312–315, 317–319	F00–F09, F30–F31, F34–F39, F50–F59, F70–F99
Violent suicide method	E953–E957	X70–X83
Non-violent suicide method	E950–E952	X60–X69

### **3.3 POPULATION-BASED REGISTERS**

The subjects in the four papers of this study were identified in Swedish population-based national registers. Suicide victims were identified in the Cause of Death Register, which is maintained by the National Board of Health and Welfare. This register contains data on the date and cause of death of all individuals registered in the Swedish Census Register at the time of death, regardless of whether the death occurred in Sweden or abroad. The causes of deaths are entered into the register on the basis of a death certificate issued by a physician. Since 1997 there are no missing deaths, even though the cause of death is unknown in up to 0.5% of the deaths.

Psychiatric diagnoses were identified in the National Patient Register, which is maintained by the National Board of Health and Welfare. It provides information on hospitalizations with dates of admission and discharge. For each discharge, one primary (main) diagnosis and up to seven secondary diagnoses can be recorded. The register is complete for all inpatient treatments in Sweden since 1987 and for psychiatry it is almost complete since 1973.

In Study I, the Census Register which is maintained by Statistics Sweden was used to identify controls from the general Swedish population.

Registers were linked using the unique civic registration number assigned to virtually all Swedish residents and immigrants (Ludvigsson et al., 2009).

### **3.4 CLINICAL RECORDS**

In Studies III and IV, data were retrieved from clinical records in addition to data from registers. These medical records were made available for our research after approval by the ethics committee and the approval by the head of department where the patient was treated. To ensure that the time for the documented follow-up data was similar for each matched pair, a research assistant truncated the control record at the date corresponding to the date of death of the case. The assistant also removed the part of the clinical record that contained data regarding the death of the case in order properly to blind the data reviewers as to whether a record belonged to a case or to a control. An extraction form was prepared listing pre-defined variables to be investigated as risk factors for suicide in the clinical records. The clinical records were reviewed manually in blocks of a similar number of matched case-control pairs. Data were recorded anonymously and transferred to a spreadsheet for analysis.

### **3.5 STUDY DESIGNS**

#### **3.5.1 Suicide and hospitalization for mental disorders in Sweden (Study I)**

Study I was a matched case-control study. All suicides in Sweden, aged 18 and above, from January 1, 1991 to December 31, 2003, were identified in the Cause of Death Register (n= 20,675). For each suicide case, 10 controls were randomly drawn from the Census Register on December 31, 1990. Matching criteria were age, sex and county of residence. The cases were eligible to be drawn as controls. The same control could be drawn as a control more than once (for different cases).

The National Patient Register provided information on primary psychiatric discharge diagnoses given to suicide cases and controls in the year before the suicide of the case.

### **3.5.2 Seasonality of suicide in Sweden: Relationship with psychiatric disorder (Study II)**

The Cause of Death Register was used to identify all suicide victims in Sweden with information on their month of death between 1992 and 2003 (n= 14,030). They were linked to the patient register to obtain information on primary and secondary psychiatric discharge diagnoses in the five years prior to the suicide.

### **3.5.3 Risk factors for suicide in schizophrenia: Findings from a Swedish population-based case-control study (Study III) and Diagnostic profile and suicide risk in schizophrenia spectrum disorder (Study IV)**

All patients below 65 years of age who were discharged for the first time with a schizophrenia spectrum diagnosis from a psychiatric department in Stockholm County between June 1984 and December 2000 (n=4,000) were identified in the National Patient Register. These individuals were linked to the Cause of Death Register to obtain information on death due to suicide. Cases were defined as those patients who died by suicide within five years from the first schizophrenia spectrum diagnosis (n=100). One control per suicide case was individually matched for each case from the same study population. Matching criteria were date ( $\pm 1$  year) and age ( $\pm 5$  years) at index diagnosis. Each control remained in the study population at risk and was eligible to later become a control again, or to become a case. The Cause of Death Register provided data for the methods of suicide for the cases and for the Stockholm County population in general for the same time period.

In addition, we included data retrieved from clinical records of cases and controls with the same time of follow up for cases and controls. We were able to trace the clinical records for 84 matched case-control pairs. The clinical records were reviewed in blocks of a similar number of matched case-control pairs, and the reviewer was blinded as to the case or control status of the clinical record.

For the fourth study, clinical information for the cases and controls was transferred into OPCRIT check lists (McGuffin et al., 1991). A software program supplied by the authors of OPCRIT was then used to give life-time diagnoses according to DSM-IV. The OPCRIT-derived diagnoses were grouped into four major diagnostic categories: schizophrenia, other psychosis, schizoaffective disorder, and mood disorder.

## **3.6 DATA ANALYSES**

### **3.6.1 Suicide and hospitalization for mental disorders in Sweden (Study I)**

To analyze the association between suicide and mental disorders, we compared the occurrence of mental disorder diagnoses in the year before the suicide and in the corresponding year for the controls. We further compared the occurrence of mental disorder diagnoses between cases and controls in the following time periods in relation to the suicide: ongoing hospitalization or discharge the same day as the suicide; discharge 1–7 days, 8–28 days, and 29–365 days before the suicide. Individuals who had been admitted more than once in the year preceding suicide could appear in more than

one of these time periods. Odds ratios (OR) of these associations together with 95% confidence intervals (CI) were calculated using conditional logistic regression models.

A separate analysis of the suicide cases with a life-time primary or secondary discharge diagnosis of a suicide attempt (registered until the day before the suicide) was made to describe their diagnoses of mental disorders in the year prior to suicide. Sex differences in the diagnostic distribution were tested using the chi-squared test, with p-values <0.05 considered to be significant. ORs of the association between suicide and a diagnosis of mental disorder in the year prior to suicide among the previous suicide attempters and their respective controls were calculated in conditional logistic regression models.

The population attributable fraction (PAF) was calculated as a percentage, taking the matched case-control design of the study into account, to estimate the proportion of suicides attributable to patients who had been hospitalized with a mental disorder in the year before suicide (Breslow and Day, 1980; Hennekens and Buring, 1987). This measure estimates the public health impact of a particular exposure and is used to estimate the proportion of disease that could be prevented if that exposure were eliminated. The SAS statistical software (version 9.1) was used for the statistical analyses.

### **3.6.2 Seasonality of suicide in Sweden: Relationship with psychiatric disorder (Study II)**

Seasonality of suicide was estimated with a Poisson regression variant of the circular normal distribution, which is an analog of the classical Edward's procedure (Frangakis and Varadhan, 2002). This method provides the month of maximum incidence for suicide together with 95% confidence intervals. It also provides an estimate of the relative risk (RR) of committing suicide during the maximum month in comparison with the month with minimum incidence during the year, and a test for significance of the RR. Stratified analyses were performed with respect to sex, history of psychiatric inpatient treatment and method of suicide. A level of significance for the RR of  $p < 0.05$  was considered to be significant.

For a graphical presentation of suicide seasonality, the monthly relative risk for suicide was calculated as a central moving average of the mean number of suicides per month over three consecutive months, divided by the twelve-month mean number of suicides in the respective categories. The SAS (version 9.1) and R (version 2.5.1) softwares were used for the statistical analyses.

