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SUICIDE AND MORTALITY RELATED TO MENTAL DISORDER IN THREE SWEDISH COHORTS

Dag Tidemalm

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# ABSTRACT

## Aims

The subject of this thesis is suicide and other premature death related to mental disorder. The overall aim is to provide knowledge to improve prevention strategies. The specific aims are as follows: *Study I*: To identify predictors of suicide in a cohort with long-term mental disorder. *Study II*: To analyse mortality by mental health service and psychiatric diagnosis in a cohort with long-term mental disorder. *Study III*: To investigate the impact of psychiatric morbidity on suicide risk following a suicide attempt. *Study IV*: To examine familial suicide risks in a total population sample.

## Methods

*Studies I and II*: Adult residents with mental disorder in Stockholm County, Sweden, were identified in 1997. This register (n=12,247) was linked to national registers. Discharges from psychiatric inpatient care during 1990–2000 and deaths during 1997–2000 were identified. Predictors of suicide in the cohort were investigated; standardised mortality ratios were calculated. *Study III*: Data on all people living in Sweden 1973–82 were linked to national registers. People hospitalised during the period 1973–82 due to attempted suicide were identified. The cohort (n=39,685) consisted of those with a studied psychiatric diagnosis present at index attempt (cases) and those without a psychiatric diagnosis within a year after the suicide attempt (reference subjects). Patients were followed for 21–31 years. Survival curves for suicide were plotted and hazard ratios computed. *Study IV*: A population-based cohort (n=7,969,645) was created by linkage of Swedish national registers. Persons with death classified as definite or uncertain suicide 1952–2003 were identified (n=83,951). Odds ratios for suicide in relatives of suicide probands were calculated in relation to relatives of controls.

## Results

*Study I*: Predictors of suicide included previous suicide attempt, a history of psychiatric inpatient care, and unmet need of a contact person. Borderline personality disorder was the strongest diagnostic predictor. *Study II*: Excess mortality was greater among those with a history of psychiatric inpatient care. The number of excess deaths due to natural causes was threefold that due to external causes. *Study III*: High proportions of suicides in all diagnostic groups took place within one year. The strongest predictors of completed suicide throughout the entire follow-up were schizophrenia and bipolar/unipolar disorder, with up to 39% suicide mortality. *Study IV*: The risk increase was threefold in full-siblings and twofold in children. The odds ratio for full-siblings was higher than that for maternal half-siblings. Odds ratios for second- and third-degree relatives were similar. Partners of suicide probands had a higher odds ratio than most biological relatives.

## Conclusions

Treatment programs for persons with long-term mental disorder should target both physical and mental health. Unmet needs may signal increased suicide risk in persons with mental disorder. Psychiatric case management should focus on more intensive aftercare during the first years after a suicide attempt in patients with bipolar and unipolar disorder or schizophrenia. The findings of Study IV are not entirely consistent with variance by degree of genetic correlation; the study could identify impact of both shared environment and shared genes in familial transmission of suicidal behaviour.

*Keywords*: suicide, attempted suicide, mortality, mental disorders, risk factors, family, follow-up studies, cohort studies, case-control studies

## LIST OF PUBLICATIONS

- I. Tidemalm D, Elofsson S, Stefansson CG, Waern M, Runeson B. Predictors of suicide in a community-based cohort of individuals with severe mental disorder. *Soc Psychiatry Psychiatr Epidemiol*. 2005 Aug;40(8):595–600.
- II. Tidemalm D, Waern M, Stefansson CG, Elofsson S, Runeson B. Excess mortality in persons with severe mental disorder in Sweden: a cohort study of 12 103 individuals with and without contact with psychiatric services. *Clin Pract Epidemiol Ment Health*. 2008 Oct 14;4:23.
- III. Tidemalm D, Långström N, Lichtenstein P, Runeson B. Risk of suicide after suicide attempt according to coexisting psychiatric disorder: Swedish cohort study with long term follow-up. *BMJ*. 2008 Nov 18;337:a2205.
- IV. Tidemalm D, Waern M, Carlström E, Runeson B, Långström N. Familial clustering of suicide risk: a total population study of 7,969,645 individuals. Manuscript.

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## LIST OF ABBREVIATIONS

5-HIAA	5-hydroxyindoleacetic acid
ADHD	Attention-deficit/hyperactivity disorder
C-CASA	Columbia Classification Algorithm of Suicide Assessment
CI	Confidence interval
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, fourth edition
HR	Hazard ratio
ICD	International Classification of Diseases
OR	Odds ratio
NIMH	National Institute of Mental Health
PAF	Population attributable fraction
SMR	Standardised mortality ratio
WHO	World Health Organization

# 1 BACKGROUND

## 1.1 INTRODUCTION

The subject of this thesis is premature death related to mental disorder, with a special emphasis on suicide. The first two studies examine death by suicide and other causes in a large cohort of people with long-term mental disorder in Stockholm, Sweden (n=12,247). The third study analyses risks of subsequent suicide according to mental disorder in all Swedes admitted to hospital after a suicide attempt during 1973–1982 (n=49,509). In the fourth study, a Swedish national cohort (n=7,969,645) is used to compare suicide risks in biological and non-biological relatives of persons who had committed suicide (n=83,951). The latter study does not explicitly look into mental disorders but is still included in the thesis, as suicide is often related to mental illness. Both mental disorder and suicidal behaviour aggregate in families. The familial aggregation of suicidality is partly dependent on the aggregation of mental disorder, to what degree is yet unknown (Brent and Mann, 2005).

Why are such studies important and why do we need more knowledge in this field? Improved prevention of premature death in those with mental disorder would of course lead to considerable numbers of saved lives yearly. It would also lead to improved health and quality of life in large numbers of people, including those involved in the social networks around persons with mental illness. Many studies about excess mortality in those with mental disorders and about suicidal behaviour have already been conducted (Allebeck, 1989, Harris and Barraclough, 1997, 1998, Hawton and van Heeringen, 2009, Mann, 2002, Maris, 2002, Ringbäck Weitoft *et al.*, 1998, Saha *et al.*, 2007, Ösby *et al.*, 2001, Ösby *et al.*, 2000a). However, much work remains to be done. A basic purpose of the present thesis and its studies of premature death is to provide relevant knowledge that may improve prevention strategies.

I initially became interested in this subject quite a few years back, working with research and development in the Stockholm mental health services. Somatic causes of death in those with mental disorder seemed like an important but somewhat neglected area. Mental health care and social service staff told me that we should look into the somatic health in these groups, as well as their mental health and social conditions. Later, it became possible to include this question in a Ph.D. project, and to combine it with an investigation of suicide, a cause of death especially associated with mental disorder. Hopefully, the studies included in this thesis will contribute to the ongoing development of strategies to prevent premature death in general and suicide in particular in people with mental illness.

## 1.2 SUICIDAL BEHAVIOUR – A GENERAL OVERVIEW

According to a minimal definition of suicidal behaviour, a suicidal act is self-directed and characterised by at least some intent to die (Mann *et al.*, 2009, Posner *et al.*, 2007). Suicide and suicide attempts are leading causes of death and morbidity worldwide. However, the reported suicide rates from different countries vary widely, from less than 1 to more than 40 per 100,000 persons per year. In the year 2000, the global suicide rate

was 16/100,000 persons, corresponding to one million suicide deaths, or one suicide every 40 seconds. Rates for attempted suicide are uncertain due to lack of national statistics, but may be up to 20 times higher than those for suicide (Bertolote and Fleischmann, 2005, World Health Organization, 2009).

Suicidal behaviour is often related to mental disorder, like severe affective disorder, schizophrenia, substance use disorder or borderline personality disorder; however, the majority of psychiatric patients never attempt suicide. Therefore, other risk factors must often be involved in the suicidal process. These risk factors are of various types, including a history of self-injurious behaviour, social isolation, marital problems, work problems, poor physical health, alcohol or substance intake, physical or sexual abuse during childhood, feelings of hopelessness, and aggressive-impulsive traits. Different risk factors seem to interact with each other (Hawton and van Heeringen, 2009, Mann, 2002, Maris, 2002, Waern *et al.*, 2002). Thus, causation of suicidal behaviour is multifactorial with complex interaction of factors; the mechanisms of interaction are largely unknown. Due to this limited knowledge of causality and to the low base-rate of suicidal behaviour, sensitive and specific risk assessment is a challenging task (Mann, 2002, Maris, 2002).

One possible way to develop knowledge on the causation of suicidal behaviour is through studies of familial clustering of suicidal acts. Several studies have shown that suicidal behaviour runs in families and to some extent independently from the familial aggregation of psychiatric disorder (Agerbo *et al.*, 2002, Brent and Mann, 2005, Brezo *et al.*, 2009, Qin *et al.*, 2002, 2003, Runeson and Åsberg, 2003). Besides mental disorders, impulsive and impulsive-aggressive behaviours in families could contribute to the familial transmission of suicidal behaviour (Brent and Mann, 2006, McGirr and Turecki, 2007, Turecki, 2001). Family, adoption, twin, molecular genetic, geographic, and migrant studies have shown that familial clustering of suicidal behaviour has both genetic and environmental causes (Baldessarini and Hennen, 2004, Brent and Mann, 2005, Turecki, 2001, Wasserman *et al.*, 2007, Voracek and Loibl, 2007, 2008).

Preventive measures against suicidal behaviour may be directed at populations and societies to reduce numbers of new cases (primary prevention), or at individuals with varying degree of identified suicidality (secondary and tertiary prevention) (Maris, 2002). Suicide rates have decreased in a number of countries, including Sweden, during the last decades (Levi *et al.*, 2003, Nordentoft, 2007). It is not known to what extent this is due to specific suicide preventive efforts on the one hand, and factors like improved socioeconomic conditions or changes in classification and reporting on the other.

### **1.3 EXCESS MORTALITY IN PERSONS WITH MENTAL DISORDER**

An increased risk of premature death from natural or unnatural causes seems to be present in all common mental disorders (Harris and Barraclough, 1998). Causes of the excess mortality in these groups include self-destructive behaviour (Harris and Barraclough, 1998), poorer quality of medical care (Druss *et al.*, 2001, Høyer *et al.*, 2000, Lawrence *et al.*, 2003, Mortensen and Juel, 1993, Ringbäck Weitoft *et al.*, 1998),

low ability or inclination to seek help for medical problems (Goldman, 1999, Jeste *et al.*, 1996, Phelan *et al.*, 2001), side effects of neuroleptics (Allison and Casey, 2001, Henderson *et al.*, 2000, Joukamaa *et al.*, 2006, Koro *et al.*, 2002a, Koro *et al.*, 2002b), heavy smoking (Brown *et al.*, 2000), substance misuse (Harris and Barraclough, 1998), unhealthy lifestyle (Brown *et al.*, 1999, McCreadie, 2003), violence from others (Hiroeh *et al.*, 2001), and, possibly, effects of the mental disorder itself (Empana *et al.*, 2006, Katon, 2003). For people with psychotic disorder, cognitive impairment may be one major obstacle to seeking medical care (Phelan *et al.*, 2001).

Generally, the relative risks of premature death in persons with severe mental disorder compared to population controls are highest for suicide. Nevertheless, excess deaths from natural causes take more lives in people with mental illness, since these causes are more prevalent (D'Avanzo *et al.*, 2003, Harris and Barraclough, 1998, Joukamaa *et al.*, 2001). Some of this excess natural cause mortality definitely seems to be preventable by improved access to medical treatment. For instance, persons with mental disorders are comparatively less likely to undergo coronary revascularization procedures after myocardial infarction (Druss *et al.*, 2000, Lawrence *et al.*, 2003, Young and Foster, 2000). Results from two recent studies suggest that this health care disparity may be reduced by organizational means (Jones and Carney, 2005, Petersen *et al.*, 2003).

