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-Diplomarbeit-

Familial Factors and Suicide
—
an Adoption Study
in a Swedish National Cohort

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Contents

Summary.....	III
Zusammenfassung	IV
Sammanfattning.....	V
1 Suicide	1
1.1 Definitions	1
1.2 Epidemiology/Magnitude of the problem.....	2
1.3 Gender and Age Differences	5
1.4 Risk Factors	7
1.5 Prevention.....	14
2 Register Studies in Sweden	17
2.1 Personal Identity Number (Personnummer).....	17
2.2 Swedish Health Registers (Overview).....	18
2.3 Use of the Registers.....	19
2.4 Ethical Considerations.....	22
2.5 Conclusion.....	24
3 Adoption Research	25
3.1 Studies Exploring the Importance of Genetic & Environmental Factors.....	25
3.2 Studies of Adoption Process and Outcomes.....	27
4 References	30
5 Manuscript for Submission.....	37
6 Eidesstattliche Erklärung.....	56

Figures

Figure 1 - Homicide and suicide rates by WHO region, 2000	3
Figure 2 - suicide in the world	4
Figure 3 - SDR Suicide and all self-inflicted injuries in 2001	4
Figure 4 - Suicide attempts per 100.000 inhabitants in Sweden 2003 by age and sex	6
Figure 5 - Suicides per 100.000 inhabitants in Sweden 2003 by age and sex	6
Figure 6- Percentage of all suicides by age and sex	7
Figure 7- Usage of the personal identity number	18

Tables & Boxes

Table 1 - Suicide as a leading cause of death, selected countries (European Region).....	3
Table 2 - Previous studies on international adoption in Sweden.....	29
Box 1 – Statistical risk factors for suicide	8
Box 2 - Informed consent and the Swedish National Health Registers.....	24

Summary

Worldwide, approximately one million people die from suicide every year and 10-20 million attempt suicide. Both genetic and environmental factors influence the risk of suicide in the population.

In a more general part, this thesis gives a broad overview over the topic of suicide, its epidemiology, risk factors and prevention strategies (chapter 1).

This is followed by a general introduction to the Swedish National Health Registers (chapter 2) that have been used in the current study. In these registers high quality data on health as well as socioeconomic indicators for the entire population can be linked using a unique personal identification number which follows each resident from birth to death. Therefore the registers provide excellent opportunities for research with large datasets and readily available information as well as long follow-up times. However, these benefits need to be weighed against ethical considerations, which are also discussed in chapter 2, together with potential problems in this kind of research.

Chapter 3 will provide a short introduction to the subject of adoption research and the situation of adoption in Sweden. While the classical adoption study – as conducted in this case – uses the process of adoption to identify influence of genetic/heritable and environmental factors, studies of adoption outcome look at adoption and the adoption process in respect to the outcomes of children with this background, their special risks and risk factors. Sweden has an outstanding position concerning international adoption with the largest population of intercountry adoptees in Europe and the highest per capita rate of intercountry adoptees worldwide.

Using the possibilities of the large Swedish Health registers, an adoption study was conducted with the intention of exploring the influence of both heritable and environmental factors on suicide further. The results from this study are presented in a manuscript (chapter 5) that will be submitted for publication in an international journal.

Zusammenfassung

Jedes Jahr sterben weltweit circa eine Million Menschen durch Suizid, weitere 10-20 Millionen begehen einen Selbstmordversuch. Sowohl erbliche Faktoren als auch Umweltfaktoren beeinflussen das Suizidrisiko.

In einem generellen Teil gibt diese Diplomarbeit einen groben Überblick über das Thema Suizid, die Epidemiologie, Risikofaktoren und Präventionsstrategien (Kapitel 1).

Im Anschluss daran erfolgt eine generelle Einführung bezüglich der Schwedischen Gesundheitsregister (Kapitel 2), die für die im Rahmen dieser Diplomarbeit durchgeführte Studie verwendet wurden. Diese Register bieten die Möglichkeit, hochwertige Daten zu Gesundheitsindikatoren sowie sozioökonomischen Faktoren für die gesamte Bevölkerung zu verknüpfen. Den Schlüssel hierfür bildet eine individuelle Personnummer, die jeden Einwohner von Geburt an bis zum Tod begleitet. Daher bieten die schwedischen Register ausgezeichnete Möglichkeiten für die epidemiologische Forschung mit leicht zugänglichen, großen Datensätzen, die sich über lange Zeiträume verfolgen lassen. Diese Vorteile müssen jedoch stets gegen ethische Gesichtspunkte abgewogen werden, welche ebenfalls in Kapitel 2 - zusammen mit potentiellen Problemen dieser Studienart - diskutiert werden.

Kapitel 3 bietet eine kurze Einführung in das Thema der Adoptionsstudien. Während die „klassische“ Adoptionsstudie – wie auch in dieser Diplomarbeit durchgeführt – den Adoptionsprozess dazu nutzt, um den Einfluss von erblichen Faktoren und Umwelteinflüssen in der Analyse zu trennen, beschäftigen sich Adoptions-Outcome-Studien damit, wie die Adoption selbst Kinder dieses Hintergrunds beeinflusst und welche speziellen Risiken oder Risikofaktoren in dieser Gruppe anzutreffen sind. In diesem Kontext hat Schweden eine herausragende Position, internationale Adoption betreffend. Schweden hat die größte Anzahl an international Adoptierten in Europa und die höchste Pro-Kopf-Rate an international Adoptierten in der Bevölkerung weltweit.

Unter Verwendung der Schwedischen Gesundheitsregister, wurde eine Adoptionsstudie zum Einfluss der erblichen Faktoren und Umweltdeterminanten auf das Suizidrisiko durchgeführt. Die Ergebnisse sind in einem Manuskript präsentiert (Kapitel 5), das zur Publikation in einer internationalen Zeitschrift eingereicht werden wird.

Sammanfattning

Varje år begår en miljon människor i hela världen självmord och 10-20 miljoner genomför självmordförsök. Både ärftliga faktorer och samhällsfaktorer påverkar risken för självmord i befolkningen. Den här uppsatsen ger först en bred överblick av problemområdet självmord (epidemiologi, riskfaktorer och preventionsmöjligheter) i en allmän del (kapitel 1).

Därefter följer en övergripande beskrivning av Sveriges hälsodataregister (kapitel 2), vilka använts för studien i uppsatsen. Data för hälsoindikatorer och socioekonomiska faktorer kan länkas ihop mellan olika register genom personnumret som följer varje invånare genom hela livet. Sveriges register öppnar goda möjligheter för den epidemiologiska forskningen genom dessa stora databaser av hög kvalitet och studiepopulationer som kan följas upp över långa tidsperioder. Dessa fördelar måste emellertid vägas mot etiska faktorer, något som också diskuteras i den andra delen av uppsatsen, liksom även metodologiska problem som förekommer vid registerstudier.

Tredje delen (kapitel 3) ger en kort introduktion till adoptionsstudier och förhållandena när det gäller adoption i Sverige. Den klassiska adoptionsstudien försöker skilja betydelsen av genetiska faktorer och miljöfaktorer genom att jämföra adopterade med icke-adopterade. Studier om "Adoption outcome" ser på adopterade själva, deras utveckling och riskfaktorer med anknytning till adoptionssituation. Sverige har en speciell position inom internationell adoption med det största antalet internationellt adopterade i Europa och den högsta andelen internationellt adopterade i hela världen.

I kapitel 5 redovisas resultat från en adoptionsstudie som genomfördes med användande av de svenska hälsodataregistren med syftet att undersöka betydelsen av genetiska och miljörelaterade faktorerens betydelse för risken att begå självmord. Resultaten presenteras i form av ett manuskript, avsett för publicering i en internationell vetenskaplig tidskrift.

1 Suicide

Suicide is an important public health problem (e.g. Krug et al. 2002, WHO 2001). Every year about one million people take their own lives, between 10-20 million attempt suicide (Benedetto – Foreword in Wassermann ed. 2001; WHO 2001). However, suicide does not only concern the victims alone, it affects a wide range of people around them: family, friends, colleagues... Those that are left behind and whose lives will also be changed forever (Nils Retterstol - Foreword in Schmidtke et al. ds 2001).

1.1 Definitions

When talking about suicide it is important to have clear definitions. Within this introduction firstly, there will be a general overview about the definitions of suicidal behaviour. As in our study, ICD-classifications were used to define suicide, this method and its validity needs to be discussed.