### **3.6.3 Risk factors for suicide in schizophrenia: Findings from a Swedish population-based case-control study (Study III)**

Odds ratios (OR) with 95% confidence intervals (CI) were used as estimates of the relative suicide risk. We first estimated ORs adjusted for gender through conditional logistic regression. In the subsequent multivariate modeling, we first included gender, educational attainment, and history of suicide attempt as covariates that were hypothesized a priori as confounding factors. We then also included covariates that had shown a potential for statistical significance in the univariate analyses. Covariates were excluded from the final model when their inclusion did not affect the risk estimates.

Methods of suicide in the schizophrenia suicide cases were compared with methods of suicide in the general Stockholm County population during 1987 to 2000, standardized

for age and gender. The analyses were performed with SAS statistical software (version 9.1).

#### **3.6.4 Diagnostic profile and suicide risk in schizophrenia spectrum disorder (Study IV)**

Conditional logistic regression was used to investigate the association of suicide with the OPCRIT-generated diagnoses. The analysis was conditioned on the risk-set structure defined by the matching process, with additional adjustment for sex and level of education (primary school, secondary school or higher, and unknown). We also controlled for country of origin (Sweden versus other countries) and age of symptom onset (<30 versus  $\geq$ 30 years) but, as they had no effect on the results, we did not include them in the final model. The analyses were conducted using SAS statistical software (version 9.1).

### **3.7 ETHICAL APPROVAL**

Studies I and II were approved by the regional research ethics committee in Stockholm, Sweden, on October 12, 2005 (Dnr 2005/1098-31). Studies III and IV were approved by the research ethics committee at Karolinska Institutet, Stockholm, Sweden, on October 15, 2001 (No. 01-375).



## 4 RESULTS

### 4.1 SUICIDE AND HOSPITALIZATION FOR MENTAL DISORDERS IN SWEDEN (STUDY I)

During the 13-year period from 1991 to 2003, 20,675 persons died by suicide in Sweden. Of these, 14,501 were men (70%) and 6,174 women (30%). During the year before the suicide, 23% of the male and 31% of the female suicide cases had been hospitalized with a mental disorder. Among the female suicide cases, the most prevalent discharge diagnosis was mood disorder (14%). In males, hospitalizations for mood disorders and for alcoholism were equally common (7%).

The ORs of the suicide risk in men and women are graphically presented in Figure 1 and Figure 2. The highest suicide risk during hospitalization compared to the general population and in the year following discharge was found for mood disorder [OR 55 (95% CI 47–65) for men and 86 (95% CI 70–107) for women]. The suicide risk in mood disorder was highest in the first week following discharge [OR 177 (95% CI 78–401) for men and OR 268 (95% CI 85–846) for women]. Compared to that for mood disorder, the suicide risks for schizophrenia spectrum disorder and for alcohol use disorder were about half and were more constant over time.

Figure 1. Suicide risk in male patients with a hospitalized mental disorder compared to the general population (OR) in the year following discharge, by diagnosis.

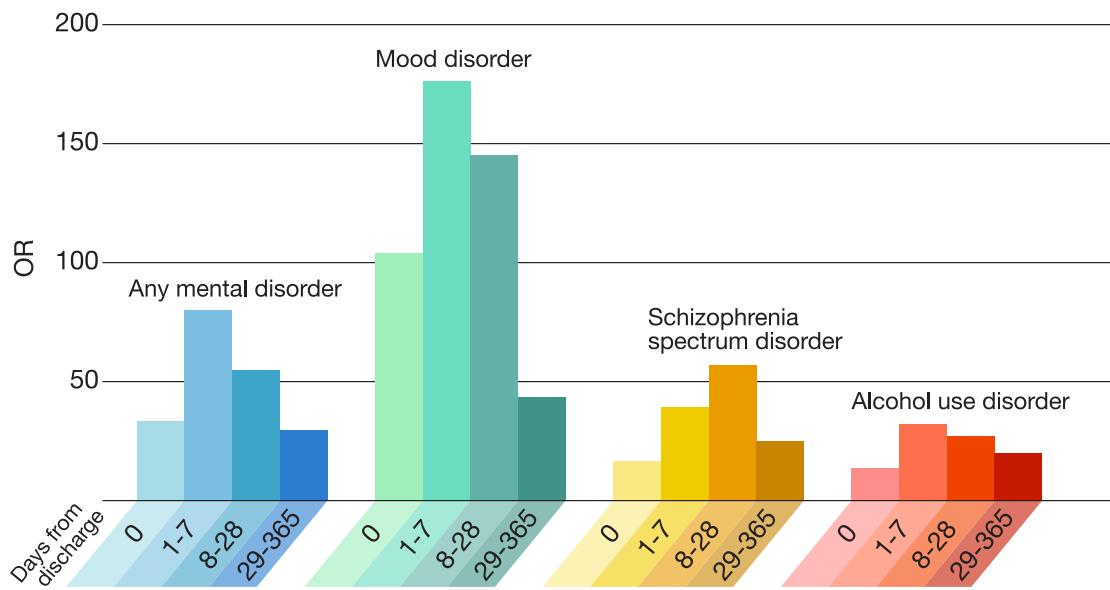
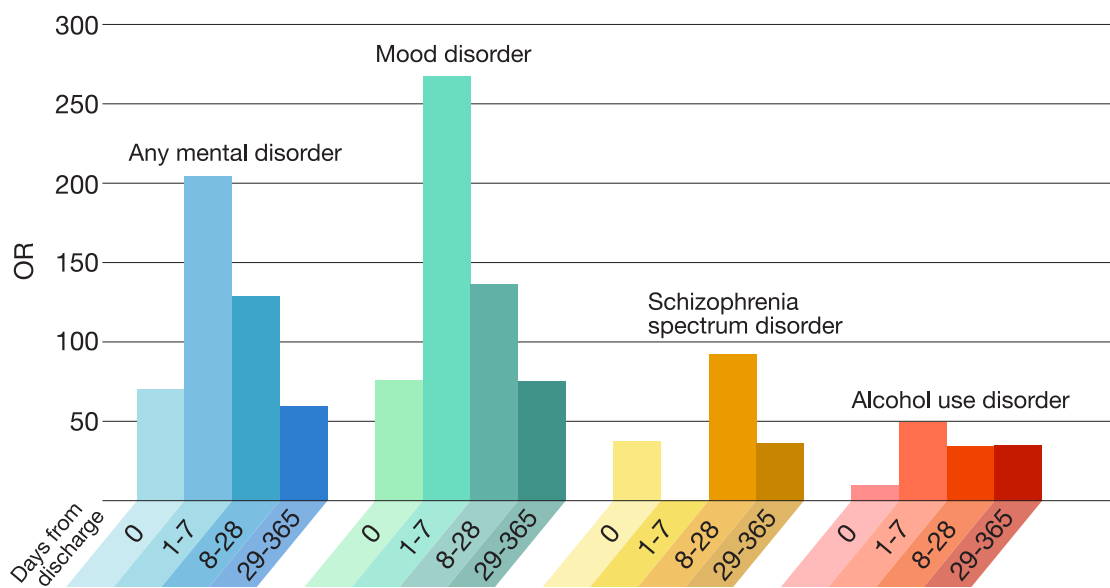


Figure 2. Suicide risk in female patients with a hospitalized mental disorder compared to the general population (OR) in the year following discharge, by diagnosis.