Patterns of mortality differ between men and women and among different psychiatric diagnostic groups (Harris and Barraclough, 1998, Hiroeh *et al.*, 2001, Ringbäck Weitoft *et al.*, 1998). Further, patterns of death causes may vary over time, since some causes of premature death among those with mental disorder are related to medical treatment and the social environment (Brown, 1997, Harris and Barraclough, 1998). Mortality patterns in those with mental disorder generally reflect living conditions relevant to health and quality of life. Increased mortality in these groups may also reflect the quality or availability of health services. Continuous study of mortality in those with mental disorder is therefore important.

Proposed preventive strategies against somatic causes of premature death generally include improved monitoring of physical health, health education, and better access to health services. In order to be effective, preventive initiatives should include various treatment settings: out- and inpatient psychiatry, community mental health care, and primary care (Kisely *et al.*, 2005, Phelan *et al.*, 2001). Social support by both professionals and persons in the private network may be very important in this context. Both can influence lifestyle factors and facilitate access to primary health care.

As mentioned in section 1.2 above, suicide rates have decreased in Sweden and in several other countries. This is probably at least in part due to preventive efforts, like improved detection and treatment of depressive disorders (including education of primary care physicians) (Isacsson *et al.*, 2009, Mann *et al.*, 2005, Rutz *et al.*, 1992), and restricting access to lethal means (Mann *et al.*, 2005, Rådbo *et al.*, 2005). Several countries, including Sweden (National Council for Suicide Prevention, 1996), have national programmes for suicide prevention. However, it could not be said that the problem is adequately addressed worldwide (World Health Organization, 2009). Also, several types of interventions often included in preventive programmes are not yet sufficiently evidence-based (Mann *et al.*, 2005).

Results from Scandinavian register studies show mixed trends across Sweden and Denmark regarding relative risks of suicide and other causes of death in people with severe mental illness, compared to the general population. One widely cited Danish study (Mortensen and Juel, 1993) found increasing relative suicide risk in patients with schizophrenia from the 1970s to the 1980s. These results were, however, not statistically significant. Two other Danish studies reported decreasing suicide rates 1981–1997 in psychiatric patients (schizophrenia, affective disorder, substance use disorder, other mental disorder), similar to the decrease in the general population (Nordentoft *et al.*, 2004, Qin *et al.*, 2006). One Swedish study found increasing relative mortality due to both suicide and somatic causes among schizophrenia patients (Ösby *et al.*, 2000b). The relative mortality in those with severe mental disorders are still at high levels in both mentioned Scandinavian countries, and in Finland as well (Mortensen and Juel, 1993, Nordentoft *et al.*, 2004, Qin *et al.*, 2006, Salokangas *et al.*, 2002, Ösby *et al.*, 2001, Ösby *et al.*, 2000a, b).

Apart from suicide prevention, can we see signs of progress in the prevention of premature death in those with mental disorder? In an editorial about a decade ago, it was remarked that poor physical health in those with mental illness had been documented by research over a period of more than 60 years. Nevertheless, the authors at that point claimed that no evidence for better medical screening and treatment of those with mental disorder could be seen (Phelan *et al.*, 2001). This still seems to be the case; to this author's knowledge, no results in the literature indicate a general improvement of the situation.

Considering the wealth of published original studies, reviews, and editorials that has quantified the problem and discussed possible solutions, this lack of progress is possibly not only due to lack of knowledge. Another reason may well be that not many large-scale prevention programs have been implemented. To take Sweden as an example, the country's mental health care system has gone through several major reorganisations from the 1960s and onwards. A number of studies have also been published about excess mortality in Swedish and other Scandinavian psychiatric patients over the years (Allebeck, 1989, Allebeck and Wistedt, 1986, Alström, 1942, Hannerz and Borgå, 2000, Hannerz *et al.*, 2001, Lindelius and Kay, 1973, Ringbäck Weitoft *et al.*, 1998, Saugstad and Ødegård, 1979, Ødegård, 1952, Ösby *et al.*, 2001, Ösby *et al.*, 2000a, b). Therefore, one might expect that large-scale preventive programs would have been implemented in the reorganisation processes. This is however not the case. Reducing premature death in mentally ill people has, to date, not been an explicit chief aim in any Swedish reorganisation of mental health care, for instance the Swedish Community Mental Health Care Reform in the mid-1990s (Stefansson and Hansson, 2001).

Interventions to decrease premature somatic death in people with psychoses are discussed extensively in the latest regional medical care program for psychoses in Stockholm County, Sweden (Stockholm County Council, 2008). Since the county is inhabited by 2 million people (21% of the Swedish population), this may be one of few exceptions to the general lack of large-scale intervention. Another example is the latest set of clinical guidelines for schizophrenia from the Swedish Psychiatric Association, where the high risk of metabolic syndrome and cardiovascular death in those with

psychotic disorder is emphasised (Swedish Psychiatric Association, 2009). It remains to be seen, however, to what extent these two sets of guidelines will be implemented.

Two main conclusions can be drawn from the data presented above:

- More knowledge relevant to preventing suicide and other types of premature death in people with mental illness is still needed.
- The knowledge already accumulated about the subject should be implemented to a higher degree.

## **1.4 THE OCCURRENCE, UNDERSTANDING, AND STUDY OF SUICIDAL BEHAVIOUR**

### **1.4.1 Definitions**

Consistent and widely accepted methods for defining and measuring various types of self-injurious behaviour are needed in research, health policies, and clinical practice. For researchers, attempts to compare studies with differing definitions of core concepts present many difficulties. For health care staff, risk assessment in individuals and documentation of outcomes for patient groups partly depend on precise definitions and coherent nomenclature. Health policy-making relies on results from research studies as well as documented experience from clinical practice. Thus, suicide prevention efforts depend, directly and indirectly, on common models providing uniform definitions of suicidal and other self-injurious acts. It is clear, however, that such universally accepted models have been lacking. This absence of conceptual clarity and consequent obstacles for evaluating results has long been considered a major problem in suicidal behaviour research (Baldessarini and Hennen, 2004, Beck *et al.*, 1975, Beck *et al.*, 1976, De Leo *et al.*, 2006, Kidd, 2003, Mann *et al.*, 2009, Maris, 2002, McIntosh, 1985, O'Carroll *et al.*, 1996, Posner *et al.*, 2007, Silverman *et al.*, 2007a, b). Preferably, an empirically grounded classification of completed suicide and other types of self-injurious behaviour would be consistent with a classification of relevant phenotypes; the latter is essential for the study of gene-environment interaction related to suicidal behaviour (Baldessarini and Hennen, 2004, Baud, 2005, Brent and Mann, 2005, Brent and Melhem, 2008, Brezo *et al.*, 2009, Mann *et al.*, 2009, McGirr *et al.*, 2009, Rujescu *et al.*, 2007, Turecki, 2001).

In research and prevention, it is important to distinguish various types of non-fatal self-injurious behaviour, especially to separate actual attempts to commit suicide (with varying degree of intent) from other kinds of self-injurious acts (Beck *et al.*, 1975, Kreitman *et al.*, 1969, Wichstrøm, 2009). One of many early attempts to address this problem was the introduction of the term “parasuicide” (Kreitman *et al.*, 1969), a term which mainly has been used in Europe. Its meaning has shifted considerably over the years, from “an event in which the patient simulates or mimics suicide” (Kreitman *et al.*, 1969) to “any acute, intentional self-injurious behaviour that creates the risk of death” (Maris, 2002), and it is today perhaps outdated. Another commonly used category is “deliberate self-harm”, defined as intentional self-poisoning or self-injury irrespective of suicidal intent (Hawton *et al.*, 2003). Some researchers claim that non-suicidal and suicidal self-harm are distinct but overlapping phenomena, not merely

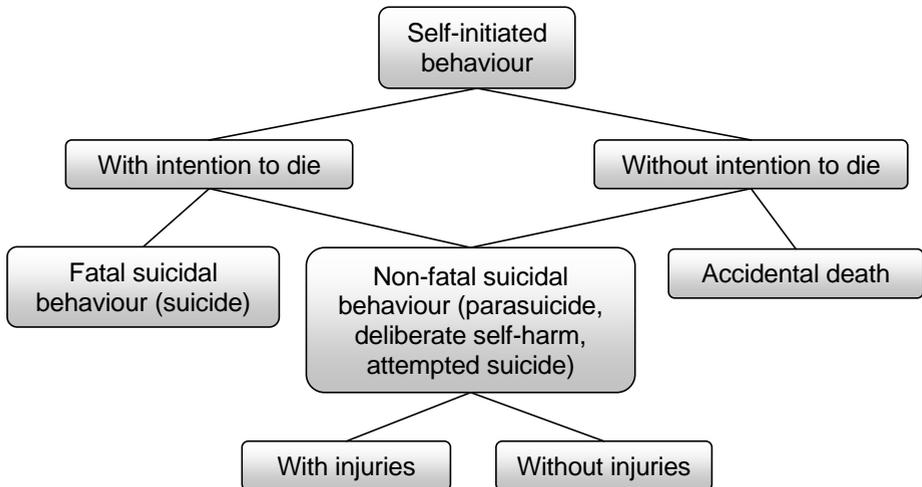
representing different levels of suicidality, and with different aetiologies (Nock *et al.*, 2006, Wichstrøm, 2009).

In the 1970s, the American National Institute of Mental Health (NIMH) proposed a system with three categories under the main category suicidal behaviours: completed suicide, attempted suicide, and suicidal ideation (Stengel and Cook, 1958). This system also includes two dimensions: intent to die, and medical lethality. Scales were developed to measure these dimensions. It was demonstrated that when taking into account the person's understanding of the planned act's lethality, suicidal intent and lethality were positively correlated (Beck *et al.*, 1975). Another suggested system uses the main category suicide-related thoughts and behaviours along with the subcategories suicidal ideation, instrumental (nonsuicidal) behaviour and suicidal acts (suicide attempt and completed suicide) (O'Carroll *et al.*, 1996). Both the mentioned systems include further subcategorisations. It seems, however, that neither of these two systems, nor any other (e.g., (Ellis, 1988, Kreitman, 1977, Maris *et al.*, 1992)), has fulfilled the need of conceptual clarity, since studies during the 2000s still mention this as an unresolved problem (Baldessarini and Hennen, 2004, De Leo *et al.*, 2006, Kidd, 2003, Mann *et al.*, 2009, Maris, 2002, Posner *et al.*, 2007).

One first step towards a widely accepted and empirically grounded classification of self-injurious behaviour may be a widely accepted nomenclature. A nomenclature can be seen as a basic set of names or labels necessary for communication between professionals in a particular field. Such a basic set of names is usually not sufficient to form, e.g., a clinically useful classification, which would need higher degree of scientific validity, detail, and exhaustiveness (O'Carroll *et al.*, 1996). Three recent efforts to provide adequate nomenclatures for self-injurious behaviour will be described briefly here.