1.1.1 General definitions

For *completed suicide* the definition of suicide worked out in 1986 by the Regional Office Working Group on Preventive Practices in Suicide and Attempted Suicide (WHO Regional Office for Europe) is set as follows (according to Bille-Brahe et al. 2004, p.12):

“Suicide is an act with fatal outcome which the deceased, knowing or expecting a fatal outcome, had initiated and carried out with the purpose of provoking the changes that he desired”.

It does not consider suicidal intentions, but takes into account knowledge about the effects of the act.

For *suicide attempts* the definition used in Europe, originated by the WHO group in its studies of parasuicide/attempted suicide, reads as follows (as cited in Wasserman & Narboni 2001):

“[Suicide attempt is]an act with non-fatal outcome, in which an individual deliberately initiates a non-habitual behaviour that, without intervention from others, will cause self-harm, or deliberately ingests a substance in excess of the prescribed or generally recognised therapeutic dosage, and which is aimed at realising changes which the subject desired via the actual or expected physical consequences”.

Suicidal thoughts or ideation are defined as wishes or behaviours that indicate people's desire to take their own lives. Suicidal thoughts can be expressed verbally, including direct statements of intent or written comments, or non-verbally, in the form of artistic creations or behaviour (Wasserman & Narboni 2001).

1.1.2 ICD-Classification for suicide mortality

In any kind of research that uses the International Classification of Diseases (ICD) as case definitions, changes in those classifications may influence the results over time. In the ICD for suicide a major change took place between the 7th and 8th revision (ICD 7 and ICD 8). While from 1958 until 1968 the ICD 7 classified all deaths from self-inflicted injury as suicides, unless there was proof or statement the death was unintentional, in 1968 an additional mode-of-death category was introduced: "circumstances undetermined". Thus suicides were not classified as such unless there was proof of intentional self-infliction (O'Carroll 1989). For usage of the ICD classification in suicide research this means that the official figures underestimate actual suicides even further. Several studies have given strong indications that within this category of undetermined deaths (in ICD revisions 8-10) actual suicides are hidden (e.g. Marusic et al. 2003, Ohberg et al. 1998, O'Carroll 1989, Phillips & Ruth 1993). By a combination of suicides and uncertain deaths the validity of figures can be improved (O'Carroll 1989). Therefore undetermined deaths should be included in the group of suicide for research purposes (Linsley et al. 2001)

1.2 Epidemiology/Magnitude of the problem

Suicide is a phenomenon that is not restricted to any part of the world. Suicide represents 1.4% of the global burden of disease. In 2001 suicide deaths exceeded both the number of deaths by homicide and war¹. Intentional injuries account for an increasing share of the burden of disease, especially among economically productive young adults. In developed countries, suicides account for the largest share of intentional injury burden (WHO 2003). In most regions of the western world the number of deaths from suicides exceeds the number of deaths from homicides by far (Figure 1).

¹ WHO Regional Director for the Western Pacific, speech in Manila, August 2005 <http://.wpro.who.int/NR/exeres/891466F6-C6AF-4228-B8BD-0F52CB398332.htm> (as seen on 25.0692006)

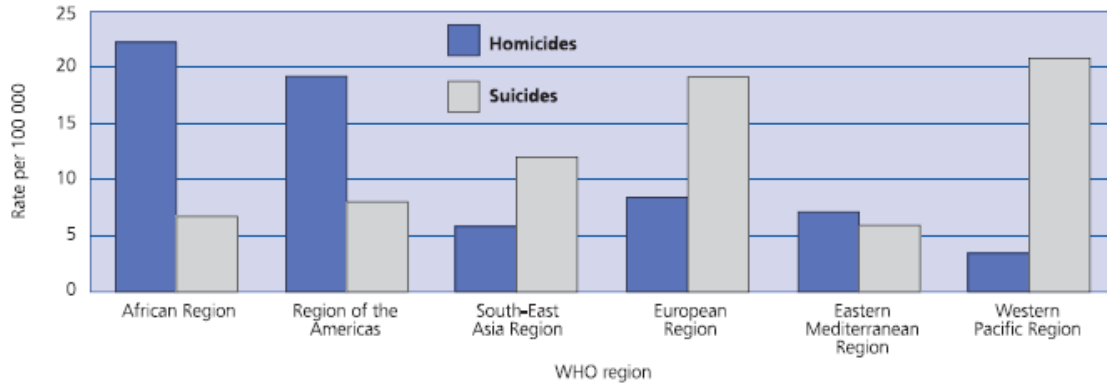


Figure 1 - Homicide and suicide rates by WHO region, 2000 (source: Krug EG et al. [eds], 2002, page11).

Among men, road traffic injuries, violence and self-inflicted injuries are among the top ten leading causes of death in the 15–44-year-old age group (WHO 2003). For men in Europe, suicide is the second leading cause of death, after traffic accidents (compare Table 1).

Table 1 - Suicide as a leading cause of death, selected countries of the European Region², 15–34-year-olds, 1998 (WHO 2001, p.39)

Both sexes	Males	Females
1. Transport accidents	1. Transport accidents	1. All cancers
2. Suicide	2. Suicide	2. Transport accidents
3. All cancers	3. All cancers	3. Suicide

Figure 2 and Figure 3 give an impression of the magnitude of the problem worldwide and in Europe with the highest suicide rates in industrialized countries and unfortunately a great lack of data in many developing countries.

² Albania, Austria, Bulgaria, Croatia, Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Israel, Italy, Kazakhstan, Latvia, Lithuania, Luxembourg, Macedonia, Malta, Netherlands, Norway, Portugal, Republic of Moldova, Romania, Slovakia, Slovenia, Spain, United Kingdom.

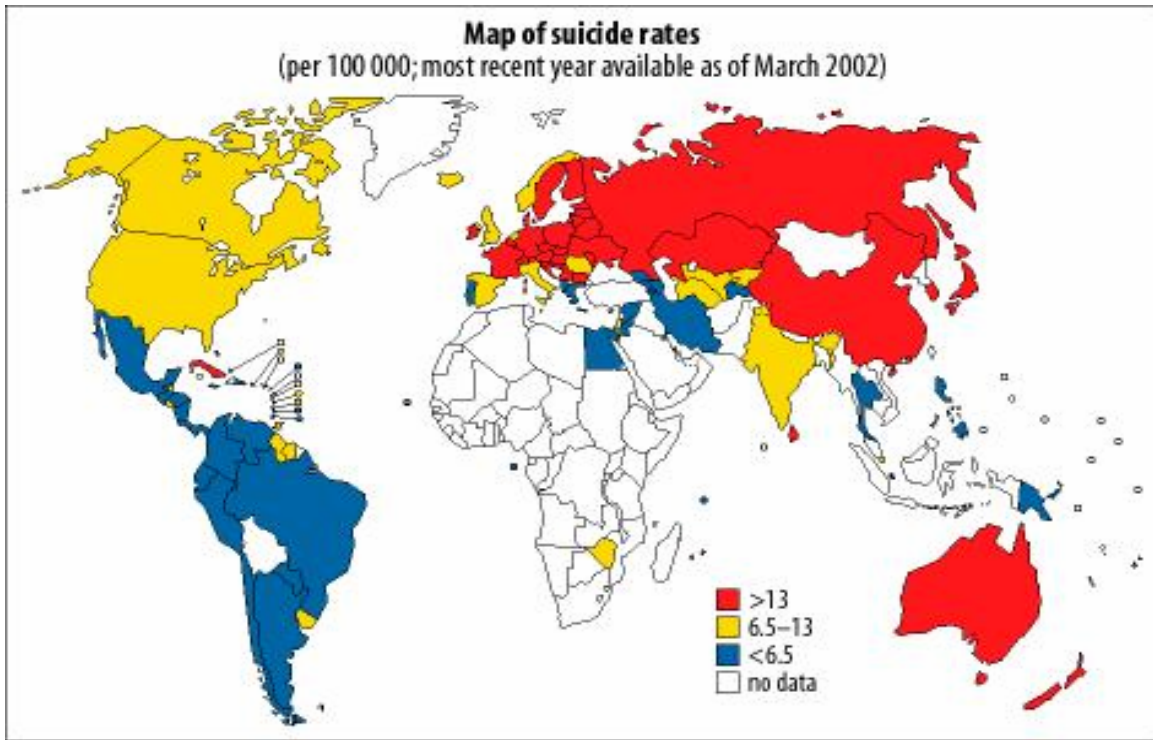


Figure 2 - suicide in the world (source: WHO http://www.who.int/mental_health/prevention/suicide/suicideprevent/en/ as seen on 23.09.2006)