The population attributable fraction (PAF) was calculated to estimate the proportion of suicides attributable to hospitalized psychiatric illness (Breslow and Day, 1980; Hennekens and Buring, 1987). Figures 3 and 4 present the PAF by diagnoses and time since discharge and show that the majority of suicides among former psychiatric patients were attributable to mental disorders that were inpatient-treated more than one month before the suicide. Of all the suicides in men and women, 457 (3%) and 312 (5%), respectively, occurred during hospitalization or on the day of discharge.

Figure 3. The proportion of all suicides in men attributable to a hospitalized mental disorder, by diagnosis and time since discharge, given as population attributable fraction (PAF).

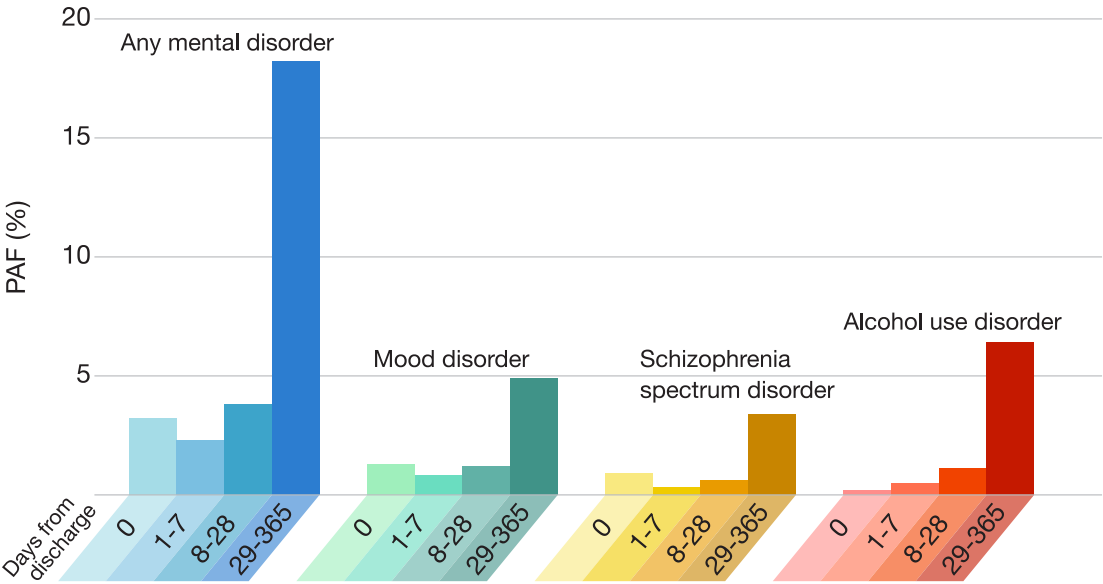
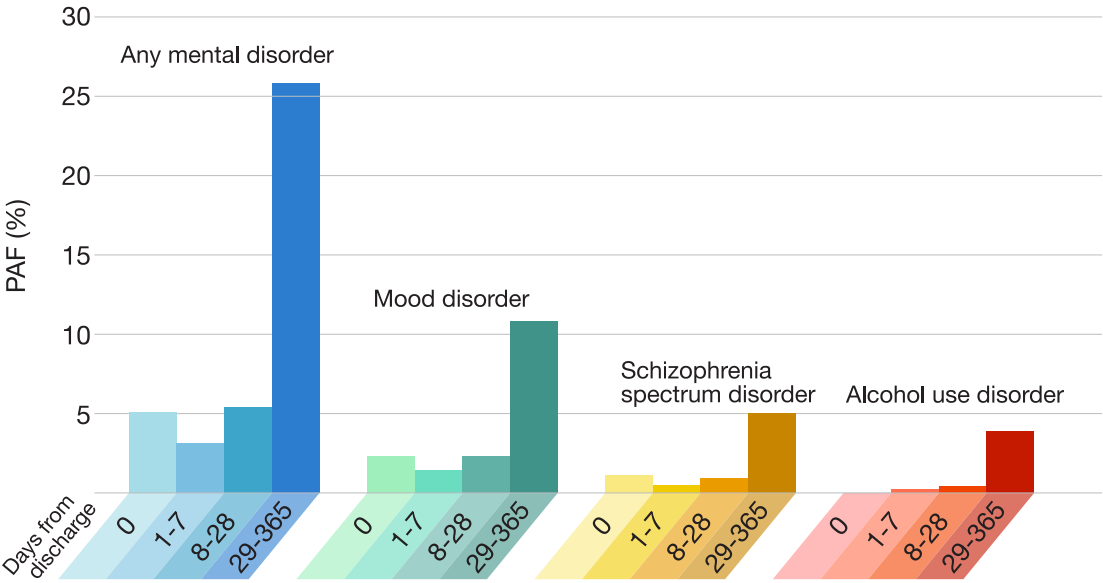


Figure 4. The proportion of all suicides in women attributable to a mental disorder that required psychiatric inpatient treatment, by diagnosis and time since discharge, given as population attributable fraction (PAF).



Among the suicide cases, 17% of males and 31% of females had previously been hospitalized due to a suicide attempt. Of these cases with previous suicide attempts, 1089 (44%) males and 908 (47%) females had been discharged with a mental disorder in the year prior to the suicide. Regarding their diagnoses, there was a higher proportion of mood disorder in women than in men (20% vs. 12%, respectively,  $p < 0.001$ ), and a higher proportion of alcohol use disorder in men than in women (16% vs. 8%, respectively,  $p < 0.001$ ), whereas there was no significant sex difference in the distribution of schizophrenia spectrum diagnoses. The suicide risk among the previous suicide attempters in the year following discharge with a psychiatric inpatient diagnosis ('any mental disorder') was about three times higher in men and twice as high in women compared to the suicide risk for the overall category of 'any mental disorder': OR 91 (95% CI 76–110) for men and 142 (95% CI 111–181) for women.

Over time, a constant proportion of 25% of the suicide victims had been hospitalized with a mental disorder in the year before suicide (23% of males and 31% of females), despite a significant decrease in psychiatric hospitalization in the population during the study period.

## 4.2 SEASONALITY OF SUICIDE IN SWEDEN: RELATIONSHIP WITH PSYCHIATRIC DISORDER (STUDY II)

There were 9,909 male and 4,128 female suicides in Sweden with information about the month of death between 1992 and 2003. During the five-year period prior to suicide, an inpatient diagnosis of a psychiatric disorder had been assigned to 34% of the male suicide victims and to 52% of the female suicide victims. Of these diagnoses, 94% were given as a primary diagnosis, with a range between 66% for personality disorder to 95% for schizophrenia.