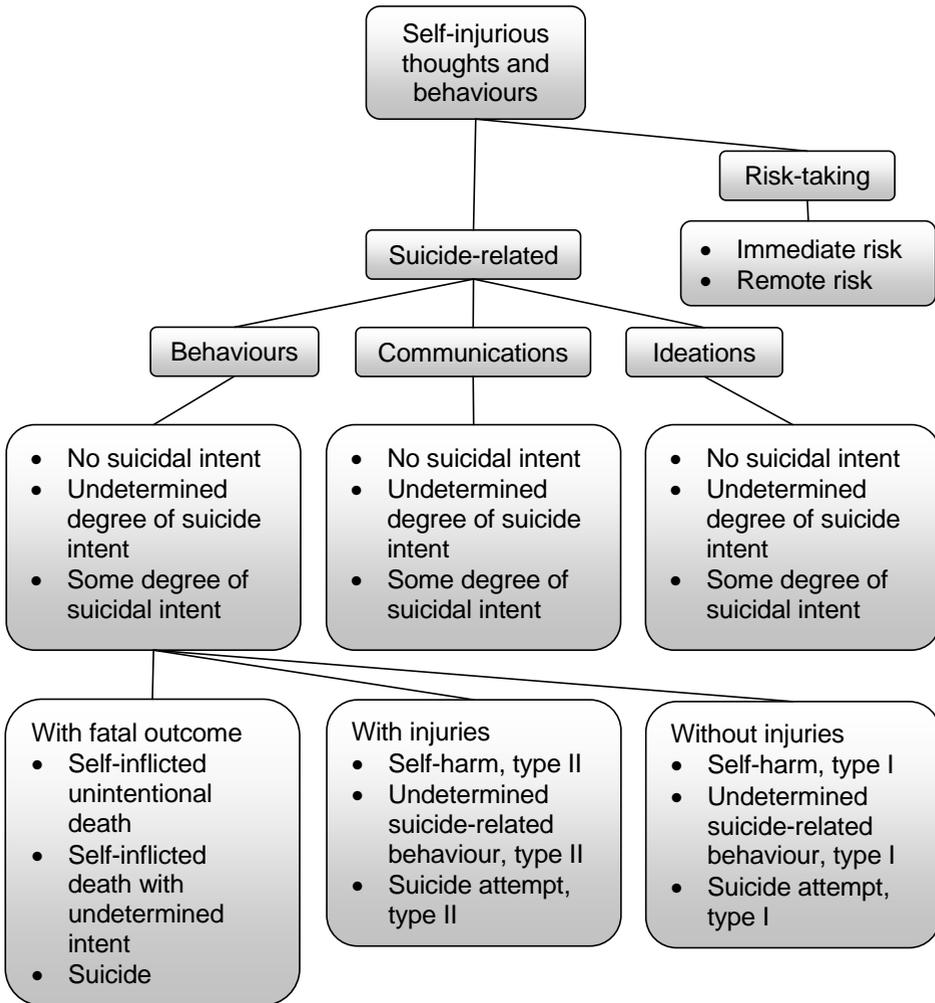
(1) One system is based on experience from WHO/EURO Multicentre Study on Suicidal Behavior; its main elements are outlined in figure 1. The main category is self-initiated behaviour of kinds which may lead to injury or death (De Leo *et al.*, 2006).

Figure 1. Nomenclature of fatal and nonfatal self-initiated behaviour (De Leo *et al.*, 2006).



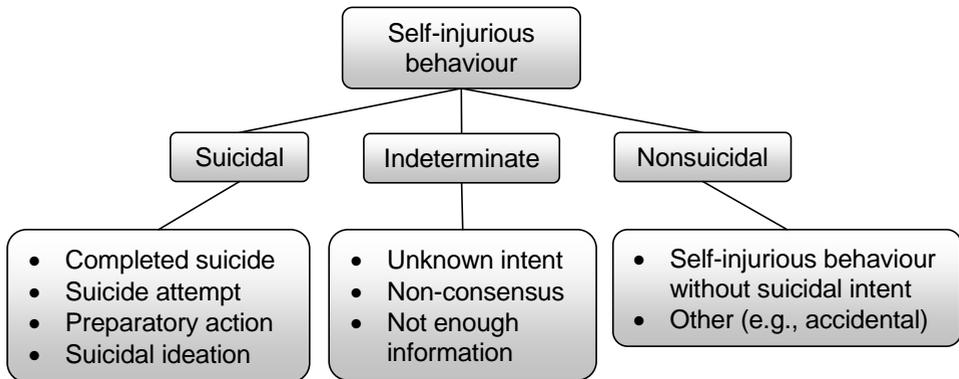
(2) Main categories of a second nomenclature are shown in figure 2. This nomenclature is a revision of a previous model, which has been widely discussed but not extensively used in research or clinical practice (O'Carroll *et al.*, 1996, Silverman *et al.*, 2007a, b). In the categories for behaviours in this nomenclature, types I and II refers to behaviour without and with injury, respectively.

Figure 2. Nomenclature of self-injurious thoughts and behaviours (Silverman *et al.*, 2007b).



(3) The nomenclature in the Columbia Classification Algorithm of Suicide Assessment (C-CASA) (Posner *et al.*, 2007) includes three types of self-injurious behaviour: suicidal, indeterminate, and nonsuicidal (figure 3).

Figure 3. Nomenclature of self-injurious behaviour (Posner *et al.*, 2007).



This model has three advantages: (1) It is uncomplicated, which should increase the probability of widespread use. (2) It places suicidal and nonsuicidal acts in two distinct subcategories, under the main category “self-injurious behaviour”. (3) It includes different types of indeterminate cases. This latter category has a number of important research applications, allowing for more detailed analyses of suicide rate trends, and analysis of the impact of misclassification (Chishti *et al.*, 2003, Hawton and van Heeringen, 2009).

The definitions of completed suicide and suicide attempt used for the studies in the present thesis are all of the same kind: they include definite and indeterminate cases, as registered in the Swedish Hospital Discharge Register (e.g., ICD10 codes X60–X84 and Y10–Y34). The indeterminate cases were included to avoid underestimation of suicide numbers (Neeleman and Wessely, 1997). The register data thus obtained do not contain detailed information about the suicidal acts. Also, the (necessary) inclusion of indeterminate cases could affect the analyses in unknown ways. On the other hand, neither register data nor standard definitions based on variables in national registers are biased by influence from the researchers.

#### 1.4.2 Occurrence

Suicide represents 2% of the global burden of disease and the trend is increasing (Bertolote and Fleischmann, 2005). The highest suicide rates are found in Eastern Europe (Finland, the Baltic states, Belarus, Ukraine, Hungary, Slovenia, and Russia), Kazakhstan, Sri Lanka, China, South Korea, Japan, and Guyana, with total rates of 20–40 in 100,000 persons per year. Suicide rates have increased by 60% worldwide in the last five decades, and suicide numbers are expected to continue to increase in the

coming years, yielding approximately 1.5 million deaths (and possibly 15–30 million suicide attempts) in the year 2020 (Bertolote and Fleischmann, 2005, Phillips *et al.*, 2002, World Health Organization, 2009). Suicide rates have increased in some countries but decreased in others during the last decades (Levi *et al.*, 2003, Nordentoft, 2007). Thus, while the global trend is increasing for completed suicide, trends are mixed across countries. Prevalences of attempted suicide are difficult to estimate, as national registers for self-injurious behaviour are lacking. One recent interview study, however, estimated the lifetime prevalence of suicidal behaviours in 80,000 individuals across 17 countries on different continents (Nock *et al.*, 2008). The cross-national lifetime prevalence for suicide attempt was approximately 3%.

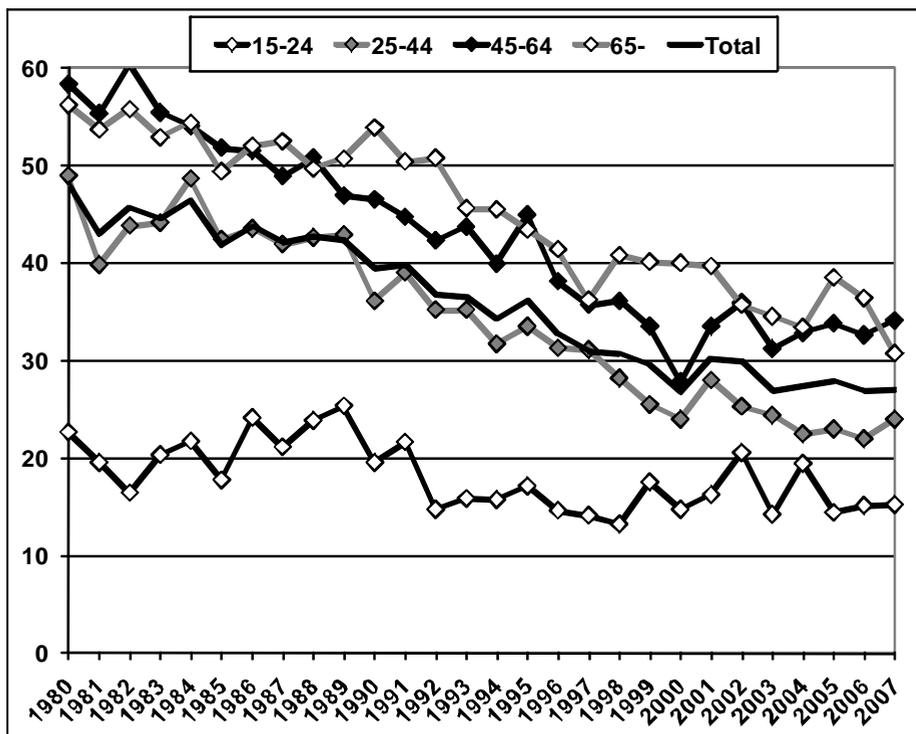
There are several potential sources of error when comparing suicide rates from different countries. Due to many reasons (e.g., social taboo or lack of resources), suicides are not always reported, and suicide registers are not always maintained properly – or even kept. Also, practices of death registration vary widely between countries. For instance, certification of suicide is made by the police in some countries, by physicians in others, and by coroners in yet others. Furthermore, what is regarded as evidence for suicide (e.g., presence of a suicide note) varies between countries (Hawton and van Heeringen, 2009, World Health Organization, 2009). Finally, misclassification of suicide (ICD10 codes X60–X84) as undetermined death (ICD10 codes Y10–Y34) may be more or less frequent in different countries (Chishti *et al.*, 2003). Consequently, although comparisons between countries and estimations of global suicide numbers are meaningful, they should not at this point be considered to be very detailed or precise. Standardisation of classification and reporting as well as improved suicide registers are needed to enable more accurate estimations in the future.

In most countries, suicide is more common in men. The global suicide rate is almost four times higher for men than for women (Bertolote and Fleischmann, 2005). China, with its large population, is a notable exception, reporting a 25% higher rate in women because of large suicide numbers in young rural women (Phillips *et al.*, 2002). In most countries, the elderly have the highest suicide rates. In later decades rates in young people have increased, particularly in men, and rates in the elderly have decreased (Hawton and van Heeringen, 2009). Suicide is a leading cause of death among young men and women (Hawton and van Heeringen, 2009, Wasserman *et al.*, 2005, World Health Organization, 2009).

Undetermined deaths are often labelled “uncertain suicide” or “unverified suicide” and included in the suicide category, to avoid underestimation of suicide numbers (Neeleman and Wessely, 1997). The presentation of Swedish suicide data below follows this principle.