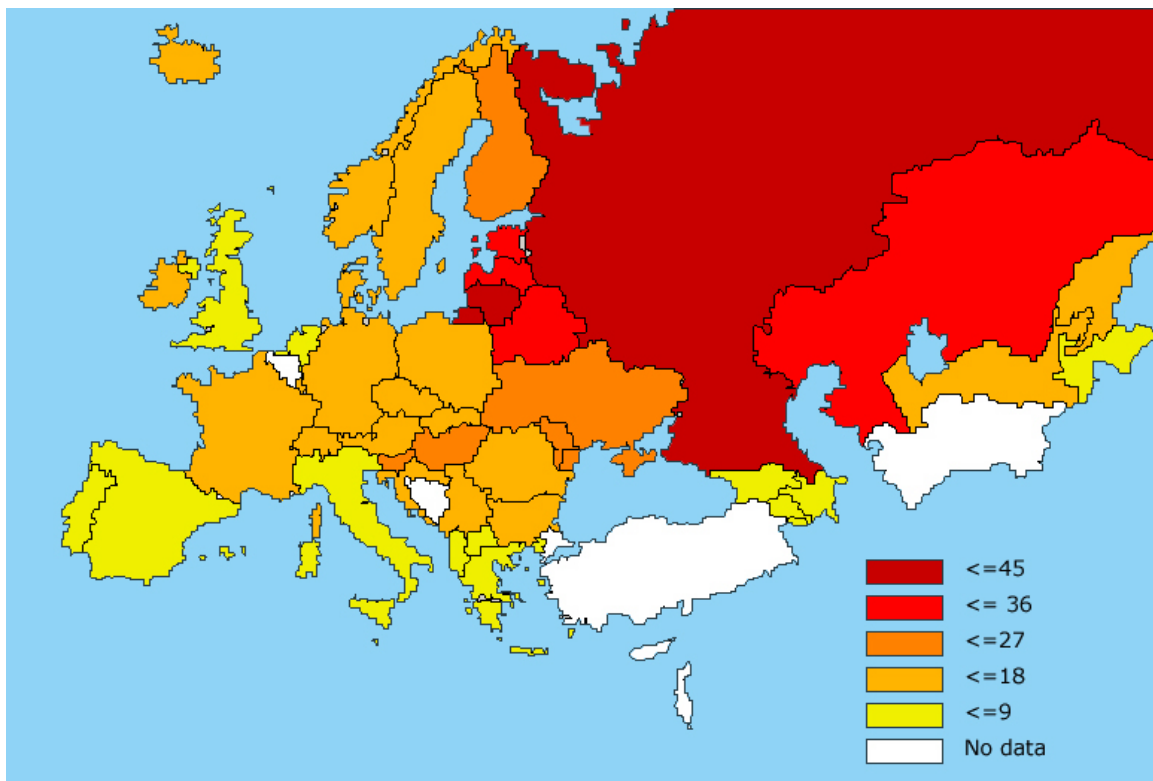


Figure 3 - SDR Suicide and all self-inflicted injuries, all ages per 100.000 in 2001 (source: WHO/Europe, European HFA Database, June 2006)

When dealing with statistics on suicide, however, caution is to be exercised. Statistics can vary from country to country, sometimes even within country depending on the source. Often suicides are not recognized as such and misclassified as accidents or natural deaths (especially in the elderly). Suicide in general is a sensitive topic, in some social contexts even more so. In some (social or religious) contexts suicide might have severe consequences (e.g. no burial on church grounds), which in turn might lead to a deliberate misclassification to spare family and friends from undesirable effects (De Leo et al. 2002).

1.3 Gender and Age Differences

For suicidal behaviour there is a pronounced gender difference. While men commit suicide 2-3 times more often than women, the gender distribution for suicide attempt is reversed (compare Figure 4 & Figure 5 for an example from the Swedish population). This gender phenomenon has been widely described and discussed (compare e.g. Canetto & Sakinofsky 1998, Hawton 2000, Qin et al. 2000). Causes have been contemplated on numerous occasions (e.g. Moscicki 1994). Explanations include amongst others different suicide methods (men tend to use more lethal methods like shooting or hanging, while women more often resort to “soft” methods like drug overdose). Supportive of this thesis would be the fact that in some Asian regions, where pesticides are a common method of suicide (lethal without immediate medical intervention), women in rural areas (with difficult access to hospital care) have similar suicide rates as men. Other hypotheses include recall bias (women might remember suicide attempts better than men), socialization (suicide attempt as a weak, female pattern of behaviour, alcohol abuse as the more common response to stress for men) or differential rates of depression and treatment (male depression is less often recognized and therefore less often treated [Rutz et al. 1995, Rutz 1999]).

Suicidal behaviour in general is strongly influenced by age. Suicide attempts have their peak in the group of teenagers and young adults (15-24 years of age). This is particularly pronounced for females. With increasing age, suicide attempts decrease on the whole, for women more strongly than for men. Gender differences disappear more and more over time until there is almost no difference in suicide attempts for men and women over the age of 65.

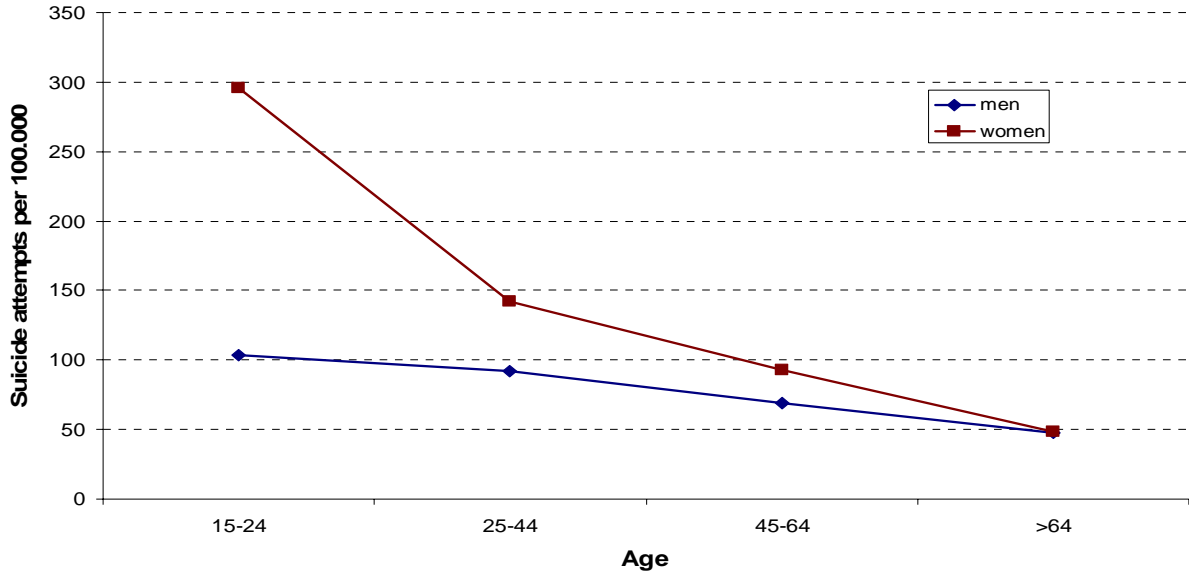


Figure 4 - Suicide attempts per 100.000 inhabitants in Sweden 2003 by age and sex (Data source: Swedish National Centre for Suicide Research and Prevention of Mental Ill-Health NASP www.ki.se/suicide)

On the other hand, rates for suicide death increase with age. For men the increase is even more pronounced than for women. As a result gender differences for suicide increase with older age. In this paper figures are presented for the Swedish population but the trends shown correspond well with global suicide rates (Bertolote 2001).