There was a general pattern of an increased suicide incidence in late spring and summer (May to August). Peaks in suicide incidence were found in June for both males (RR=1.16,  $p<0.001$ ) and females (RR=1.10,  $p=0.10$ ). The seasonal amplitude was more evident in suicides with a history of inpatient treatment for a psychiatric disorder than in those without such a history. Suicide by violent methods showed significant peaks in June for both males (RR=1.20,  $p<0.001$ ) and females (RR=1.19,  $p=0.02$ ). For non-violent suicides, seasonal peaks were found in May or earlier, but these peaks were not statistically significant. There was a general tendency for the seasonal amplitude to be higher in violent than in non-violent suicides. The highest suicide seasonality peaks were found in violent suicides with a history of inpatient-treated psychiatric disorder, with a significant suicide peak in early July for males (RR=1.23,  $p=0.003$ ) and in June for females (RR=1.34,  $p=0.003$ ).

When suicide seasonality was analyzed with respect to eight defined psychiatric diagnoses, peaks in suicide incidence in late spring and summer were found in most diagnoses. However, statistical significance was reached only in some of these groups. Male suicides with a history of depression presented a statistically significant peak in July, with the highest peak for violent methods (RR=1.31,  $p=0.03$ ). In female suicides with a history of neurotic, stress-related or somatoform disorder, a significant peak was found in May, the highest peak also being for violent suicides (RR=1.67,  $p=0.003$ ). For suicides in several other diagnostic groups, borderline significant seasonality peaks were identified. An exception to the general pattern of suicide peak in spring/summer was found in non-violent suicide victims with a history of schizophrenia, where a significant peak was found in February for females (RR=3.31,  $p=0.01$ ).

The graphical presentation of the suicide seasonality patterns (Figs. 5 and 6) illustrates the more pronounced seasonality patterns in suicides with a history of psychiatric inpatient-treatment and in violent suicides.

Figure 5. Relative risk (RR) of suicide in Sweden by month in men.

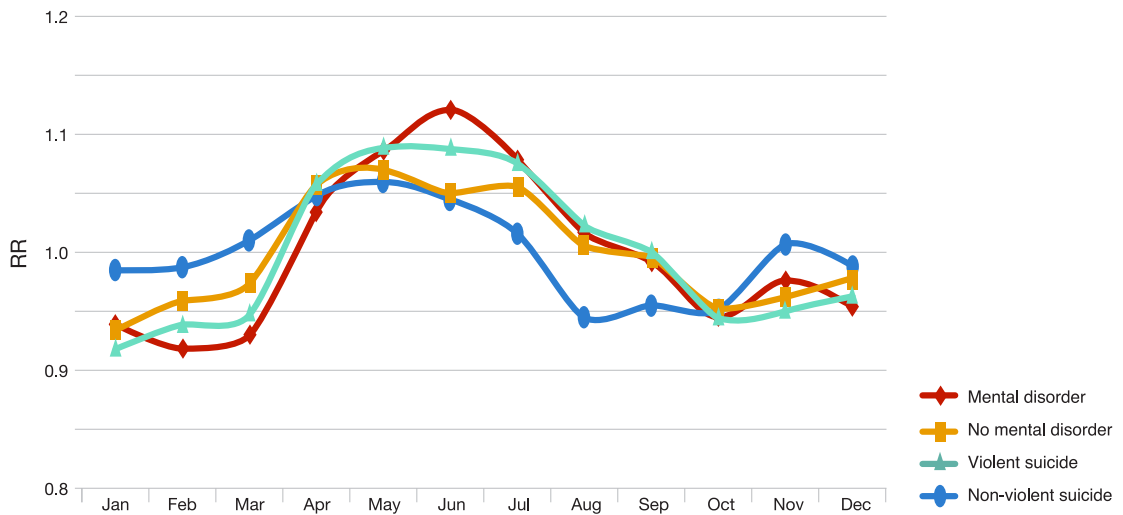
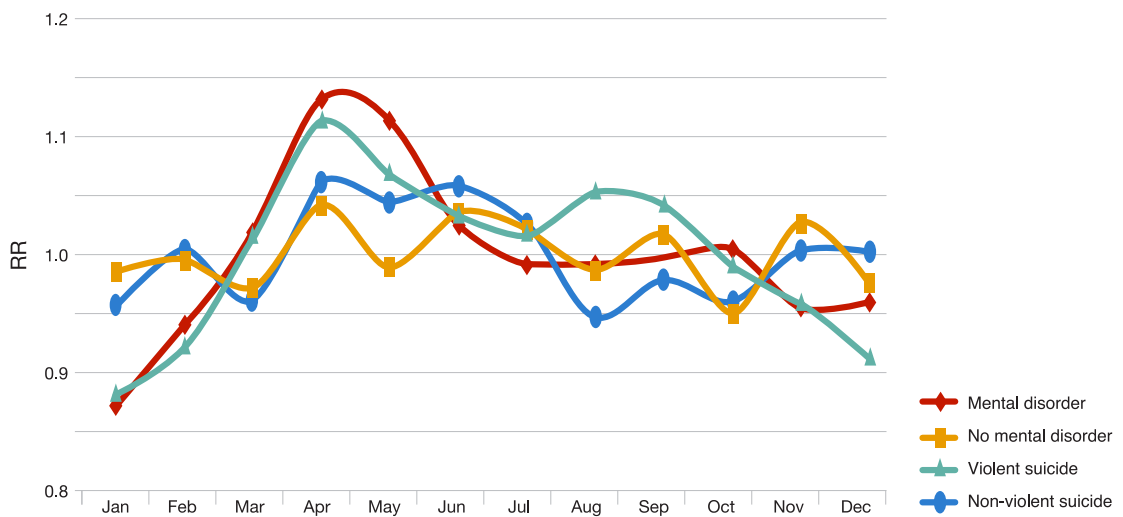


Figure 6. Relative risk (RR) of suicide in Sweden by month in women.



### **4.3 RISK FACTORS FOR SUICIDE IN SCHIZOPHRENIA: FINDINGS FROM A SWEDISH POPULATION-BASED CASE-CONTROL STUDY (STUDY III)**

Of the 84 patients with schizophrenia who committed suicide, 54% were men and 46% women. In multivariate analyses, the following factors were found to be associated with a significantly increased suicide risk: Swedish origin (OR 3.6, 95% CI 1.3–9.9), educational attainment of secondary school level or higher (OR 2.9, 95% CI 1.03–8.0), age  $\geq 30$  years at onset of symptoms (OR 4.8, 95% CI 1.1–21.2), and a history of a suicide attempt requiring non-psychiatric medical treatment (OR 5.0, 95% CI 1.6–15.4). There were also tendencies for an increased risk of suicide being associated with having been married or cohabiting, and with a longer total duration of hospitalization.

Gender did not significantly affect the suicide risk, nor did a history of self-discharge, compulsory in-patient treatment, substance use disorder or a family history of mental disorders or suicide.

Suicide by ‘jumping’ and ‘other method’ (including jumping in front of a vehicle) were more frequent than in the general population, while poisoning was less common.