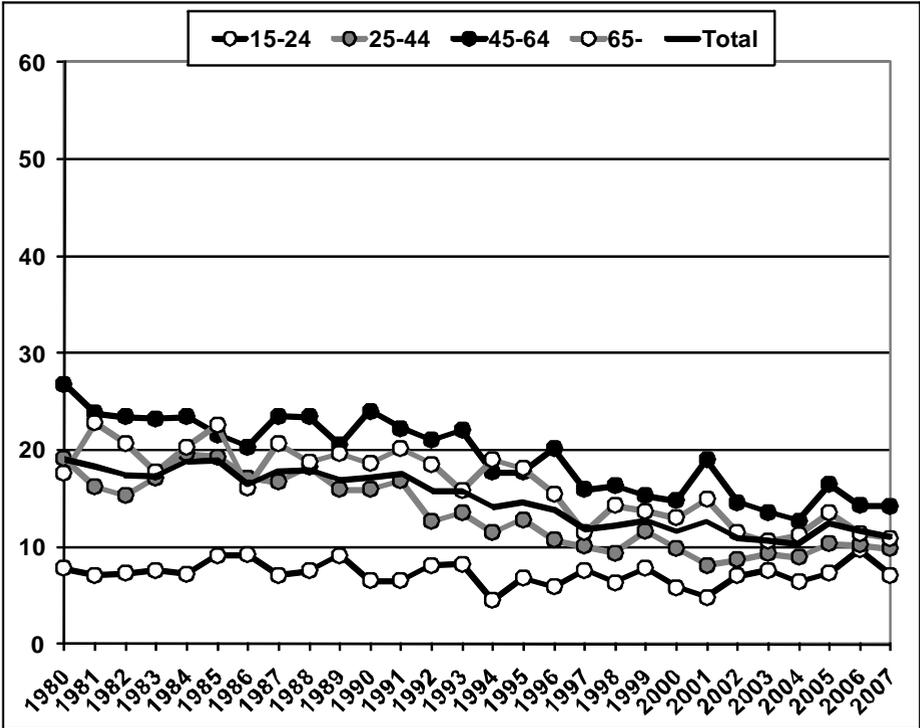
In Sweden, the total suicide rate including undetermined deaths decreased 1980–2007, from 33 to 19 per 100,000 persons per year (ages 15 and above). The decrease has been less pronounced in the 2000s (Karolinska Institutet School of Public Health, 2009). Details of this trend by age are shown in men (figure 4) and women (figure 5).

Figure 4. Suicide rates<sup>a</sup> including undetermined death in men according to age in Sweden 1980–2007.



<sup>a</sup>Deaths in 100,000 person-years, ages 15 and above (Karolinska Institutet School of Public Health, 2009).

Figure 5. Suicide rates<sup>a</sup> including undetermined death in women according to age in Sweden 1980–2007.



<sup>a</sup>Deaths in 100,000 person-years, ages 15 and above (Karolinska Institutet School of Public Health, 2009).

In 2007, approximately 1,400 persons died by suicide (1,100) and undermined death (300) in Sweden, 1,000 men and 400 women (Karolinska Institutet School of Public Health, 2009). A brief overview of suicide statistics for Sweden 2007, including undetermined deaths, is shown in table 1.

Table 1. Rates and numbers<sup>a</sup> for suicide and undetermined death in Sweden 2007.

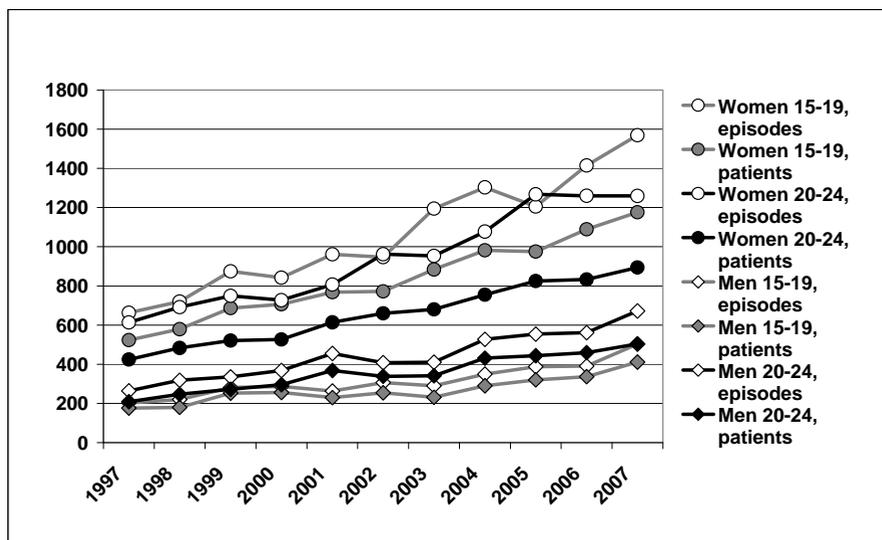
		Suicide	Undetermined death	Total
Men	Number	796 (78%)	223 (22%)	1,019 (100%)
	Rate	21	6	27
Women	Number	323 (76%)	101 (24%)	424 (100%)
	Rate	8	3	11
Both sexes	Number	1,119 (78%)	324 (22%)	1,443 (100%)
	Rate	15	4	19

<sup>a</sup>Deaths per 100,000 person-years and total number of deaths, ages 15 and above (Karolinska Institutet School of Public Health, 2009).

Figures 4 and 5 show that the decreasing trend observed for other age groups in Sweden during the last 15 years is not reflected in the youngest age groups (15–24 years). Furthermore, rates of self-injurious behaviour in young people increased substantially during the same period, especially in women. The rates of hospitalisation after self-injurious behaviour (suicide attempt, undetermined intent, and other self-injurious behaviour) in young women (16–24 years) increased from approximately 210 to 370 per 100,000 between 1993 and 2007 (National Board of Health and Welfare, 2009).

Figure 6 shows the trends 1997–2007 in young people 15–24 years according to sex and five year age classes. Numbers of inpatient episodes as well as numbers of individual patients due to self-injurious behaviour increased in both sexes and all ages. The increase was especially pronounced in women aged 15–19 years, from approximately 500 patients and 600 episodes to 1,200 patients and 1,600 episodes. The patterns were similar when considering sizes of birth cohorts during the period (Beckman *et al.*, 2010). There is general concern that mental ill-health (e.g., depression, anxiety, and alcohol misuse) is common in Swedish youth, particularly in young women, and that the prevalence is increasing in both sexes (National Board of Health and Welfare, 2009, National Prevention of Suicide and Mental Ill-Health, 2007, Swedish Government, 2006).

Figure 6. Self-injurious behaviour<sup>a</sup> leading to hospitalisation in Swedish youth. Numbers of patients and inpatients episodes 1997–2007 (Beckman *et al.*, 2010).



<sup>a</sup>Suicide attempts (ICD10: X60–84) and self-harm of undetermined intent (ICD10: Y10–34) as registered in the Swedish Hospital Discharge Register.

To summarise some important trends in the last decades:

- Globally, suicide rates are increasing but trends are mixed; rates have decreased in a number of countries.
- Suicide rates have decreased by 40% in Sweden in the last 30 years, but the decrease has been less pronounced during the last decade.
- In Swedish youth, suicide rates have not decreased and rates of self-injurious behaviour have increased during the last 15 years.

Absolute numbers of suicide deaths are still high in Sweden and strategies to prevent self-injurious behaviour in young people need further development. The increased rates in later years could signal higher suicide rates in the future, since a previous suicide attempt is a strong predictor of completed suicide (Hawton and van Heeringen, 2009, Mann, 2002).

Study III in the present thesis analysed short- and long-term suicide risks after attempted suicide. Apart from obvious benefits of knowing more about groups with high suicide risk, such studies may aid intervention directed at people who have attempted suicide. Preventive methods for the time period following a self-injurious act are probably crucial for preventing negative trends in self-injurious behaviour from turning into negative trends in completed suicide.

### **1.4.3 Models of suicidal behaviour**

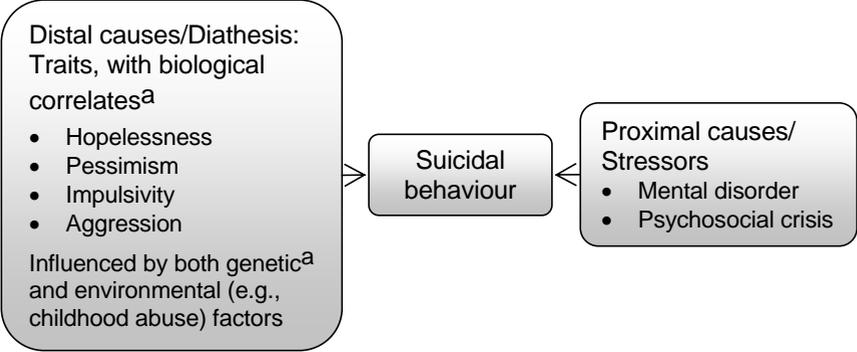
#### *1.4.3.1 Three perspectives on suicidal behaviour*

Beyond nomenclature models, there are several different models attempting to describe and explain how suicidal behaviour actually comes about. Three perspectives are commonly found in such models. They view suicidal behaviour from different angles: (1) causality, (2) risk and protective factors, and (3) the individual suicidal process. These three partly overlapping perspectives will be described below, with examples from existing models.

#### *1.4.3.2 Causality*

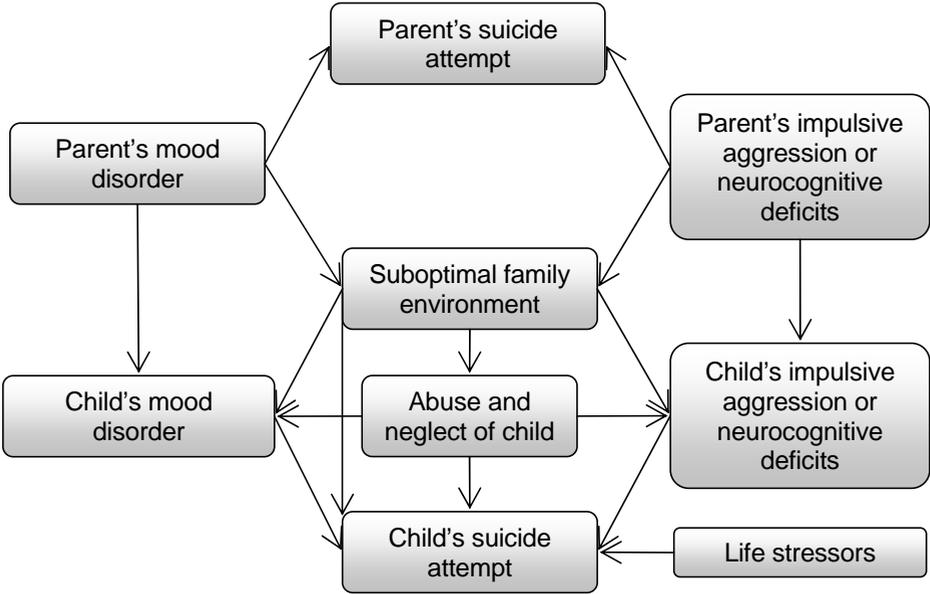
Distal and proximate factors causing suicidal behaviour can be described with a stress-diathesis model. One such model (Mann, 2003) is briefly described in figure 7 below; it focuses on diathesis and stressors from the individual's perspective. Figure 8 includes the same stress-diathesis perspective in a model illustrating familial processes leading to suicidal behaviour in adolescents (Brent and Mann, 2006). To develop such causal models further, we need more knowledge of gene-environment interaction leading to suicidal behaviour. One possible way to generate such knowledge is through study of genes related to intermediate phenotypes, like trait aggression/impulsivity or neurocognitive functioning (Brent and Mann, 2006, Mann *et al.*, 2009).

Figure 7. A stress-diathesis model of suicidal behaviour (Brent and Mann, 2006, Hawton and van Heeringen, 2009, Mann, 2003).



<sup>a</sup>Hypothetically speaking, for instance noradrenaline- and serotonin-related.

Figure 8. Familial pathways to early-onset suicidal behaviour (Brent and Mann, 2006).



### 1.4.3.3 Risk and protective factors

The second perspective is included in a model (Maris, 2002) with two dimensions: (1) factors leading to or protecting from suicidal behaviour with corresponding prevention (primary, secondary, tertiary), and (2) main individual and societal areas of relevance. A simplified version of the model is presented in figure 9. The complete model also includes other categories, interaction and feedback patterns, and a timeline with an individual's suicidal career, from birth to suicide or other death.