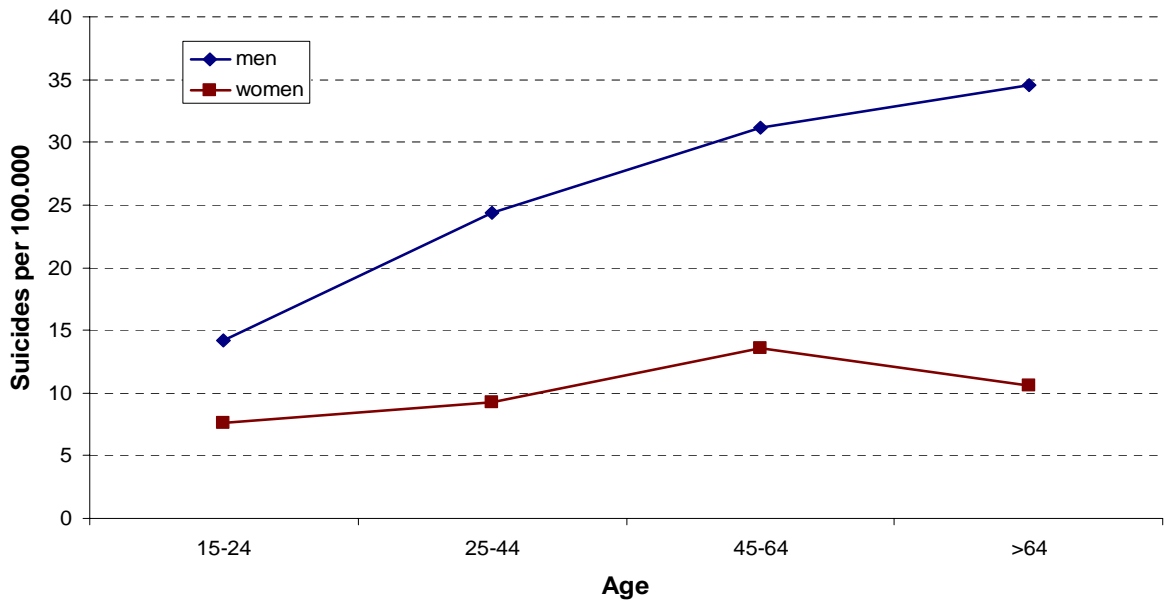


Figure 5 - Suicides per 100.000 inhabitants in Sweden 2003 by age and sex (Data source: Swedish National Centre for Suicide Research and Prevention of Mental Ill-Health NASP www.ki.se/suicide)

The relationship between suicide and age can be examined in two ways. First, looking at suicide rates there is a clear increase with age with the lowest rates in the youngest and the highest rates in the oldest age groups. However, even though the rates increase with age, the total numbers decrease due to successively smaller age cohorts. Looking at the age distribution of all suicide cases there is a clear peak in the middle age group between 35-44 years which is particularly pronounced for men (compare Figure 6).

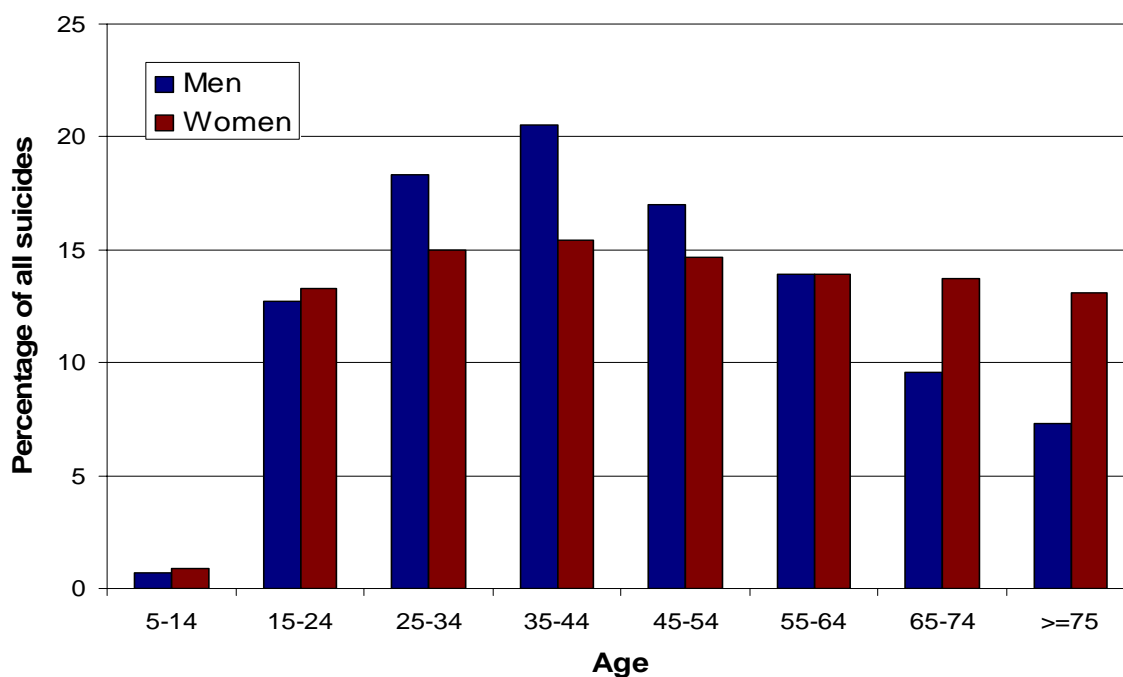


Figure 6- Percentage of all suicides³ by age and sex (Data from WHO statistics in Krug et al. 2002, p. 188).

1.4 Risk Factors

Suicidal behaviour is a complex and multifactorial issue. There are no certain predictors, but rather a multitude of factors that add to the risk and interact. The topics of gender and age have already been discussed above.

Several risk factors and certain risk groups have been identified. There are numerous ways of looking at them. A rough overview is given in the categorisation by the American Psychological Association (see Box 1).

³ Based on data from countries reporting to the World Health Organization: most recent year available between 1990 and 2000

A different way to classify risk factors is to divide them into psychiatric, biological, societal and environmental factors (e.g. De Leo et al. 2002) which will be applied in this thesis. Often forgotten in this context are protective factors which will be dealt with at the end of this passage.

Statistical risk factors for suicide (American Psychological Association)	
Demographic	<ul style="list-style-type: none">• Males in general• Gays, lesbians, bisexuals• Single, divorced, separated, widowed• Teens and the elderly• People who are living alone or who are socially isolated• Whites, Native Americans• Physicians, psychiatrists, psychologists, dentists, police officers, attorneys (white male psychologists have the highest professional suicide rate)• The unemployed
Clinical	<ul style="list-style-type: none">• Major depression• Chronic emotional or physical pain• Terminal illness• Loss of physical functioning, including neurological disorders• Loss of body parts or physical integrity• HIV, AIDS• Dialysis, dependence on others for health care• Co-morbidity
Individual	<ul style="list-style-type: none">• History of prior attempts• Family history of suicide• Family history of physical or sexual abuse or drug abuse

Box 1 – Statistical risk factors for suicide (Source: Frank A. Jones Jr., MD, University of Medicine and Dentistry of New Jersey Robert Wood Johnson Medical School)⁴

1.4.1 Psychiatric Factors

Several psychiatric and psychological factors are associated with suicidal behaviour: major depression, affective disorders, schizophrenia, anxiety and conduct disorders, personality disorders, impulsivity, eating disorders, alcoholism and substance abuse (Krug et al. 2002, Wasserman 2001, WHO 2001).

⁴ <http://www.apa.org/monitor/nov01/suiciderisk.html> (as seen on 28.09.2006)

Depression

The highest association is between suicide and depression. Depression is thought to be involved in approximately 65-90% of all suicidal actions (Krug et al. 2002). This is particularly applicable if depression is untreated (when the depression is unrecognized, the patient is not compliant or the patient or therapist consider the case as untreatable).

Schizophrenia

Also closely associated with suicide is schizophrenia. The risk for suicide in people with schizophrenia is about 40 times higher than in the general population, around one in ten people with schizophrenia will eventually die from suicide (De Hert & Peuskens 2000).

Alcohol and other substance abuse

For alcohol and substance abuse there is a particular relationship to suicidal behaviour. Overall, at least one of the factors or both are found in 25-55% of all suicidal behaviour which is clearly a higher rate than in the general population (Murphy 2000). However, especially for alcohol and substance abuse, interactions and comorbidities play an important role. Alcohol abuse can often be a sign of depression (especially by men alcohol can be used as some kind of self-medication), but might also lead to depression itself. Another factor is that alcohol (and drugs) lower the threshold for risk-taking and precipitate impulsive behaviour which in turn make suicide more likely. Furthermore alcohol abuse may also be a marker of stress and problems that lead up to suicidal action. Thus it is difficult to distinguish and determine the actual causes of suicidal behaviour and substance abuse (De Leo et al. 2002).