### **4.4 DIAGNOSTIC PROFILE AND SUICIDE RISK IN SCHIZOPHRENIA SPECTRUM DISORDER (STUDY IV)**

A DSM-IV schizophrenia spectrum diagnosis (i.e. schizophrenia, schizophreniform or schizoaffective disorder) was assigned by OPCRIT to 50% of the 84 suicide cases and 62% of the 84 controls. DSM-IV criteria for schizophrenia were met by 41% of cases and 51% of controls; for schizoaffective disorder by 8% of cases and 10% of controls; for other psychosis by 23% of cases and 25% of controls; and for mood disorder by 26% of cases and 12% of controls.

Using the schizophrenia diagnosis as a reference, suicide risk was significantly higher in patients meeting criteria for a mood disorder diagnosis with an adjusted odds ratio of 3.3 (95% CI 1.2–9.0). There was no significant difference in suicide risk between schizophrenia and schizoaffective disorder or other psychoses.

## 5 DISCUSSION

### 5.1 METHODOLOGICAL CONSIDERATIONS

#### 5.1.1 Case-control studies

As the aims of Studies I, III and IV included the study of associations between different exposures (risk factors and risk indicators) and outcome (suicide), an analytical study design was applied. There are three main types of design of analytical studies, namely cross-sectional study, cohort study and case-control study. For Study I, both a cohort and a case-control design would have been possible, although the case-control design made the data more manageable than the alternative of comparing the suicide cases with the entire Swedish population. For Studies III and IV, a case-control design was the best alternative because data collection from case records was costly and time-consuming.

Several different sampling methods for controls are available in the design of case control studies. In the present thesis, Studies I, III and IV are designed as matched case-control studies.

In Study I, cases were drawn from the entire Swedish population of 18 years and older. Controls were drawn from the Census Register on December 31, 1990, the day before the start of the study. In the analysis of psychiatric inpatient treatment in the year prior to the suicide, only information for controls who were alive at the date when the case died was included. Since suicide is a rare outcome in the population, the rare disease assumption is applicable in this study design. The rare disease assumption is a term applicable in case-control studies in which it can be shown that when the prevalence of the disease is low in each exposure group (less than about 20%), then the odds ratio approaches the relative risk, which in this study is the incidence-rate ratio (Rothman et al., 2008). This means that the odds ratio in Study I estimates the incidence-rate of suicide in hospitalized psychiatric patients compared to incidence-rate of suicide in the general population.

In the study described in papers III and IV, the cases were all consecutive suicides within five years of diagnosis with schizophrenia or schizoaffective disorder. Sampling of a control was done at the time of death of the case, a method which is called 'density sampling'. Through this study design, the odds ratio estimates the incidence-rate ratio, both with and without the rare disease assumption (Rothman et al., 2008).

The reason for matching is that it may increase efficiency in the statistical analyses. For example, inefficiency would occur in an unmatched study in strata which have controls but no case and vice versa. Matching forces the controls to have a similar distribution of the matching factor, such as sex. However, one must bear in mind that matching in case-control studies does not prevent confounding and that matching may itself introduce bias (Marsh et al., 2002). Matching on too many factors is termed overmatching and may harm validity and statistical efficiency (Rothman et al., 2008).

In Study I, individual matching of cases to controls was done by age, sex and county of residence. The fact that matching was done by sex means that the suicide risk estimates for men and women cannot be directly compared. The matching by county was done



because the sensitivity of the health care registers as well as the structure of the health care system may vary between different regions in Sweden.

In Studies III and IV, one control was individually and randomly matched with each case from the same study base by date ( $\pm 1$  year) and age ( $\pm 5$  years) at index diagnosis. In these studies, no matching was done on sex but this factor was instead controlled for in the statistical analyses. This allowed us to compare the suicide risk in men with that in women suffering from schizophrenia.

### **5.1.2 Seasonality studies**

The aim of Study II was to assess seasonal suicide patterns. A number of different methods have been developed for this purpose (Hakko et al., 2002). Our method is a modified version of the Edward's test which has been widely used in epidemiological research of seasonality in general, although less so in the study of suicide seasonality (Hakko et al., 2002; Rothman et al., 2008). The modified version of the Edward's test applied in our study provides the ratio (a relative risk, RR) of the peak-to-trough occurrence of suicide over the year together with its 95% confidence interval. It also provides a test for significance of the RR (Frangakis and Varadhan, 2002).

### **5.1.3 Internal validity**

A major goal with an analytical epidemiological study is to draw inferences from the result of the study to the entire population and other similar populations. For this to be appropriate, both the internal and external validity need to be high. The internal validity can be defined as the extent to which the cause-and-effect relationships in a study are true for the population of the study. The factors discussed below are important to consider as they may affect the internal validity.

#### *5.1.3.1 Bias*

Another word for bias is systematic error. This is a deviation of the results from the truth, and is caused by systematic error in collecting or interpreting data (Hennekens and Buring, 1987). There are many types of bias that can occur in scientific studies. One of them is selection bias, which means that an error has occurred when choosing the subjects to take part in the study. In the case-control studies of the present thesis (Studies I, III and IV), selection bias was minimized since all cases as well as controls were taken from the same population.

Information bias, which could have been introduced into Studies III and IV when reading the clinical records, was minimized since data were collected in a blind way from the records. A possible trend in misclassification during the data collection process was virtually eliminated by reading a similar number of matched case-control pairs' records in blocks.

Recall bias was not an evident problem since all data were prospectively recorded both in the registers and in the clinical records.

Ascertainment bias of psychiatric diagnoses was limited by the fact that only inpatient diagnoses were available. A possible under-reporting of exposures in Studies III and IV was probably of the same proportion in both cases and controls. This would minimize

the differences between the groups and introduce a non-differential misclassification between cases and controls which would lead to lowered risk estimates.

Confounding bias means a mixing of the effect of the exposure under study on the outcome with that of a third factor that is associated with the exposure and an independent risk factor for the outcome. The consequence of confounding is that the estimated association is not the same as the true effect. For instance, in the present studies, the risk of suicide is affected not only by the presence of psychiatric illness but also by age. Age is also related to the risk of psychiatric illness (exposure) and can therefore be hypothesized to be a confounding factor.

There are several approaches that can be used in the study design and statistical analysis to handle the issue of confounding. To reduce the impact of age as a confounding factor, matching on age was done in Studies I, III and IV. As sex is also a probable confounding factor in these studies, matching was also done on sex in Study I. In Studies III and IV, however, adjustment for sex was made in the statistical analyses instead.

Socioeconomic status is often a confounding factor. However, since socioeconomic status is known to be associated with the mental disorder itself (Mortensen et al., 2000), we chose not to adjust for that in Study I.

With regard to Study II, factors such as age and socioeconomic status do not vary over the season of the year and are not therefore likely to be confounding factors (Rothman et al., 2008). Although suicide seasonality may vary between age groups, it was not the aim of our study to investigate this and we did not adjust for these factors in Study II.

#### *5.1.3.2 Random error*

Another factor which affects the internal validity is random error. This means that the values recorded in a sample may by chance differ more or less from the population from which it is drawn. Such random error can be seen as the result of fluctuations around a true value because of sampling variability. The term precision is used in epidemiology as a measure of random error.