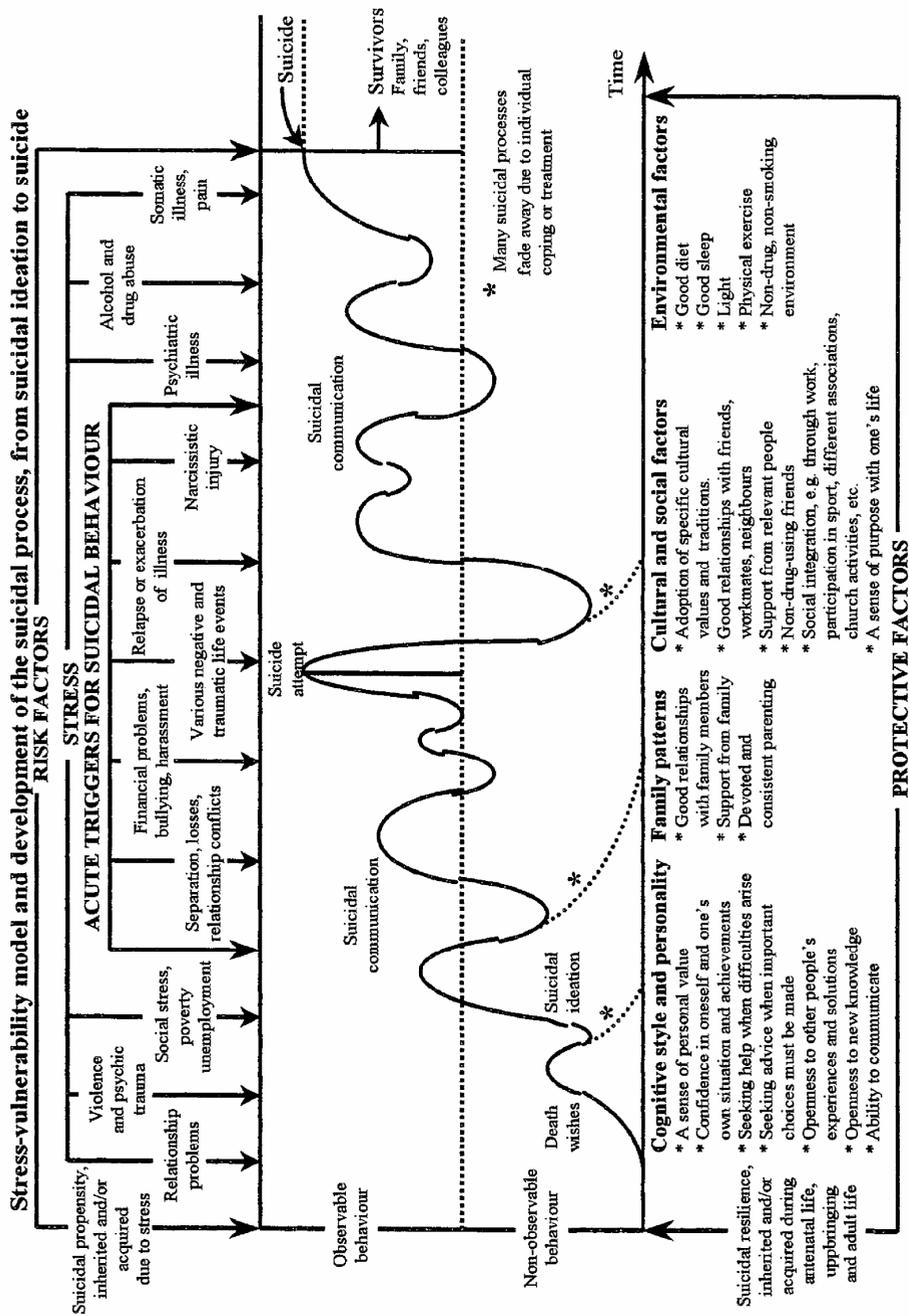
Figure 9. Factors that may lead to or protect from suicidal behaviour (Maris, 2002).

	<b>Predisposing factors (Primary prevention)</b>	<b>Predictors/ risk factors/ vulnerabilities (Secondary prevention)</b>	<b>Protective factors</b>	<b>Trigger factors (Tertiary prevention)</b>
<b>Psychiatric diagnosis</b>	History of mental illness	Diagnosed severe mental disorder	Treatment	E.g., depressive or schizophrenic episode
<b>Family history/ genetics/biology</b>	Family history of suicide	Substance misuse	Improved physical health	Low 5-HIAA, alcohol excess, physical illness, pain
<b>Personality/ psychology</b>	Adverse childhood experiences	Impulsivity, anger, suicidal ideas	Hopefulness, cognitive flexibility, coping skills	Hopelessness, death as escape, revenge
<b>Sociology/ culture</b>	Adverse economic or social circumstances	Social isolation, marital or work problems	Social support, intact marriage, children	Stress, object loss, retirement

### 1.4.3.4 The suicidal process in the individual

The third perspective is exemplified by a model (Beskow, 1979, Wasserman, 2001) including risk and protective factors and the stress-diathesis perspective, but also a detailed description of the suicidal process in the individual (figure 10). The suicidal process is illustrated on a timeline, with non-observable suicidal ideation and observable suicidal communication or behaviour. The conceived end-point of the process is either fading away of the suicidal process (due to treatment or coping) or completed suicide.

Figure 10. A stress-diathesis model, including the development of the suicidal process in the individual (Wasserman, 2001).



One study of youth suicides in Sweden revealed two distinct types of individual suicidal process: (1) A long process, with mental disorder, complicated relationships, substance misuse, and several instances of suicidal behaviour before the completed act, which often was under the influence of drugs. (2) A short process, with less of obvious suicidal intention, “a death without warning”. A shorter suicidal process with less of previous communication was more frequent in those with adjustment disorder or major depression, compared to schizophrenia and borderline personality disorder (Runeson *et al.*, 1996).

All four epidemiological studies included in the present thesis treat risk factors for premature death, especially suicide. In Study I and II severe mental disorder is viewed as one potential stressor or proximate cause of suicide. Study III and IV may contribute to our understanding of the suicidal process in individuals and of stress-diathesis processes leading to suicidal behaviour, respectively.

#### **1.4.4 Research in suicidology**

##### *1.4.4.1 Different research approaches, suicide prevention*

A selection of approaches to suicide research will be discussed in this section. Overviews of research methods in suicidology with their respective limitations and strengths have been presented elsewhere (Bertolote and Fleischmann, 2005, Goldney, 2002, Leenaars, 2002, Leenaars *et al.*, 1997, Malafosse, 2005, Waern, 2000). Usually, the implicit or explicit aim for suicide research is improved suicide prevention. The relationship between research and suicide prevention is interesting, since suicide and attempted suicide are rare events. This implies a need to study large samples to find variables associated with suicidal behaviour. However, large studies (e.g., national register studies, see below) often do not provide in depth information about each case. Thus, results from larger studies are frequently not nuanced enough to be directly applicable to preventive efforts. On the other hand, smaller studies with, e.g., in depth interviews of relatives of suicide victims or survivors of attempted suicide may be statistically underpowered. For these and other reasons, there is a need to take results from different suicide research approaches into account, when translating research into suicide prevention (Goldney, 2002, Leenaars, 2002).

##### *1.4.4.2 Register studies*

Studies I–III in the present thesis are cohort studies, and risks of suicide or other causes of death were investigated in groups of people during specific time periods. Study IV is a case-control study, and risks of suicide in relatives of people who had committed suicide were examined. All four studies were conducted using databases created by linkage of Swedish national registers. Many of the national registers in Sweden have been maintained for several decades and they are generally linkable through the Swedish personal identification number. This number is an identifier assigned to individuals at birth or immigration. Such registers are generally not found outside Scandinavia. In terms of statistical power, they offer unique possibilities for epidemiological and public health research (Kamper-Jørgensen *et al.*, 2005). Another

strength of data obtained from national registers is that they usually lack bias introduced by the study's researchers or informants.

Register studies of suicidal behaviour also have limitations: (1) It is often not practically possible to validate or access more detailed information on study variables. (2) The statistical issues are not uncomplicated. Studies of large samples, like the register studies in this thesis, generally have more statistical power than studies of smaller samples. However, since suicide is a rare event, comparing outcomes in subgroups or measuring effects of interventions may be difficult even in very large samples (Gunnell and Frankel, 1994, Leenaars *et al.*, 1997). (3) What actually constitutes a result statistically stable enough for conclusions is far from uncontroversial (Goodman, 2001, Poole, 2001, Weinberg, 2001). (4) Use of national register data may facilitate long-term follow-up. However, diagnostic systems and other important factors change over time, sometimes making comparisons difficult.

#### *1.4.4.3 Family studies*

Study IV in this thesis is an example of a family study of suicidal behaviour. Such studies typically compare rates of suicidal behaviour in relatives of people with and without suicidality. While family studies have varied widely in size, outcome, choice of proband or comparison group, and method of case assessment, they have generally provided strong evidence for familial aggregation of suicidal behaviour (Agerbo *et al.*, 2002, Baldessarini and Hennen, 2004, Brent *et al.*, 1996, Brent and Mann, 2005, Egeland and Sussex, 1985, Qin *et al.*, 2003, Runeson and Åsberg, 2003). Genetically close relatives (e.g., parents and biological children) more often live together than more distant relatives (e.g., cousins). Consequently, family studies cannot disentangle relative impact of genes and environment. Thus, family studies of suicidal behaviour need be complemented by, e.g., genetic studies (Brezo *et al.*, 2009, Caspi *et al.*, 2003, Jokinen *et al.*, 2009).

A not unavoidable but common limitation of register-based family studies of suicidal behaviour stems from the choice of controls. When matched general population controls are used in comparison to suicide victims (e.g., (Qin *et al.*, 2003)), the effects of other deaths in relatives (e.g., accidents) are not taken into account. Thus, using controls who died of other causes than suicide can be an advantage (Brent and Mann, 2005, Runeson and Åsberg, 2003).

#### *1.4.4.4 Psychological autopsies*

The psychological autopsy method is based on interviews with survivors of the suicide victim who could provide relevant information, for instance relatives, friends, employers, colleagues, or health care staff. The aim is detailed study of the suicidal process in the deceased individual (Beskow *et al.*, 1990, Litman *et al.*, 1963). This method has been used in studies of Swedish men (Beskow, 1979), women (Åsgård, 1990), youth (Runeson, 1990), and elderly (Waern, 2000). Detailed and nuanced information of each studied suicide is a major advantage of the psychological autopsy. One limitation is the danger of systematic bias introduced by interviewers or informants.

#### 1.4.4.5 Quality registers

The Swedish national quality registers for different health problems constitute a promising resource for future research in suicidology. Approximately 70 registers have been established in the Swedish health services during the last decades, containing individual data on patient problems, treatments, and outcomes. The aim of the quality registers is to create a knowledge system for active use in quality improvement of healthcare services (Quality Registries, 2009, Swedish Association of Local Authorities and Regions (SALAR), 2007). No specific quality register of suicide attempts has yet been established in Sweden. However, the quality registers for bipolar disorder, psychosis, ADHD, and eating disorders include data on suicide attempts and self-harm.