Previous suicidal behaviour

The relationship between previous suicidal behaviour (suicidal ideation and suicide attempts) and completed suicide is largely dealt with in literature.

Few studies have considered suicidal ideation as a predisposing factor for suicide and results have not been conclusive. Suicidal ideation is a common phenomenon, especially in teenage years. It may be part of the normal development process in adolescence, when teenagers are trying to understand the meaning of life and death (Wasserman & Narboni 2001). More than half of high school students experience occasional suicidal ideation to some degree in their lives. It is much more common in adolescents than in adults also more in girls than in boys.

Suicidal ideation is also strongly associated with other psychopathology, especially depression. There are indications that suicidal ideation is a predictor for suicide attempts. Occurrence of suicide attempts increases with intensity of suicidal ideation (Lewinsohn et al. 1996).

One of the most important predictors for suicide death (or further suicide attempts), on the other hand, is a previous suicide attempt (e.g. Hawton 1998, Hawton et al. 1998, Suominen et al. 2004). The highest risk is within the first 6-12 months after the initial suicide attempt: nearly 1% of suicide attempters will die within one year after the attempt (De Leo et al. 2002). Around 10% of people admitted to psychiatric treatment for a suicide attempt will complete suicide at some point later in their lives. Furthermore 10-50% will commit at least one further suicide attempt after the first one (Retterstøl & Mehlum 2001).

However, suicide attempters are a heterogeneous group. There are differences in the intent to die, over which there is discussion whether it should be included in the definition of suicide attempt or not, but which is hard to define (Bille-Brahe et al. 2004, Hawton & van Heeringen 2000, Schmidtke et al. 2004). Differing definitions of suicide attempt (including or excluding intent to die, misclassification of intent to die) might be partly responsible for incongruent results in this area.

There are violent and less violent methods of suicide. The first is thought to be stronger associated with later suicide as well as with familial transmission (Runeson & Asberg 2003, Rydén et al. 1990).

Repetition of suicide attempts seems to be a predictor: repeated suicide attempts are associated stronger with later suicide than single attempts (Forman et al. 2004).

To put this into perspective, however, it needs to be acknowledged that the majority of people who commit suicide have not committed a previous suicide attempt (De Leo et al. 2002).

1.4.2 Biological Factors

Suicidal behaviour is highly familial (Brent & Mann 2005). Data from twin, adoption and family studies suggest that heritable factors contribute to the risk of suicidal behaviour. In recent years molecular biological research has tried to identify certain genes involved in the onset of suicidal behaviour.

Familial Factors

A family history of suicide has been known to increase risk for suicide at all stages of life (e.g. De Leo et al. 2002, Roy et al. 2000). As risk for suicide is also associated with several psychiatric conditions, e.g. like schizophrenia (see 1.4.1) which in turn have strong heritable traits themselves (Shih et al. 2004, Sullivan et al. 2003, Tsuang et al. 2004, Tienari & Wynne 1994, Wahlberg et al. 1997), transmission of psychiatric disorders may partially account for the familial aggregation of suicidal behaviour. However, there is growing recognition that transmission of suicidal behaviour cannot be explained by transmission of psychiatric disorder alone (Brent & Mann 2005).

When talking about heritable factors it is always important to bear in mind that there usually are great interactions between the heritable part of parental diseases and the environmental part. To separate these influences and study the importance of each part twin and adoption studies are good options (see chapter 3.1).

The classic adoption study by Schulsinger et al. (1979) shows a six times higher rate of suicide in biological parents of suicidal adoptees compared with biological parents of non-suicidal adoptees. This strongly points to a genetic rather than an environmental effect. However, Schulsinger et al. did not account for major psychiatric disorders in their study. In a later adoption study of mood disorders Wender et al. (1986) found a 15 times higher rate of suicide in biological relatives of mood-disordered adoptees with a diagnosis of “affective reaction” which suggests a familial association between impulsive aggression and suicide.

In several twin studies a significantly greater concordance in monozygotic than in dizygotic twins could be shown for both, suicide and suicide attempts (Roy et al. 1991, Roy et al. 1995, Roy & Segal 2001). Here, the transmission of psychiatric disorders is also a possible confounding factor (Roy et al. 2000). However, in another twin study these results could be confirmed even after controlling for psychopathology (Statham et al. 1998).

Molecular Genetic Factors

Evidence for the heritability of suicidal behaviour has recently also been derived from molecular genetic studies (for a concise review see Courtet et al. 2005).

On the whole there is evidence that genes of the serotonergic system are involved in susceptibility to suicidal behaviour, independent of psychiatric diagnosis. Decreased serotonin

function has been seen in suicide attempters and suicide victims (Mann et al. 1999). Low levels of Tryptophan hydroxylase (TPH – the enzyme involved in the biosynthesis of serotonin), as well as low blood platelet monoamine oxidase (MAO) have been associated with suicidal behaviour or a family history of suicidal behaviour (Roy et al. 1999).

THP1 (one of the genes responsible for encoding serotonin synthesis) may be associated with suicidal behaviour in general. 5-HTT (serotonin transporter) seems to be linked to violent and repeated suicide attempts and MAOA (gene for monoamine oxidase A) may act on aggressiveness (Courtet et al. 2005).

However, genetic factors do not influence the risk of suicide alone but rather determine the susceptibility for suicidal behaviour in interaction with environmental factors. In a recent study Caspi et al. (2003) found a functional polymorphism in the promoter region of the serotonin transporter (5-HTT) gene to moderate the influence of stressful life events on depression and suicidal behaviour, thereby indicating a gene-by-environment interaction.

1.4.3 Societal and Environmental Factors

Apart from the individual factors like biological and personal factors, society and environment also play a certain role in the origins of suicidal behaviour. Social class, educational level, occupation, residency and housing, marital status but also employment situation or general societal economy have been associated with suicidal behaviour.

Social class, education, occupation and employment

Risk of suicide is inversely related to social class: the lower the social class, the higher the suicide rate (Platt & Hawton 2000). The same is true for suicide and education: suicide rates generally decrease with increasing educational level (Centre for Epidemiology, National Board of Health and Welfare 2000). However, there are certain occupational groups that are at high risk for suicide despite their social class and educational level. They include the medical professions and allied disciplines (e.g. Platt & Hawton 2000). The relationship between unemployment and suicide is slightly more complicated. In general, unemployment is also associated with an increased risk for suicide, though results have not always been consistent (e.g. De Leo et al. 2002, Platt & Hawton 2000).

Residency

There are considerable differences between rural and metropolitan areas in regards to suicidal behaviour. Several studies from Western countries have suggested that suicide rates are generally higher in urbanized areas than in rural areas (e.g. Isometsa et al. 1997, Mortensen et al. 2000, Qin et al. 2000). However, this is largely due to an accumulation of risk factors in urban areas such as substance abuse, psychiatric disorders and less stable familial situations. Qin (2005) found a significant variation of suicide risk associated with urbanicity by sex and age groups: Living in an urban region increases risk of suicide for young women, while among men risk was reduced.

Other studies have found high suicide rates in men in rural areas, especially farmers. Explanations for those include social isolation and greater difficulties in detecting warning signs. In Eastern Europe and parts of south East Asia herbicides are an easily available method of suicide, particularly in rural areas. In combination with inferior access to medical care this contributes to increasing rates of suicide in rural areas (compare De Leo et al. 2002).

1.4.4 Life events

Certain negative life events have been known to precipitate suicides or suicide attempts. It is important to acknowledge that neither the simple occurrence nor the number of life events is the decisive, but rather the way a person perceives those events and the meaning he or she attributes to them (Kolves et al. 2006, Wasserman 2001b & 2001c). In a recent study by Kolves et al. (2006) the authors found that men were more susceptible to life events as a risk factor for suicide than women.