Calculating p-values and confidence intervals is a means to assess the precision of an estimate, i.e. how near the value found in the samples is to the value in the population. As the confidence intervals provide more information than p-values, this measure was given priority in the present studies (Hennekens and Buring, 1987).

The precision of the psychiatric diagnoses is a factor to be discussed in this context, since diagnostic accuracy may differ between clinicians. In Study I, a less than optimal accuracy in diagnostic quality would affect cases and controls to the same degree and thereby lower the risk estimates. The quality of the psychiatric diagnoses is further discussed below.

#### **5.1.4 External validity**

The external validity concerns the validity of (causal) inferences as they pertain to people outside the population under study (Rothman et al., 2008). The factors below should be considered in this context.

#### 5.1.4.1 *Quality of suicide diagnoses*

As a number of reports have suggested that a proportion of undetermined deaths are in fact suicides, an issue of debate in the research into suicide is whether or not undetermined deaths should be included in the research into suicide. One of the investigations in this field re-evaluated causes of death among former Swedish conscripts, and found that 19% of 47 undetermined deaths should be re-evaluated as suicides (Allebeck et al., 1991). A similar study from Finland investigated the circumstances of 190 undetermined deaths of which 61 deaths were suspected as being caused by suicide (Ohberg and Lonnqvist, 1998). Among these 61 deaths, 87% had earlier communicated suicidal intent, and 34% had made suicidal threats. Compared to all the 190 undetermined deaths, these figures represent 18% and 11%, respectively. The authors estimated that about 10% of undetermined deaths may have been suicides. A study in England compared 188 suicides with 185 undetermined deaths ('open verdicts'), of which 26 cases were excluded since suicide was unlikely or impossible (Linsley et al., 2001). It was found that the social class, method used, age, and proportion of suicide victims who had left a suicide note differed between the groups. It was also found that a higher proportion among the undetermined deaths was female, but that the history of psychiatric morbidity did not differ. Due to the similarities in psychiatric morbidity, these authors suggested that undetermined deaths should be included in all suicide research after excluding cases in which suicide was unlikely, but they also proposed that criteria should be developed to help decide which undetermined deaths should be included in research into suicide.

In Study I, both definite suicides and undetermined deaths were included to avoid an under-estimation of suicides. We did not attempt to decide what proportion of the undetermined deaths were not suicides, so that some of the undetermined deaths may not have been suicides. Whether a death in Sweden is to be classified as suicide, undetermined, or accidental is decided by the forensic examiner. However, by including deaths classified as undetermined deaths, we believe that we could more accurately follow trends for all suicides, although the proportion of deaths classified as suicides and undetermined deaths may have changed over time and between regions. The advantage is that we did not have an incomplete sample, and we have avoided the under-estimation of suicides. In Studies II–IV, however, only definite suicides were included to increase the specificity in the research questions. As we wished to study suicide seasonality in relation to defined mental disorders in Study II, it was thought that the association could be more evident if only certain suicides were included. In Studies III and IV, it was decided to study only risk factors for certain suicide.

#### 5.1.4.2 *Quality of psychiatric diagnoses*

An area of controversy in the field of psychiatric epidemiology is the nature of psychiatric diagnoses since they are not, as yet, based on biological measurements. Instead they are constructed as syndromes of a set of symptoms derived from expert opinion. Criteria also differ between the two diagnostic systems currently in use, ICD-10 and DSM-IV. For instance, the time of psychotic symptoms required for a diagnosis of schizophrenia differ in that, according to ICD-10, one month is required and, in DSM-IV, six months. Re-assessments of the schizophrenia diagnosis in the Swedish patient register have found an agreement ranging from 86–94% between clinical schizophrenia ICD-diagnoses and the corresponding diagnoses in DSM-III, DSM-III-R, or DSM-IV (Dalman et al., 2002; Ekholm et al., 2005). However, studies are lacking

about the quality of most of the other diagnostic categories used in Studies I and II. Nevertheless, under the assumption that the majority of diagnoses given by psychiatrists in Sweden adhere to the definitions in ICD-10 and DSM-IV, the results of the present studies can be generalized to apply to similar populations.

## **5.2 FINDINGS AND IMPLICATIONS**

### **5.2.1 Suicide and hospitalization for mental disorders in Sweden (Study I)**

In Study I, the main result was that the greatest suicide risk during hospitalization and in the year following discharge was found for mood disorder with the risk peaking in the first week following discharge. Compared to that for mood disorder, the suicide risk for schizophrenia spectrum disorder and alcohol use disorder was about half and was more constant over time.

Previous studies of suicide risk for different mental disorders after discharge have shown conflicting results. One study reported the highest suicide risk in the first month for depression in men but for neuroses in women (Goldacre et al., 1993), whereas another study found no clear differences in suicide risk between five different mental disorders (Ho, 2003). In line with our results, a study from Denmark found the highest suicide risk after discharge for affective (mood) disorders and that the suicide risk following discharge with a substance use disorder declined more slowly than for affective or schizophrenia spectrum disorders (Qin and Nordentoft, 2005).

An additional finding of this study was that, among the male suicide victims, similar high proportions were recently hospitalized for alcohol use disorder as for mood disorder. This suggests that, in men, similar attention should be paid to the long-term risk of suicide following hospitalization for alcohol use disorders as for mood disorders. We also found a more evident increased suicide risk for men than for women with a previous suicide attempt, compared with the suicide risk for the overall category of 'any mental disorder'. This suggests that for suicide prevention, men with a previous suicide attempt should be given extra attention by health care services.

The PAF shows that the majority of suicide victims among psychiatric patients had been discharged more than one month before the suicide. Thus, although the relative risks were high during hospitalization and soon after discharge, the present results imply that for a substantial reduction of the number of suicides in the population, suicide preventive activities need to be long-term.

The finding that a constant proportion of the suicide victims had been hospitalized with a mental disorder in the year before suicide suggests that psychiatric services have continued to identify and hospitalize patients who later will commit suicide to the same degree over the study period, in spite of the significant decrease in psychiatric hospitalization in the general population.

The notion that suicide risk was found to vary by type of mental disorder, time since discharge, and sex should be taken into account when planning suicide-preventive efforts by the health care services.

### **5.2.2 Seasonality of suicide in Sweden: Relationship with psychiatric disorder (Study II)**

In Study II we found an increase in suicide incidence in spring and early summer. This seasonal variation was more evident in suicide victims with a psychiatric inpatient history than in those without. The seasonal variation was found in most of the eight diagnostic groups under study, with significant peaks in males with a history of depression and in females with a history of a neurotic, stress-related, or somatoform disorder.