## 1.5 SUICIDE PREVENTION

### 1.5.1 Primary, secondary, and tertiary prevention

Primary preventive efforts occur on the community level and include promotion of societal protective factors like improved physical health in the population and increased coping skills in children, or reduction of societal risk factors like mental disorders, alcohol or substance misuse, access to firearms, violence, poverty, and social isolation. Secondary and tertiary preventive interventions occur on the individual level and include assessment of suicide risk, treatment of mental disorders (especially major depression), individual-specific treatment of suicidal behaviour, and removal of the means for suicide in persons identified as suicidal (Mann, 2002, Maris, 2002).

### 1.5.2 Evidence-based prevention

Since suicide is a rare event even in most risk groups, risk assessment and prediction are difficult (Leenaars *et al.*, 1997, Mann, 2002, Maris, 2002, Oquendo *et al.*, 2006). This is clearly a serious obstacle to preventive efforts. On the other hand, a large percentage of people who commit suicide seek professional help before the act, giving an opportunity for prevention (Isacsson *et al.*, 1992, Mann, 2002, Pirkis and Burgess, 1998). But which methods should be used? It has been acknowledged that substantially more evidence of the efficacy of suicide preventive methods is needed (Hawton *et al.*, 2000, Hawton and van Heeringen, 2009, Isaac *et al.*, 2009, Linehan, 2008, Mann *et al.*, 2005). So far, adequate treatment of depression and consequently (primary care) physician education in depression recognition and treatment (Mann, 2002, Rutz *et al.*, 1992, Tiihonen *et al.*, 2006), lithium treatment for mood disorders (Cipriani *et al.*, 2005), dialectical behavioural therapy for borderline personality disorder (Linehan *et al.*, 2006), and restricting access to lethal methods (Mann, 2002, Rådbo *et al.*, 2005) have been considered evidence-based interventions. Training of gatekeepers (persons in contact with vulnerable populations trained in identifying at-risk individuals), cognitive therapy, problem-solving therapy, interpersonal psychotherapy, mentalisation-based treatment for borderline personality disorder, and intensive care plus outreach have shown promising results (Bateman and Fonagy, 2008, Hawton *et al.*, 2000, Isaac *et al.*, 2009, Mann *et al.*, 2005).

## **2 AIMS**

The overall aim of this thesis was to study premature death related to mental disorder, with a special emphasis on suicide.

- Objectives for study I: To identify predictors of suicide in a cohort with long-term mental disorder
- Objectives for study II: To analyse mortality by mental health service and psychiatric diagnosis in a cohort with long-term mental disorder
- Objectives for study III: To investigate the impact of coexisting psychiatric morbidity on suicide risk following a suicide attempt
- Objectives for study IV: To estimate suicide risks in biological and non-biological relatives of probands who had committed suicide

## **3 METHODS**

### **3.1 STUDIES I AND II**

#### **3.1.1 The cohort**

The National Board of Health and Welfare, the Stockholm County Council and the Stockholm County Association of Local Authorities conducted a survey in 1997, in order to identify the target population for the Community Mental Health Care Reform (Stefansson and Hansson, 2001). Staff from psychiatry and social services were requested to identify all adult individuals with a long-term disabling mental disorder who were in contact with the services. For each individual, staff completed a questionnaire that covered sociodemographic variables and variables related to psychiatric and social service interventions. At the time of the survey, Stockholm County had 1.8 million inhabitants, of which 1.4 million were aged 18 years or older. This corresponds to about one fifth of the Swedish population in 1997. The inclusion criteria specified residents of Stockholm County aged 18 years or older, with mental disorder causing long-term disability requiring psychiatric care or support from social services. Individuals with mental retardation or dementia and no other mental disorder were excluded. The specified duration of disability was six months or more.

The survey resulted in a register containing data on 12,247 individuals, entitled “Need of care and support in those with mental functional impairments in Stockholm County”. This register was linked by personal identification number to the Swedish Hospital Discharge Register and the Cause of Death Register. All three registers are held by the Epidemiological Centre of the National Board of Health and Welfare. All discharges from psychiatric inpatient care between January 1, 1990 and December 31, 2000, and all deaths that occurred in the cohort between January 1, 1997 and December 31, 2000 were identified.

#### **3.1.2 Statistics**

In bivariate analyses, the chi-square test and Fisher’s exact test were used to test differences in proportions; the Mann-Whitney U test was used to test differences in continuous variables; bivariate logistic regression was used to calculate odds ratios (ORs). Multiple logistic regression was used to investigate predictors of suicide in the cohort. Variables associated with suicide in the bivariate analyses were included in the multiple regression.

Further, standardised mortality ratios (SMRs) and 95% confidence intervals were calculated by a person-years at risk method, for the entire cohort, for the subgroups from psychiatric and social services and for the subgroups with and without psychiatric inpatient care. Person-years at risk 1998–2000 were calculated for each 5-year age group, gender and calendar year. The reference population was the population of Stockholm County. The number of excess deaths for each cause of death was calculated by subtracting the expected number of deaths from the observed number of deaths.

## **3.2 STUDY III**

### **3.2.1 The cohort**

Data on all people living in Sweden during 1973–82 (n=9.4 million) were linked to the Hospital Discharge Register, the Cause of Death Register, 1970 population and housing census, and education and migration registers (the last three held by Statistics Sweden). People aged 10 or older who had been admitted to inpatient care in Sweden during 1973–82 because of suicidal behaviour, defined as a definite or an uncertain suicide attempt were identified (n=49,509). To avoid confounding effects of being in the asylum seeking process people were excluded who had immigrated within two years before baseline (n=860). Cases were defined as those with one of the studied psychiatric diagnoses present at discharge from the index admission for a suicide attempt or at discharge from the first inpatient episode beginning within one week after this index episode (n=12,681). Those without a diagnosis of mental disorder within one year after the suicide attempt were used as reference subjects (n=27,004). People with psychiatric diagnoses other than those studied, or a diagnosis after one week but within one year after the suicide attempt (n=8,964) were not included. The study cohort thus consisted of 39,685 people, 18,642 men and 21,043 women.

Eight psychiatric disorders were studied: schizophrenia (code 295, ICD8), bipolar and unipolar disorder (296.1–9), other depressive disorder (296.0, 300.4), anxiety disorder (300, except 300.4), adjustment disorder or post-traumatic stress disorder (307), alcohol abuse or dependence (303), drug abuse or dependence (304), and personality disorder (301). The potential confounders of age, educational level, and immigrant status were introduced as covariates in the regression analyses.

### **3.2.2 Statistics**

Patients were followed from discharge after attempted suicide to a definite or uncertain suicide, death other than suicide, first emigration, or end of follow-up (December 31, 2003). Thus, patients were followed up for 21–31 years. Kaplan-Meier survival curves were used to plot temporal patterns of suicide after a suicide attempt. Absolute and relative mortality from suicide after a suicide attempt were determined for each diagnostic category and sex. Cox regression models were used to compute hazard ratios (HRs). Finally, population attributable fractions (PAFs) for suicide were calculated. In this context, the PAF is an estimate of the percentage of suicides among people who had previously attempted suicide that would not have happened without each studied coexistent psychiatric disorder.

## **3.3 STUDY IV**

### **3.3.1 The cohort**

A population-based national cohort (n=7,969,645) was created by linking the Cause of Death Register and the Multi-Generation Register (held by Statistics Sweden). In the sample, all deceased persons in Sweden during 1952–2003 with death classified as either definite or uncertain suicide according to the Cause of Death Register were identified.

### **3.3.2 Statistics**

A case-control method was used to estimate familial suicide risks for different classes of biological and non-biological relatives of suicide probands. For example, the odds ratio for siblings was estimated by designating each individual who had committed suicide in turn as a proband. For that proband, all possible case pairs were specified consisting of a proband plus all full-siblings (who had committed or not committed suicide). For each case-sibling pair, five control pairs were randomly selected. Control pairs were matched to case pairs by relation type, gender, and year of birth. To ensure equivalent periods of risk, it was also required that the control sibling who was matched to the proband was alive and had not emigrated at the date of the proband's suicide. This matching procedure was used for the probands' first-, second-, and third-degree relatives, monozygotic twins, adopted children, adopted parents, and partners. First-degree relatives include parents, full-siblings, and children. Second-degree relatives are grandparents, uncles/aunts, half-siblings, nephews/nieces, and grandchildren, while third-degree relatives include cousins. Partners were defined as couples who had had children together. Odds ratios comparing relatives of suicide probands and relatives of controls were calculated for each class of biological or non-biological relatives, using conditional logistic regression.

## 4 RESULTS

### 4.1 STUDY I

Predictors of suicide included previous suicide attempt (OR=3.2, 95% CI 2.1–4.9), a history of psychiatric inpatient care (3.1, 1.6–6.0), and unmet need of a contact person (1.9, 1.2–3.0). Borderline personality disorder was the strongest diagnostic predictor of suicide in the subgroup with psychiatric inpatient care (1.9, 1.1–3.2).

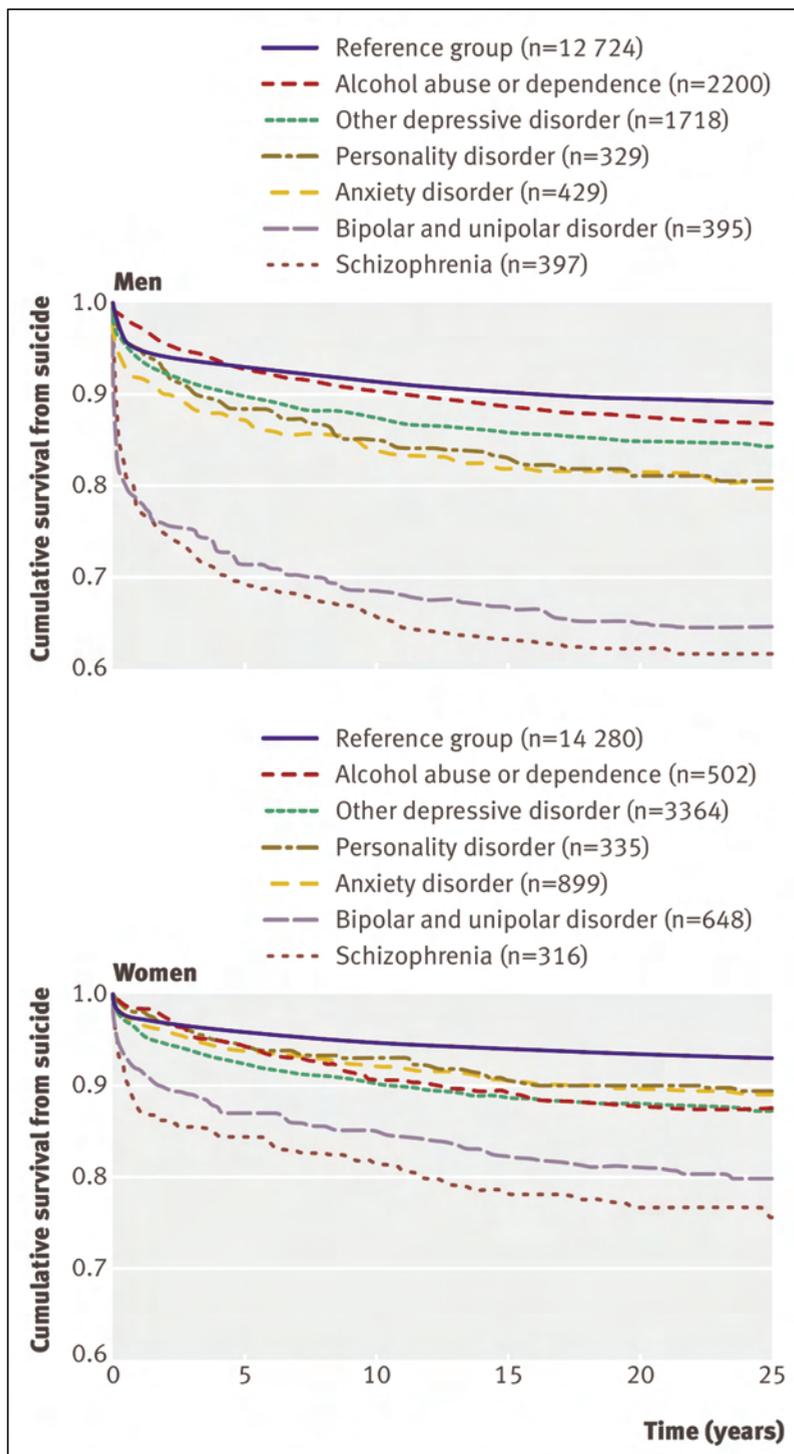
### 4.2 STUDY II

Mortality was increased in both sexes, for natural and external causes and in all diagnostic subgroups. Excess mortality was greater among those with a history of psychiatric inpatient care (men: SMR=4.2, 95% CI 3.7–4.7; women: 2.7, 2.4–3.1), especially in those with substance use disorder (men: 6.1, 4.7–7.8; women: 3.9, 2.5–5.8). Relative mortality was similar for those in contact with psychiatric and social services, respectively (men: SMR≈3; women: SMR≈2). For the entire cohort, the number of excess deaths due to natural causes (e.g., ischaemic heart diseases) was threefold that due to external causes (304 vs. 113).