Negative life events that precede a suicide or suicide attempt can be actual and threatened losses (Wasserman 2001b):

- loss of a significant other (e.g. partner, relative, friend) through separation or death, thus including divorces
- loss of national or cultural affiliation
- loss of health (somatic as well as mental health)
- others' loss of health or life (for young women abortion, regardless if voluntary or involuntary)
- loss of employment, study opportunities and financial position

Hospitalization or discharge from hospital can be a risk factor, especially for chronically ill or psychiatric patients. Changes in life situations as well as fear of change are further factors. Relationship problems should be accounted for. Lastly traumas as violence, physical and mental abuse as well as war and natural disasters can play an important role in the genesis of suicidal actions (Wasserman 2001b).

1.4.5 Protective Factors

Traditionally, suicide research has been mainly focusing on risk factors. Studies on protective factors are still rare and a new field, even though already Durkheim (1897/1951) described some protective factors in his work. Durkheim described a protective effect of high religious integration. Results from recent studies on this topic have been mixed (De Leo et al. 2002). Especially when talking about suicide rates in highly religious communities a potential underreporting bias needs to be seriously considered (compare 1.2).

Another observation of Durkheim is less controversial and coherent with recent results: the protective effect of marriage and parenthood. Marriage and parenthood lower the risk for suicide (Hoyer & Lund 1993). Parenthood (especially with young children) lowers the risk for suicide significantly, even independent of marital status. This effect is stronger for women than for men (Qin & Mortensen 2003). During pregnancy Marzuk et al. (1997) found a significantly reduced risk for suicide. The effect of marriage is less clear. It is often discussed that it might be the presence of children - and not marriage itself – that protects women from suicide. Divorce, especially in men, has been established as an important risk factor (compare Kposowa 2000), but studies on the protective effect of marriage have so far been inconclusive. On the whole, the study of protective factors constitutes an interesting and promising field for future research that will also convey new possibilities and perspectives for suicide prevention.

1.5 Prevention

Prevention of suicide is a challenge to society. Preventing suicide includes identifying the problem in its various dimensions, understanding risk (and protective) factors, developing interventions and evaluating the success of those.

According to the WHO suicide is an urgent problem in health politics. The WHO and the United Nations have suggested strategies for suicide prevention and some European countries have implemented national suicide prevention programmes accordingly.

In a worldwide approach to improve knowledge on risk factors and the situation in general, several large studies have been launched by the WHO. The WHO/EURO Multicentre Study on Suicidal Behaviour (Schmidtke et al. 2004) has been an important step in that direction in Europe. Worldwide the SUPRE-MISS (WHO Multisite Intervention Study on Suicidal Behaviors [MISS] within the WHO worldwide initiative of the prevention of suicide [SUPRE]) aims to identify both specific risk factors and specific interventions effective for the reduction of suicidal behaviour (Bertolote & Fleischmann 2005).

Prevention efforts have been made as early as 1900. So far there has not been a major breakthrough yet. In evaluations mixed results have been reported (Bertolote 2004).

Generally there are two ways to approach the problem: the health care approach and the public health approach. While the health care approach focuses on patients, relatives and health care personnel, the public health approach targets the general public with focus on specific areas such as school, workplace, organizations or housing areas (Wasserman 2001d).

According to Bertolote (2004) some of the major interventions to prevent suicide are:

- ***Reduction of access to methods and means of suicide***

This is an effective approach. It has been shown that reducing the access to means of suicide like closing hot spots (e.g. “popular” bridges or railway tracks) has reduced the number of suicides (Lester 1998).

- ***Treatment of people with mental disorders***

On a general level the association between better treatment of psychiatric disorders and decreasing suicide rates is not very clear. However, when considering specific disorders like depression there is good evidence for a preventive effect (as has been discussed before in chapter 1.4.1).

- ***Improvement of media reporting***

There is evidence that “spectacular” reporting of suicides in the media can trigger a cluster of suicides (Hawton & Williams 2002, Schmidtke et al. 2001). Interventions at this point have shown to be effective (Schmidtke & Schaller 2000).

- ***Training of primary health care personnel***

An impressive example is the decrease of suicides in Gotland (Sweden) after a specifically designed programme to train General Practitioners (Rutz et al. 1989).

- ***School-based programmes***

School-based suicide programmes have been established in several countries, e.g. New Zealand, USA and Sweden. Most aim at promoting better physical and mental health, which in turn helps suicidal pupils and their schoolmates to improve their life skills, social competence and capacity to relate to and maintain relationships with others. On the other hand early recognition of pupils at risk is vital in order to start early intervention (Wasserman & Narboni 2001).

- ***Availability of hotlines and crisis centres***

There is no evidence towards the effectiveness of suicide prevention, but it seems their efficacy to help people in crisis in general is far greater than their impact on suicide rates.

2 Register Studies in Sweden

Sweden has a long tradition of national registers with high quality data on health as well as socioeconomic indicators for the entire population. These data can be linked using a unique personal identification number. The registers are held by the Swedish National Board of Health and Welfare and Statistics Sweden and provide excellent opportunities for research.

2.1 Personal Identity Number (Personnummer)

The personal identity number is typical to all Nordic countries. It is an individual number that follows each resident from birth to death and thus makes it possible to identify and follow individuals even if they move house or marry (and change their name). It enables researchers to follow individuals through time within the registers. In Denmark, Finland, Iceland and Sweden it is possible to link data from different sources (after ethical committee approval) whereas in Norway there are more restrictive policies.

The personal identity number in Sweden was introduced in 1947 (and modified 1967). It is formed by date of birth, birth number (three-digit-number even for women, uneven for men, thus automatically indicating the person's sex) and a check digit. Personal identity numbers are allocated by the Swedish tax authorities at birth or immigration to Sweden (Swedish Tax Agency 1999 & 2004).

Information in the population register includes amongst others name, personal identity number and coordination number, place of birth, citizenship, information on family status (civil status, date of marriage, spouse, children, parents, adoption), address, property, parish and municipality, immigration to and emigration from Sweden. All changes and old information are saved as well (Swedish tax agency 2004).

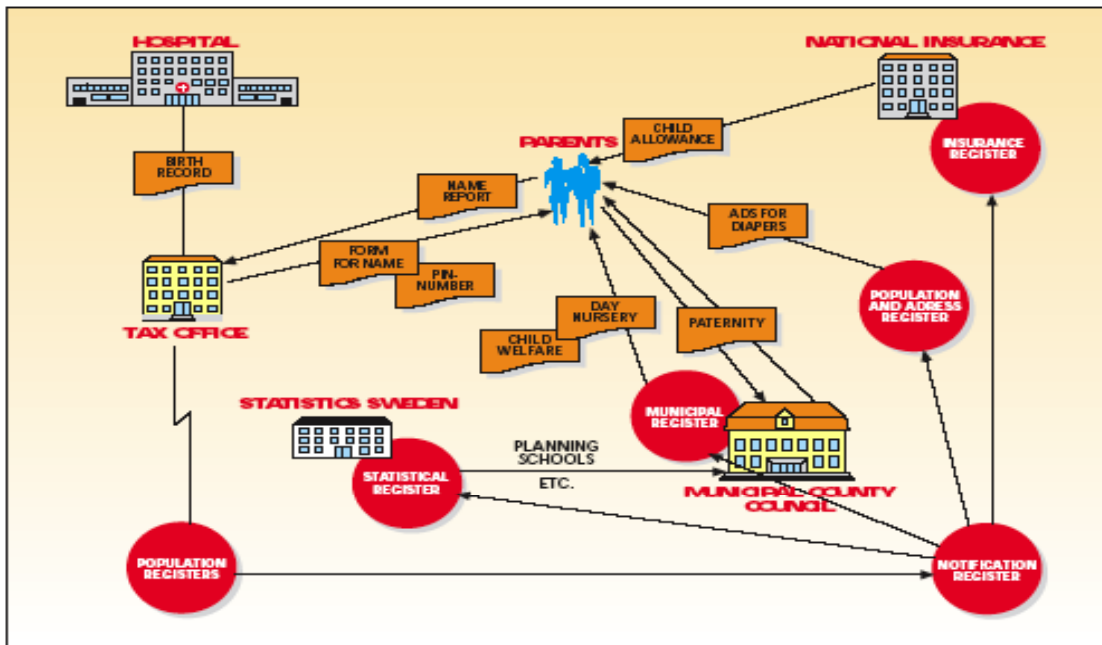


Figure 7- Usage of the personal identity number (Swedish Tax Agency 2000, p. 12)

2.2 Swedish Health Registers (Overview)

National person identified health registers are kept at the Swedish National Board of Health and Welfare (Socialstyrelsen). They cover the whole Swedish Population and linkage to other data sources is possible.