Our finding of a larger seasonality effect in suicides with a history of psychiatric inpatient treatment is partly supported by an Italian study which reported that suicides attributable to a psychiatric history, somatic illness or to unknown causes, showed a higher seasonality with a peak in spring–summer than did suicides attributable to ‘sentimental’ or financial reasons (Rocchi et al., 2007). A study from Denmark found inconclusive results, with suicide seasonality varying over time with gender and history of psychiatric treatment (Yip et al., 2006). A more recent Danish report, published after our study, compared seasonality trends in suicide cases with and without a history of inpatient treatment for mood disorder (Postolache et al., 2010). The authors found a spring peak in both groups, with a higher seasonality effect in those with a previous mood disorder diagnosis. They therefore concluded that there is a need to further investigate whether an exacerbation of mood disorders in spring triggers seasonal peaks of suicide. In a study of 115 male suicide victims in Canada, suicides related to major depressive disorder dominated in the spring–summer (Kim et al., 2004). A previous Swedish study found a suicide peak in the spring–early summer (April–June) in alcohol use disorders, but also a suicide peak in the fall–winter (October–December) in DSM-IV major depressive disorder with melancholic or psychotic features (Bradvik and Berglund, 2002), in contrast to the seasonality pattern in the present study. In the study by Kim (Kim et al., 2004), the majority of male suicide victims with schizophrenia died in the fall–winter, whereas in our study a suicide peak in winter was observed for non-violent suicides with a schizophrenia diagnosis.

Although there are some differences between psychiatric diagnoses, the overall pattern of a suicide peak in spring and summer suggests that suicide seasonality is a phenomenon associated with several psychiatric diagnoses. This implies that pathophysiological processes associated with an increase in suicidal behavior in spring/early summer may be similar in different psychiatric syndromes, and therefore provide similar expressions of suicidality. The seasonality phenomenon of suicidality may be seen as a separate nosological entity, not clearly linked to current psychiatric diagnostic categories.

### **5.2.3 Suicide in schizophrenia (Studies III and IV)**

We found that in schizophrenia, including schizoaffective disorder, higher educational attainment, age  $\geq 30$  years at onset of symptoms and a history of suicide attempt were associated with an increased risk of suicide within five years after a first clinical schizophrenia in-patient diagnosis. In contrast to what is found in the general population and most other mental disorders, gender did not significantly affect the suicide risk, nor did substance use disorder or a family history of mental disorder or suicide. Table 3 shows the significant risk factors for suicide in schizophrenia identified in this thesis together with comparable risk estimates from a comprehensive meta-analysis of risk factors in suicide (Hawton et al. 2005).

Table 3. Significant risk factors for suicide in schizophrenia identified in this thesis and comparable results from a comprehensive meta-analysis of risk factors in suicide in italics (Hawton et al., 2005).

<b>Risk factor</b>	<b>OR</b>	<b>95% CI</b>
>9 years of education <sup>a</sup>	2.9	1.03–8.0
<i>Higher education</i>	2.9	0.9–9.9
Age at onset of psychiatric symptoms $\geq 30$ years <sup>a</sup>	4.8	1.1–21.2
<i>Comparison not available</i>	–	–
History of suicide attempt <sup>a</sup>	5.0	1.6–15.4
<i>Attempted suicide in past</i>	4.1	2.8–6.0
Swedish origin <sup>a</sup>	3.6	1.3–9.9
<i>White ethnicity</i>	4.6	1.2–17.3
DSM-IV mood disorder <sup>b</sup>	3.3	1.2–9.0
<i>Depression (past)</i>	3.0	2.1–4.5
<i>Depression (recent)</i>	6.2	1.3–29.9

<sup>a</sup> Multivariate analyses.

<sup>b</sup> Adjusted for sex and education.

A higher suicide risk in schizophrenia associated with higher education has been reported previously (Drake et al., 1984; Hawton et al., 2005). This, together with the tendency for an increased risk of suicide being associated with having been married or cohabiting, suggests that a higher level of function prior to the onset of schizophrenia may contribute to a greater sense of loss due to the illness, and thereby increase the suicide risk. As this contrasts with findings in the general population, these findings suggest that certain suicide risk factors may differ from those in the general population and from patients with other psychiatric diagnoses.

Our finding regarding ethnicity can be interpreted in several ways. White ethnicity has been associated with a higher suicide risk in schizophrenia (Hawton et al., 2005) as well as in the general population (Montross et al., 2005). Although it is probable that a higher proportion of the individuals of Swedish origin than of the immigrants were of white ethnicity, our finding of a greater suicide risk associated with being of Swedish origin was due to a high proportion of controls with a foreign country of birth (42%). This is higher than the proportion with an immigrant background among schizophrenia patients in the Swedish city of Malmö (29%) (Zolkowska et al., 2001) and among the Swedish general population (9–11%) during the period of study (Statistics Sweden 2001). One may speculate that there can be a differential inclination to admit schizophrenia patients depending on their ethnic background. If foreign-born individuals with schizophrenia were more likely than those born in Sweden to be admitted for psychiatric treatment when suicidal, the risk that they would complete suicide would decrease, and consequently, in the present study, they would be more likely to be found in the control group. The country from which most immigrants originated was Finland; 7 cases and 16 controls. One may therefore also consider the

possibility that those Finns who immigrate to Sweden are less prone to suicide than those who remain in Finland. Another possibility is that our result was a chance finding.

The finding that the proportion of patients who was assigned a DSM-IV diagnosis of psychosis by OPCRIT was higher among controls appears consistent with findings that immigrants have a higher likelihood of being diagnosed with psychosis (Cantor-Graae and Selten, 2005; Coid et al., 2008). Our result suggests that this pattern persists also after diagnostic reassessment with OPCRIT. However, adjustment for country of origin did not significantly affect the association between diagnostic profile and suicide risk in study IV suggesting that ethnicity was not an important confounding factor for this association.

We also found that a DSM-IV mood disorder diagnosis was associated with a more than three-fold increase in the risk of suicide within five years from diagnosis. The suicide risk in patients with a DSM-IV diagnosis of other psychosis or schizoaffective disorder did not, however, differ from that of schizophrenia. This shows the need for a repeated diagnostic evaluation when assessing the suicide risk in patients with schizophrenia spectrum disorder.

The over-representation of violent suicide methods in schizophrenia compared to all suicides suggests that suicides among schizophrenia patients may be less preventable than suicides in the general population by restricting the availability of pharmacological means of suicide. Instead, other general preventive strategies, such as barriers at bridges and observation by cameras at railways, may be more valuable for decreasing suicides in this patient group.

### 5.3 SUGGESTIONS FOR FUTURE RESEARCH

As is shown in this thesis, a large proportion of the suicide victims are known by the psychiatric services, and are therefore important targets for suicide prevention. In clinical practice, it is often necessary to assess the imminent suicide risk. Studies that explore risk factors for suicide on a short term from an event, such as discharge from hospital, would be of direct clinical value. Another important issue to be further explored is how co-morbidity between different mental disorders affects the suicide risk. More knowledge is also needed of how suicide risk patterns among psychiatric patients differ between age groups.

Regarding suicide in schizophrenia, our results suggest that there is a considerable diagnostic delay in the diagnosis of schizophrenia and schizoaffective disorder. Therefore, research into the suicide risk among patients with psychotic symptoms but who are not yet given a schizophrenia diagnosis appears to be needed. More knowledge is also needed as to how psychotropic drugs affect the suicide risk in schizophrenia. However, since randomized controlled studies are difficult to perform for ethical, economic and practical reasons, observational studies can also be used to increase knowledge in this area. This issue will be further explored in the material used for Studies III and IV in this thesis.