### 4.3 STUDY III

Figure 11 shows survival graphs for suicide by psychiatric disorder. Those with a diagnosis of schizophrenia or bipolar/unipolar disorder had the highest short-term risk of suicide. In the group with schizophrenia, 22% of the men and 13% of the women died from suicide within one year after the index suicide attempt; the corresponding proportions for bipolar/unipolar disorder were 23% and 9%. More than half of all the suicides in these two groups occurred within the first year of follow-up (21–31 years). Generally, high proportions of all suicides in the cohort took place within one year. The survival curves show differences in temporal patterns between the diagnoses. For instance, the proportion of all suicides occurring during the first years was considerably lower for alcohol abuse/dependence than for schizophrenia and affective disorders.

Figure 11. Survival graphs for suicide by psychiatric disorder in people admitted to hospital during 1973–1982 for attempted suicide in Sweden and followed to 2003.



The strongest predictors of completed suicide throughout the entire follow-up were schizophrenia (men: HR= 4.1, 95% CI 3.5–4.8; women: 3.5, 2.8–4.4) and bipolar/unipolar disorder (men: 3.5, 3.0–4.2; women: 2.5, 2.1–3.0). These relative risk estimates correspond to 39% suicide mortality in men and 24% in women with schizophrenia; in bipolar/unipolar disorder the proportions were 36% and 20%, respectively.

The highest population attributable fractions for suicide among former suicide attempters were found for other depression in women (PAF=9.3), followed by schizophrenia in men (4.6), and bipolar/unipolar disorder in women (4.1) and men (4.0). The high population attributable fraction in women with other depression was due to high prevalence; this group did not have a very high hazard ratio for suicide (1.7, 1.5–1.9).

#### **4.4 STUDY IV**

There were 83,951 individuals who had committed suicide; the lifetime prevalence for suicide was 1.2% (95% CI 1.1–1.2). Table 2 shows odds ratios for suicide in relatives of suicide probands, compared to relatives of controls. Regarding first-degree relatives of suicide probands, risk increase was higher in full-siblings (OR=3.1, 2.8–3.5) than in children 2.0 (1.9–2.2). The odds ratio for full-siblings (3.1, 2.8–3.5) was higher than that for maternal half-siblings (1.7, 1.1–2.7). Relative risks for second- and third-degree relatives were similar. For instance, nephews/nieces had an odds ratio of 1.6 (1.4–1.9) and cousins 1.5 (1.3–1.8). Table 2 shows further that the odds ratio for suicide was higher for partners of suicide probands (2.3, 95% CI 2.2–2.5) than for most biological relatives.

Table 2. Relative risks for suicide in biological and non-biological relatives of probands who had committed suicide (n=83,951), in a national cohort of 7,969,645 individuals.

Relation to proband	Number of dyads	Concordant pairs	0	1	2	3	4	Odds Ratio (95%CI)
<b>First-degree relatives</b>								
Sibling	10,451,878	338						3.1 (2.8-3.5)
Child	13,714,253	923						2.0 (1.9-2.2)
Adoptee	66,564	12						1.4 (0.7-2.6)
<b>Second-degree relatives</b>								
Maternal half-sibling	1,121,888	21						1.7 (1.1-2.7)
Paternal half-sibling	1,482,456	24						1.2 (0.8-1.9)
Nephew or niece	11,247,095	154						1.6 (1.4-1.9)
Grandchild	12,698,233	247						1.3 (1.2-1.5)
<b>Third-degree relatives</b>								
Cousin	20,542,261	84						1.5 (1.3-1.8)
<b>Non-biological relatives</b>								
Spouse	7,538,548	882						2.3 (2.2-2.5)
Adopted child	206,692	11						1.3 (0.7-2.5)
<b>Twins</b>								
Twin (MZ)	14,018	4						15.4 (5.4-43.8)
Twin (DZ)	19,664	3						3.0 (1.0-9.7)
Twin (OS)	21,814	4						5.2 (1.9-14.4)

## 5 DISCUSSION

In contrast to most previous studies that are based on clinical cohorts, studies I and II are based on a large cohort that includes severely mentally ill both with and without psychiatric contact. The sample is probably close to the total population with severe mental disorder in Stockholm County. The two studies are to our knowledge the first to study unmet needs as predictors of suicide and to compare mortality in such a cohort. Regardless of whether treatment was delivered by psychiatric or social services, mortality in the cohort was at similar high levels as in previous Swedish studies of individuals with severe mental disorder who were hospitalised during earlier decades (Allebeck and Wistedt, 1986, Ringbäck Weitoft *et al.*, 1998, Ösby *et al.*, 2001, Ösby *et al.*, 2000a).

Some methodological issues should be discussed: (1) Inclusion was determined by service providers and what constitutes a “mental disorder causing long-term disability” may vary in different service settings, which may introduce bias (Abrams *et al.*, 2008). This approach, however, allowed inclusion of persons without psychiatric contact, which is a major strength of the studies. (2) Diagnostic data are lacking for those with outpatient psychiatric care only. (3) The results were not adjusted for length of duration of mental disorder. The increased mortality is greatest in the early course of mental disorder (Høyer *et al.*, 2000, Lawrence *et al.*, 2000, Mortensen and Juel, 1993, Ösby *et al.*, 2001, Ösby *et al.*, 2000a); therefore, excess mortality in the cohort is probably underestimated, due to survivorship bias. This, however, does not affect the conclusions of the studies. (4) Due to organisational differences, the variable “unmet need of a contact person” may have somewhat different connotations among psychiatric and social services staff, respectively. However, a perceived unmet need of a contact person probably reflects social isolation and lack of social support, which is a risk factor for suicide (Lambert, 2003, Mann, 2002). (5) Self-harm may be a criterion for receiving a diagnosis of personality disorder, and individuals with personality disorder often have another psychiatric diagnosis as well. Potential confounding effects of these facts were not taken into account in the analyses of personality disorder diagnoses. (6) Psychiatric inpatient diagnoses received 1990–2000 only were included in the analyses. Diagnoses received before 1990 were not taken into account, which could affect the comparisons per mental disorder. On the other hand, this choice eliminated short, single episodes of a particular disorder occurring many years before the investigation. (7) The follow-up started just after a major reorganisation of the Swedish mental health services; thus, confounding cohort and period effects cannot be ruled out.

Suicide mortality was strongly elevated in the cohort, as expected; the SMRs for suicide reported here are in line with previous studies (Harris and Barraclough, 1997, Mortensen and Juel, 1993, Ösby *et al.*, 2000a). Social service and psychiatric staff identified unmet needs that later proved to predict suicide in the cohort. Borderline personality disorder was the diagnosis most strongly associated with suicide among persons with a history of psychiatric in-patient treatment. Suicide risk in those with a personality disorder is often underestimated, and prevention of suicide can be especially difficult in these groups (Lambert, 2003, Paris, 2002). The number of excess

deaths from natural causes was threefold that of external causes. This is in line with previous studies (D'Avanzo *et al.*, 2003, Harris and Barraclough, 1998, Joukamaa *et al.*, 2001, Stark *et al.*, 2003) and underlines the need for physical health interventions for this vulnerable group.

The high risk of premature death in those with a substance use disorder is well-known (Harris and Barraclough, 1998, Swartz *et al.*, 1998). Substance use disorders often co-occur with other diagnosed or undiagnosed mental disorders. Treatment of those with concurrent substance use disorder and other mental disorder is considered difficult; validated treatment strategies are lacking (Bellack *et al.*, 2006, Goldsmith and Garlapati, 2004, Hayes *et al.*, 2003, Swartz *et al.*, 1998, Ziedonis *et al.*, 2005). Proposed treatment strategies for this group include integrated mental health and substance abuse treatment (Hickie *et al.*, 2005, Swartz *et al.*, 1998, Ziedonis *et al.*, 2005) or behavioural treatment for substance abuse developed specifically for people with severe and long-term mental disorders (Bellack *et al.*, 2006).

The excess mortality in this group is not only a health care problem, but also a societal problem. It is essential that those with a long-term severe mental disorder actually receive the social support and assistance to which they are legally entitled. Social support can include focus on lifestyle factors and facilitate access to primary care and medical and psychiatric services. A general, broad range improvement of medical care and social services for this group is possibly the most effective means for reduced mortality on a large scale.

The results of Study III showed that type of psychiatric morbidity in suicide attempters is related to risk of subsequent suicide. Substantial differences in suicide risk across the diagnostic categories were found. The rate of suicide after a previous suicide attempt was particularly increased among men and women with schizophrenia or bipolar and unipolar disorder. Also, death from suicide was heavily skewed towards the first years after the suicide attempt particularly in people with schizophrenia or bipolar and unipolar disorder, probably because of intense, symptom rich phases. The results suggest that attempted suicide in those with schizophrenia or bipolar and unipolar disorder is particularly worrying and underlines the need for more focused care during the first years after a suicide attempt.

By using an epidemiological framework and a total population sample we tried to minimise the selection bias and power problems in previous studies of smaller clinical samples. The national cohort we followed for at least 21 years is the largest with data on people who have attempted suicide and on psychiatric morbidity. One limitation of our study was that we included only people with suicide attempts that led to an episode of inpatient care. Furthermore, we did not study the contribution of physical illness (Goodwin *et al.*, 2003, Suokas *et al.*, 2001) or multiple psychiatric comorbidity. We did not analyse subcategories of the diagnostic groups because of the small numbers of suicides in some subgroups. Also, a narrow definition for bipolar disorder was used in Sweden during the years of inclusion; primarily for patients with more obvious manic symptoms and similar to the type I diagnosis for bipolar disorder by the DSM-IV. Thus these results might not be generalisable to a broader phenotype for bipolar disorder. Furthermore, among the disorders labelled as manic depressive in the ICD8, the

depressed type (296.2), which could be labelled recurrent severe depression, contributed strongly to the high risk of suicide in the bipolar and unipolar group.

Also, we defined coexistent psychiatric morbidity as any disorder diagnosed within one week of the suicide attempt. People who attempted suicide may have been diagnosed as having one or more psychiatric disorders before or after this period, thereby resulting in misclassification of patients with coexistent psychiatric morbidity as reference subjects. Therefore we tested the effect of an alternative definition of reference subjects on estimates of suicide risk across diagnostic categories. The exclusion from the reference group of those receiving a psychiatric diagnosis beyond one year after the suicide attempt yielded similar hazard ratios and population attributable fractions across the diagnostic groups. It is most likely that many subjects in the reference group had subclinical psychiatric morbidity. Our estimates are therefore probably an underestimation of the true risks conveyed by coexistent psychiatric morbidity in people who attempted suicide.