Some of the most important registers are:

- ***The Patient Discharge Register***
(Covers all health care episodes in public and private hospitals since 1987)
- ***The Cancer Register***
(Covers all malignant primary tumours since 1958)
- ***The Medical Birth Register***
(Holds medical data on all births since 1973)
- ***The Register of Congenital Malformation***
(Includes information about malformation diagnoses of child/foetus, since 1965)
- ***The Cause of Death Register***
(Covers all deaths since 1952 recorded on data medium, on paper much further back)
- ***The Prescription Drug Register***
(Newest register that contains all prescription drugs sold as from July 1, 2005)

Data in those registers can amongst others be linked to data from the census (held every 5 years), the crime register, information about social welfare and child welfare.

For men data on military conscripts is available and can also be linked containing information at recruitment (e.g. psychological assessments etc.).

(Swedish National Board of Health and Welfare 2003 or 2006).

2.3 Use of the Registers

The Swedish National Health registers constitute a unique “goldmine“ for research. Every year there is a multitude of research articles published in international journals, with results that have implications worldwide.

2.3.1 Possibilities

There are many advantages of the registers. They provide high quality data which is readily available with long follow-up periods. Registers include both sexes, all age groups, all parts of the countries. This is an advantage, because many studies focus mainly on middle aged, white men thus providing a selection bias in a way that women, children and the elderly are not represented and results might not be valid for these groups (in lack of other information results are applied to all). Data can be individually linked thus not leaving correlations at an aggregate level and existing registers can also be cross linked opening a huge number of new possibilities and opportunities. The studies using the national registers are time and cost effective, because the data is already at hand and does not have to be collected from scratch for each new study (compare Swedish National Board of Health and Welfare 2003, Rosen 1993 & 2002). In the following a few examples of those possibilities will be provided (for a concise review see Swedish National Board of Health and Welfare 2003 and Rosen 2002).

Important results due to large sample sizes

One remarkable example is the study of a possible association between newborn vitamin K injection and childhood cancer.

In a large case-control study by Golding et al. published 1992 in the BMJ the authors found a significant association between intramuscular vitamin K injection to newborns and childhood cancer. As in many countries worldwide vitamin K is routinely administered to newborns as a preventive measure against brain haemorrhage. The results caused some uproar as this would

greatly affect common practices. Sweden was one of the countries affected and the government commissioned a new study on the topic. The resulting Swedish study by Ekelund et al. published one year later (1993) also in the BMJ did not show such increased risk. By linkage of hospital admission, birth and cancer register the study could be completed in only 3 months and had a study population of about 1.5 million (2.300 cases of childhood cancer and 1.3 million controls) thus exceeding the number of the case-control study (195 cases, 558 controls) by far. Later studies have been able to confirm and replicate the Swedish results and prevention policies in several countries were influenced by it (compare Rosen 2002).

Early detection of medical complications

The Medical Birth Register has otherwise also produced interesting results on the risk of smoking during pregnancy, but also pregnancy outcomes e.g. after the Chernobyl accidents (Rosen 2002). In this context the Register of Congenital Malformation is to be mentioned which was established in 1965 as a reaction to the thalidomide tragedy and serves as an early warning-system to pick up on such events earlier in the future and prevent further damage (Swedish National Board of Health and Welfare 2003).

Monitoring of social inequalities

By connecting data from the health registers with data from census and housing data a study of social inequalities and health risks is possible. In this context socioeconomic differences for several diseases can be assessed. Hallquist et al. (1998) found for example, that low socioeconomic status is associated with myocardial infarction in men and even though myocardial infarctions have been decreasing over time, the relative risk for manual workers actually increased in Sweden.

Studies by Ringbäck Weitoft et al. (2000) have drawn attention to the adverse situation of lone mothers who have clearly higher risks of being admitted to hospital for a multitude of illnesses or even die earlier than mothers in a relationship, even after controlling for financial situation and socioeconomic factors. Recent studies also indicate elevated risks, for injuries and addiction as well as suicide and other preterm deaths for lone non-custodial fathers and lone childless men (Ringbäck Weitoft et al. 2004).

2.3.2 Limitations

Obviously, as in any kind of study, there are important limitations to register studies. Some concern the data collection. As data is collected continuously and generally (not specific to each study), it is collected without specific diagnostic criteria in advance. The focus lies more on outcomes. Another major limitation of this kind of study is that the number of variables collected is strictly limited, which makes it harder to control for confounders (Centre for Epidemiology, National Board of Health and Welfare 2000). However, this problem can in some cases be dealt with by combining data collection from specific research projects with national health data, e.g. data from twin register, where additional information is collected for specific research projects (Karolinska Institutet - Department of Medical Epidemiology and Biostatistics 2006).

2.3.3 Special statistical considerations

When dealing with large data bases and huge amounts of data certain statistical considerations have to be taken into account that differ slightly from considerations in smaller studies. Power, for example, is much less often an issue when you deal with study populations of one million or even more. On the other hand there is the problem of mass-significance. When considering a confidence interval of 95%, if results become statistically significant, it means that in 95% it will not have been a chance finding. This implies however, that in 5% it will. Especially in the age of advanced computer technology it is easy to run a multitude of statistical analyses. Here great caution is to be exercised, because if 100 analyses are run, 5 might turn out as statistically significant purely by chance. Therefore, particularly in this type of study research questions must be well formulated and hypotheses generated accordingly.

Standardisation of data is another issue. In long follow up periods classifications (e.g. ICD) will be changed. Here it is vital to check if the variable changes or if it can be used throughout time. Changes in population & exposition need to be considered like in all cohort studies following large populations over long time. In registers like the Swedish Health registers data quality is crucial. From continuous evaluations so far a constant and good quality has been indicated (Centre for Epidemiology, National Board of Health and Welfare 2000, Swedish National Board of Health and Welfare 2003). The Cause of Death Register covers all deaths, however the underlying medical reports are missing in about 0.5% of cases. The accuracy of

diagnoses are investigated usually every second year by independent studies of random samples (Official Statistics of Sweden 2004). In cases of unclear circumstances of death, the National Board of Forensic Medicine may initiate an autopsy (National Board of Forensic Medicine 2004)

2.4 Ethical Considerations

2.4.1 Data collection

In general, person identified information can be collected and stored only after the explicit informed consent of the individual. Person identified health information has been considered particularly important as well as sensitive, therefore in addition to the rules that follow from the EU directive, Sweden has special legislation for health data: the Health Data Act, which contains basic rules for the collection and procession of health data. Currently these rules permit and prescribe the collection of person identified information by central government authorities without acquiring the consent from the individual. However, person identified health data can solely be used for research, statistics, and follow-up of health care (Swedish National Board of Health and Welfare 2006).

At regular intervals the authorities have the duty to inform the general public about the existence and content of the person identified registries.

2.4.2 Principles of public disclosure and confidentiality

In Sweden, all information kept by the public authorities is considered public property and therefore must be shared with the general public if requested (→ principle of public disclosure). However, if the information is person identified and might be potentially harmful to the individual if made public, it is protected from public disclosure (→ secrecy). In this context the Swedish law also requires all research using person identified data to be approved by an ethics committee. This committee can either call for the researcher to acquire personal approval to use the data from the research subjects, or it can substitute the informed consent of the individual by a committee approval if the research is considered to be of great importance for society (Swedish National Board of Health and Welfare 2006).

2.4.3 Informed consent, personal integrity and the public good

Beauchamp & Childress (2001) define in their standard setting work four principles of biomedical ethics:

1. Respect for Autonomy
2. Nonmaleficence (doing no harm)
3. Beneficence (acting for the patient's benefit)
4. Justice

These four principles influence each other, often even contradict each other. Ethical considerations always include balancing them against each other and making the best possible decision which will be a trade off between advantages and disadvantages.

Informed consent (“an individual’s autonomous authorization of a medical intervention or participation in research“ Beauchamp & Childress 2001, page 78) is an important part of the principle of autonomy.

Even though the actual term “informed consent” wasn’t institutionalized until the Helsinki Declaration (Tokyo version from 1975), the concept was established as early as 1947 in the context of the Nürnberg processes where it was agreed that - after the atrocities of the Nazi regime - research should never again be conducted without the individuals’ consent (Wunder 2001). The Swedish registers follow the Helsinki Declaration⁵ and are also governed by national legislation.