For clinical use, it would also be of value if studies of risk factors were complemented by studies of their predictive value. The predictive value is a measure of the usefulness of a factor, such as a symptom, in predicting an outcome, such as suicide.

A method that has been shown to reduce suicide rates is the restriction of suicide methods (Mann et al., 2005). Our results, as well as previous reports, have shown that suicide methods in schizophrenia differ from those found in the general population. To improve the possibility of restricting the availability of suicide methods for psychiatric patients, more research into the suicide methods used by patients suffering from various mental disorders would be of value.

Studies of suicide seasonality may help to increase knowledge about the biological processes that affect suicide risk. Investigations of suicide seasonality in relation to specified clinical symptoms and biological characteristics rather than broad diagnostic syndromes may be an interesting approach. The study of suicide seasonality in relation to family history of suicidal behavior or other impulsive behavior could also add information about the etiology of suicide seasonality. A study of whether serotonergic drugs affect the suicide seasonality could test the hypothesis that serotonergic functioning is related to suicide seasonality. As most of the studies of suicide seasonality have been carried out in the northern hemisphere, additional studies from areas near the equator and the southern hemisphere are needed to replicate findings of a lack of or reversed suicide seasonality compared to the results from the northern hemisphere.



## 6 CONCLUSIONS

- The greatest suicide risk during hospitalization and in the year following discharge was found for mood disorder with the risk peaking in the first week following discharge. Compared to that for mood disorder, the suicide risks for schizophrenia spectrum disorder and alcohol use disorder were about half and were more constant over time.
- The majority of suicide victims among psychiatric patients had been discharged from psychiatric inpatient treatment more than one month before the suicide. This implies that suicide preventive efforts need to be long-term.
- Over time, a constant proportion of 25% of the suicide victims had been hospitalized with a mental disorder in the year before suicide. This suggests that psychiatric services have continued to identify patients who later will commit suicide to the same degree over the study period, despite a significant decrease in psychiatric hospitalization in the general population.
- A history of inpatient-treated psychiatric disorder appears to be associated with an increase in suicide seasonality, especially in violent suicide methods. This increase is found in several psychiatric disorders.
- In schizophrenia, risk factors for suicide include higher educational attainment, higher age at onset of symptoms, and a history of a suicide attempt requiring medical treatment. Gender did not significantly affect the suicide risk, nor did substance use disorder or a family history of mental disorder or suicide.
- Among patients with a schizophrenia spectrum disorder, a mood disorder diagnosis increased the risk of suicide by a factor of more than three.

## 7 POPULÄRVETENSKAPLIG SAMMANFATTNING

Det är känt sedan tidigare att dödligheten i suicid är högre bland män än bland kvinnor och att psykisk sjukdom och tidigare suicidförsök ökar suicidrisken påtagligt. Det är även känt att fler suicid sker på vår och försommar. Däremot har man begränsad kunskap om vad som särskiljer suicidrisken vid olika psykiska sjukdomar. Det övergripande målet i denna avhandling var därför att öka kunskapen om suicid vid olika psykiska sjukdomar.

Dödsorsaksregistret användes för att identifiera personer avlidna genom suicid i Sverige, och förekomsten av psykiatriska diagnoser inhämtades ur patientregistret. Denna information ligger till grund för samtliga delstudier. För delstudier tre och fyra studerades även journaler.

### **Studie 1: Suicid och sjukhusvård för psykisk sjukdom i Sverige**

Den första studien omfattade alla 14 501 män och 6 174 kvinnor äldre än 17 år som avlidit genom suicid mellan 1991–2003. Deras psykiatriska vård under året före suicidet jämfördes med den psykiatriska vård som kontrollpersoner ur allmänna befolkningen fått. Därigenom kunde suicidrisken beräknas under och året efter sjukhusvård för en psykiatrisk diagnos. Fyra diagnostiska grupper studerades: alla psykiska sjukdomar, affektiva sjukdomar (depression eller bipolär sjukdom), alkoholmissbruk samt psykossjukdomar inkluderande schizofreni.

Av de personer som suiciderat hade 23 procent av männen och 31 procent av kvinnorna vårdats inlaggande för en psykisk sjukdom någon gång under det föregående året. Högst suicidrisk förelåg vid depression eller bipolär sjukdom. Vid en sådan diagnos var suicidrisken jämförd med den i befolkningen förhöjd 177 gånger för män och 268 gånger för kvinnor under första veckan efter utskrivning. Totalt för hela det år när sjukhusvård givits för depression eller bipolär sjukdom var suicidrisken förhöjd 55 gånger för män 86 gånger för kvinnor. Vid psykossjukdom och alkoholmissbruk var suicidrisken ungefär hälften så stor och mer konstant under året.

Våra resultat visar hur suicidrisken under och efter inlaggande vård skiljer sig mellan olika diagnoser. En viktig målgrupp för att minska antalet suicid i Sverige är patienter som sjukhusbehandlats för depression.

### **Studie II: Säsongsvariation av suicid i Sverige: Relation till psykisk sjukdom**

I den andra studien studerades säsongsvariationen för 14 030 suicid mellan 1992 och 2003. Psykiatriska diagnoser givna under de fem åren före självmordet delades in i åtta grupper för att studera om olika diagnoser medför olika säsongsvariation. Vi fann att fler självmord sker på vår och försommar. Ökningen av suicidtal på vår och försommar var tydligare bland individer som tidigare vårdats för en psykiatrisk diagnos men ingen tydlig skillnad fanns mellan olika diagnoser.

Att suicidtal under vår och försommar är särskilt förhöjda bland patienter med psykisk sjukdom skulle kunna bero på en säsongsbunden biokemisk obalans bland patienter med psykisk sjukdom. Även en större sårbarhet för psykosociala påfrestningar bland dessa patienter under vår och försommar är tänkbar. Orsakerna behöver dock studeras vidare.

### **Studie III och IV: Riskfaktorer för suicid vid schizofreni**

Delstudierna tre och fyra omfattade patienter diagnostiserade med schizofreni mellan 1984 och 2000 i Stockholms län. De 84 patienter som hade suiciderat inom fem år med denna diagnos jämfördes med 84 patienter som inte suiciderade. Vi fann en trefaldigt förhöjd suicidrisk hos de patienter som hade högre utbildning (mer än grundskola) och en femfaldigt förhöjd risk för de som insjuknat med de första psykiatriska symtomen i en ålder över 30 år och för de som gjort ett suicidförsök som krävt sjukhusvård. Man såg en trend till högre suicidrisk för de som levde eller hade levt med en partner. Faktorer som däremot inte påverkade suicidrisken var patientens kön, tvångsvård, beroendeproblematik eller ärftlighet för suicid. Vid en diagnostisk genomgång av alla patienter framkom att de patienter som även uppfyllde kriterier för depression eller bipolär sjukdom hade en tre gånger förhöjd suicidrisk.

Resultaten tyder på att vissa riskfaktorer för suicid bland patienter med schizofreni skiljer sig från dem man ser i befolkningen och vid flera andra psykiska sjukdomar. Detta är viktigt att känna till vid vården av patienter med schizofreni, liksom att en affektiv diagnos höjer suicidrisken påtagligt.

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