Specific treatment of patients who have attempted suicide is often discussed on the basis of previous suicide attempts (Hawton *et al.*, 1998) and an estimate of suicidal intent. Our results imply that interventions should take into account coexistent mental disorder and the time that has elapsed since the previous suicide attempt.

Study IV is the first national cohort study to provide estimates of familial suicide risk in half-siblings, grandchildren, cousins, and spouses. A major strength of the study is the total population cohort; the statistical power was sufficient to identify shared environmental effects. Some limitations should, however, be considered: (1) We only used non-detailed register data. (2) National registers are subject to "left censoring", missing data before the date at which the register started. (3) Despite the large size of the cohort, some results were possibly non-significant due to small numbers; thus, the possibility of type II errors cannot be excluded.

We found evidence for familial aggregation of suicide: risks were higher in relatives of suicide probands than in relatives of controls. A comparison of first-degree-relatives showed that siblings had a significantly higher odds ratio than children/parents, despite same degree of genetic correlation. Further, despite differing degrees of genetic correlation, similar odds ratios were observed in second- and third-degree relatives. Thus, findings are not entirely consistent with variance by degree of genetic correlation. These results suggest effects of shared environment in the familial clustering of suicide. Spouses of suicide probands had a comparatively high odds ratio. Due to the possibility of assortative mating (preferential mating between individuals with a similar phenotype), it is uncertain to what extent this result is due to shared genes or shared environments. The risk increase for full-siblings was higher than that for maternal half-siblings (both usually grow up together). The odds ratio for cousins (who seldom live in the same family) was higher than one. These two results point to effects of shared genes.

## 6 CONCLUSIONS

Treatment programs for persons with long-term mental disorder should target physical as well as mental health. Unmet needs may signal increased suicide risk in persons with severe mental disorder. Methods to improve suicide prevention in those with a borderline or other personality disorder should be further developed and implemented.

Psychiatric case management should focus on more intensive aftercare during the first years after a suicide attempt in patients with coexistent bipolar and unipolar disorder or schizophrenia. Further studies are needed to identify the characteristics within the diagnostic categories of bipolar and unipolar disorder, schizophrenia, and other disorders, including comorbidity, that confer a higher risk for completed suicide.

Results of Study IV confirm that a family history of suicide is a risk factor for suicide. The study could identify impact of both shared environment and shared genes in familial transmission of suicidal behaviour.

## 7 FUTURE STUDIES

Hopefully, the results from Study I–IV can give contributions to preventive efforts to reduce suicide and other premature deaths. However, a number of studies are needed to complement these results. These include:

- A long-term follow up of mortality and morbidity in the cohort examined in Study I and II, with survival analyses and controlling for social variables derived from national registers
- Further follow-ups of similar cohorts as in Study III, for later decades (1983–1992 and so on), to compare outcomes during different time periods
- Analyses of somatic and psychiatric (including substance misuse) co-morbidity in the cohort investigated in Study III
- Analyses of subdiagnoses (e.g., psychotic and affective disorders) in the cohort analysed in Study III
- Analyses of suicide attempt methods (e.g., violent, nonviolent) in the cohort analysed in Study III
- Comparison of age classes in the cohort analysed in Study III
- Comparison of suicide risks in the cohort studied in Study IV, taking into account the time period between the suicides in each studied pair

## 8 SVENSK SAMMANFATTNING

### 8.1 SYFTEN

Ämnet för denna avhandling är förtida död relaterad till psykisk sjukdom, med en särskild tyngdpunkt på suicid. Det övergripande syftet är att bidra med relevant kunskap för att kunna förbättra preventiva strategier. Delstudiernas syften är som följer.

- *Studie I:* Att identifiera prediktorer för suicid i en grupp personer med långvarig psykisk sjukdom
- *Studie II:* Att analysera mortalitet per vård- eller stödverksamhet (i psykiatri eller socialtjänsten) och per psykiatrisk diagnos i en grupp personer med långvarig psykisk sjukdom
- *Studie III:* Att undersöka inverkan av olika psykiska sjukdomar på risken för fullbordat suicid efter ett första suicidförsök
- *Studie IV:* Att beräkna risker för suicid hos släktingar och andra nära relationer till personer som begått suicid

### 8.2 METODER

#### 8.2.1 Studie I och II

Under 1997 genomfördes en enkät riktad till psykiatri- och socialtjänstpersonal i Stockholms län. Syftet var att identifiera invånare 18 år eller äldre med psykisk sjukdom svår nog att leda till långvarigt funktionshinder, dvs. målgruppen för den 1995 inledda s.k. psykiatrireformen. Enkäten resulterade i att Socialstyrelsen med tillstånd av Datainspektionen upprättade personregistret ”Psykiiskt handikappades vård och omsorgsbehov i Stockholms län”, med data för 12 247 individer. Detta register länkades via personnummer till de svenska slutenvårds- och dödsorsaksregistren.

I gruppen med 12 247 personer identifierades alla utskrivningar från psykiatrisk sjukhusvård mellan 1990 och 2000 och alla dödsfall mellan 1997 och 2000. Sedan genomfördes statistiska analyser. Multipel logistisk regression användes för att undersöka prediktorer för suicid inom gruppen. Med andra ord undersöktes om vissa subgrupper hade extra hög risk för suicid. Jämförelsemåttet i logistisk regression är oddskvot (OR), en kvot mellan två sannolikheter eller risker. Standardiserade mortalitetskvoter (SMR) för alla dödsorsaker jämfört med befolkningen i Stockholms län beräknades för hela gruppen och för subgrupper. Med SMR jämförs risken för att dö i en viss grupp jämfört med risken i en viss befolkning, t.ex. i ett län eller land.

#### 8.2.2 Studie III

Data för alla personer bosatta i Sverige 1973–82 länkades till slutenvårdsregistret, dödsorsaksregistret och andra nationella register. Alla som hade vårdats på sjukhus i Sverige 1973–82 på grund av ett suicidförsök identifierades (49 509 personer). Gruppen som sedan studerades bestod av 39 685 personer. I denna grupp ingick de som fått en av de studerade psykiatriska diagnoserna i samband med det första

suicidförsöket (fall, 12 681 personer) och de som inte fått någon psykiatrisk diagnos under året efter suicidförsöket (jämförelsegrupp, 27 004 personer).

Personerna följdes under 21–31 år. Överlevnadskurvor framställdes grafiskt med Kaplan-Meieranalys. Sådana kurvor visar hur många procent av en grupp som fortfarande är i livet vid varje tidpunkt på en tidsaxel. Hasardkvoter (HR, en form av relativ risk) beräknades med Coxregression.

### **8.2.3 Studie IV**

En databas med uppgifter om 7 969 645 personer skapades genom samkörning av dödsorsaksregistret och flergenerationsregistret. Alla avlidna personer 1952–2003 med säkert eller osäkert suicid som angiven dödsorsak identifierades (n=83 951).

Oddsquoter för suicid hos släktingar och andra nära relationer till personer som suiciderat (fall) jämfört med personer som inte suiciderat (kontroller) beräknades med logistisk regression. Första-, andra- och tredje gradssläktingar, enäggstvillingar, adoptivbarn, adoptivföräldrar och partner ingick i jämförelserna. Förstegradssläktingar är föräldrar, helsyskon och barn. Andragradssläktingar är far- och morföräldrar, syskon till föräldrar, halvsyskon, syskonbarn och barnbarn. Tredje gradssläktingar är t.ex. kusiner. Partner definierades som par med gemensamma biologiska barn.

## **8.3 RESULTAT**

### **8.3.1 Studie I**

Att tidigare ha gjort ett suicidförsök (OR=3,2, 95 % CI 2,1–4,9), att ha vårdats på psykiatrisk vårdavdelning (3,1, 1,6–6,0) och att ha ett ouppfyllt behov av kontaktperson (1,9, 1,2–3,0) var prediktorer för suicid. Borderline personlighetsstörning var den starkaste diagnostiska prediktorn (1,9, 1,1–3,2). (CI betyder ”konfidensintervall” och är ett mått på hur statistiskt säkert ett beräknat värde är.)

### **8.3.2 Studie II**

Överdödligheten var högre i den grupp som hade vårdats på psykiatrisk vårdavdelning (män: SMR=4,2, 95 % CI 3,7–4,7; kvinnor: 2,7, 2,4–3,1), särskilt hos dem med missbruksdiagnos (män: 6,1, 4,7–7,8; kvinnor: 3,9, 2,5–5,8). Överdödligheten var likartad i de grupper som (primärt) hade kontakt med psykiatrin respektive socialtjänsten. Det beräknade antalet extra dödsfall 1998–2000 jämfört med befolkningen i Stockholms län var 417. Antalet extra dödsfall var tre gånger högre för naturliga dödsorsaker (t.ex. hjärtinfarkt) än för yttre dödsorsaker (t.ex. suicid), 304 respektive 113.

### **8.3.3 Studie III**

En stor andel av alla suicid i gruppen inträffade inom ett år efter det första suicidförsöket. De starkaste prediktorerna för suicid under hela uppföljningstiden (21–

31 år) var schizofreni (män: HR= 4,1, 95 % CI 3,5–4,8; kvinnor: 3,5, 2,8–4,4) och bipolär/unipolär sjukdom (män: 3,5, 3,0–4,2; kvinnor: 2,5, 2,1–3,0). Dessa hasardkvoter motsvarar 39 % suiciddödlighet hos männen och 24 % hos kvinnorna med schizofreni. För bipolär/unipolär sjukdom var andelarna 36 % respektive 20 %.

#### **8.3.4 Studie IV**

I gruppen förstegradssläktingar till personer som suiciderat var den relativa risken för suicid högre hos helsyskon (OR=3,1, 95 % CI 2,8–3,5) än hos barn 2,0 (1,9–2,2). Oddskvoten för helsyskon (3,1, 2,8–3,5) var högre än den för halvsyskon på mammans sida (1,7, 1,1–2,7). De relativa riskerna för andra- och tredje gradssläktingar var likartade. Till exempel hade syskonbarn oddskvoten 1,6 (1,4–1,9) och kusiner 1,5 (1,3–1,8). Oddskvoten för suicid var högre för partner till personer som suiciderat (2,3, 2,2–2,5) än för alla första-, andra- och tredje gradssläktingar utom helsyskon och tvåäggstvillingar.

### **8.4 SLUTSATSER**

Behandlingsprogram för personer med långvarig psykisk sjukdom bör inriktas på både kroppslig och mental hälsa. Uppfyllda behov av vård, stöd eller service kan signalera ökad suicidrisk hos personer med psykisk sjukdom. De befintliga suicidpreventiva metoderna för personer med borderline eller annan personlighetsstörning behöver vidareutvecklas och implementeras.

Psykiatrisk behandling bör inriktas på extra intensiv eftervård under de första åren efter ett suicidförsök hos patienter med bipolär sjukdom, unipolär sjukdom eller schizofreni. Fler studier behövs för att närmare identifiera vad som ger förhöjd suicidrisk i bipolär sjukdom, unipolär sjukdom och schizofreni, inklusive komorbida tillstånd.

Resultat från Studie IV bekräftar att tidigare suicid i familjen är en riskfaktor för eget suicid. Studien kunde identifiera effekter av såväl miljöfaktorer som genetiska faktorer i ansamlingen av suicid i familjer.

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