Interestingly, in Swedish discussions on the subject not only the principles autonomy, justice, beneficence and nonmaleficence are considered, but also the principle of solidarity is discussed in this context which does not appear in the original works by Beauchamp & Childress (2001). This reflects a strong emphasis on the public good.

Decision about register research is always a trade off between benefits and risks. One of the most important risks is the potential threat to personal integrity by registration. Studies show that for around 4% of the Swedish population this is an issue. A personal consent would solve this problem. However, due to the extent of the registers and the magnitude of the study population no register research would be possible anymore and the results would be lost for the general public (thus restricting the benefits for the public and the public good). Therefore,

⁵ developed by the World Medical Association as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects; <http://www.wma.net/e/policy/b3.htm> as seen on 22.09.2006

in Sweden the government has given informed consent on behalf of the population as benefits are considered to outweigh the risks (Rosén 1993 and 2002).

[To apply Informed consent on the Swedish National Registers] „would substantially hamper clinical work and take resources from other important health service tasks. Here the principles of doing good and justice or solidarity outweigh that of autonomy“...

„The knowledge derived from information on past and present patients and will contribute to the benefits of future generations“ (Rosén 2002).

„The conclusion is that it would be unethical not to take advantage of the abundant source of data represented by the disease registers“ (Rosén 1993).

Box 2 - Informed consent and the Swedish National Health Registers

2.5 Conclusion

In conclusion the Swedish Health Registers provide an excellent data source for epidemiological research. The results derived from these data sources have had great importance not only for Sweden and the Scandinavian countries, but worldwide. When talking about ethical decisions, the point of financial resources should never be underestimated. Using already existing data - instead of starting from scratch in every new study – is also rational from an economical perspective. Especially in times of scarce financial resources such an approach can save money which in turn can be invested in other necessary fields within the health sector. Moreover it saves time that can be dedicated to data analysis and bringing out important results more quickly (illustrated with the vitamin k example above), which might even save lives.

Therefore, to take the words from Mans Rosén (2002), head of the Epidemiological Centre at the Swedish national Board of Health and Welfare, it would be “unethical not to use the registers”!

3 Adoption Research

Looking at studies with adoptees as study population there are two main types used in different research areas.

One type is the “classical” adoption study using the adoption process as a “natural experiment” where children are through non-study related circumstances separated from their birth families and brought into new surroundings which can be used to study the influence of genetic/heritable and environmental factors for a multitude of outcomes.

The other type of study is the adoption research looking at adoption and the adoption process in respect to the outcomes of children with this background, thus referring to the specific group of adoptees, their special risks and risk factors.

3.1 Studies Exploring the Importance of Genetic & Environmental Factors

“Because adopted children are raised in families in which they have no genetic relationship with their parents, and possibly none with their siblings, they provide a rare opportunity to study the relative importance of genetic, shared environmental, and nonshared environmental influences on the development of child characteristics and behaviours.”
(Haugaard & Hazan 2003)

In the above citation the distinct features of adoption studies are well expressed.

Adoption studies are based on the assumption that individuals separated at birth, or shortly afterwards, share their genes, but not subsequent environmental experiences with their biological relatives. On the other hand, adoptees share their environment and related experiences throughout their development and growing up with their adoptive relatives, even though they don't share genes with them. This makes it possible to study familial aggregation of certain diseases or disorders without the confounding effects of shared environments (Roy et al. 2000).

The assumption behind this is that individual differences result from either genetic or environmental factors. If genetic factors have a predominant role, then individuals who are genetically related should be more similar than those who are not. If environmental factors pose major influences then individuals who have been reared in the same environment should

be more similar than those who have grown up in different environments (Haugaard & Hazan 2003).

However, neither genetic nor environmental factors act on their own. They are considerably intertwined. For example there are certain genetic factors that may have influence on a person's ability to shape an environment in which they can develop best. If genetic factors predispose a person to e.g. aggressive behaviour this in turn will influence the likelihood of experiencing negative life events like conflicts with friends and family, or potential marriage or divorce (Rutter 2006).

Adoption designs have been used in a variety of studies concerning a multitude of diseases and disorders. Some of the most prominent and elaborate ones have been carried out in the field of schizophrenia research. Both understanding and treatment of schizophrenia have been inhibited amongst others by insecurity about etiological factors. Adoption studies have helped to clarify these problems by providing evidence for both, genetic and environmental factors, as well as joint effects (Tienari & Wynne 1994).

In suicide research adoption studies have been providing a valuable resource together with twin studies implying that both genetic and environmental factors as well as the interaction between them play important roles in the genesis of suicidal behaviour (compare 1.4.2).

However, there are also ethical considerations when talking about adoption studies or, more precisely when considering the effects of genes and environment separately.

In Nazi Germany the results from studies concerning the importance of hereditary factors in mental disorders were misused to justify the doctrine of "racial hygiene" and the eugenic movement (Cooper 2001). Similar consequences in more recent days can be found in China, where a new eugenic law was formed as recent as 1994 (Mao 1997).

In a different, but also important context ethical consequences of knowledge about genetic factors come to mind concerning possible genetic screenings before job contracts or within insurance companies. This needs to be thoroughly weighed against the advantages of such research concerning better treatment, but also better prevention opportunities as discussed above.

In conclusion this is a very valuable type of research that will continue to have great importance, amongst others especially in the field of suicide research where molecular genetic research has not come to sustainable conclusions yet, but, as all other research addressing the

topic of nature/nurture discussion, needs to be treated with great care concerning the implications and possibilities of misuse.

3.2 Studies of Adoption Process and Outcomes

Historically, studies of adoption outcome have constituted the smaller proportion of overall adoption studies. However, it is an important field that is gaining importance with time as the number of adoptions is constantly rising. In most urbanized countries there has been increasing interest in adoption with growing numbers of couples with difficulty to conceive children. On the other hand the number of children for adoption within these countries has decreased with improved birth control methods, changes in abortion legislation, but also changed attitudes towards single mothers as well as improved societal support for this group, thus bringing international adoption more and more into focus.

About 30 000 children are adopted internationally per year in the world and over 100 countries are involved. Sweden has a special relation to international adoption: it is the country with the largest population of intercountry adoptees in Europe (over 44 000 adoptees today), and the highest per capita population of intercountry adoptees in the world (Cederblad et al. 1999, Selman 2002). Intercountry adoptees make up about 0.5% of the Swedish population and approximately 1 child out of 10 immigrating to Sweden under the age of seven without Sweden as country of birth is internationally adopted.

Previous studies from our research group have highlighted several problem areas for international adoptees in Sweden (Table 2). Suicide is one of them.

After adjustment for major sociodemographic confounders, intercountry adoptees have pronouncedly higher risks to die from suicide (OR 3.6 [95% CI 2.1-5.9] or attempt suicide (3.6 [3.1-4.2]) than their non-adopted peers (Hjern et al. 2002). In an adult population national adoptees also exhibit significantly higher risks than non-adopted peers for both suicide attempt (2.8 [2.2-3.5]) and suicide death (2.5 [1.8-3.3]), but international adoptees still showed even more pronounced risks for these outcomes: suicide attempt (4.5 [3.7-5.5]) and suicide death (3.6 [2.6-5.2]) after adjustments for sex, age and socioeconomic factors (von Borczyskowski et al. 2006).

In both studies the hypotheses of heritable factors were discussed, however the first study (Hjern et al. 2002) did not have any information on the international adoptees' biological

parents (as they are outside of Sweden and therefore not included in the registers). The study by von Borczyskowski et al. (2006) had access to information about the national adoptees' biological parents and a certain association between biological parents' risk factors and suicide in the adopted away offspring was found. However, the cohort was too young and not enough national adoptees with information on their biological parents were included to provide satisfying results in this respect. Thus the following study was initiated to explore the influence of heritable traits and environmental factors for suicide in an adoption design (section 5).

Table 2 - Previous studies on international adoption in Sweden

	Hjern et al. 2002	Lindblad et al. 2003	Hjern et al. 2004	von Borczyskowski et al. 2006	Vinnerljung et al. in print
Birth cohort	1970-79	1968-75	1973-82	1963-73	1973-82
Total N	871,088	743,358	989,871	1,274,312	989,871
Outcome variables	<p>Indicators of mental health disorders (Suicide death, suicide attempt, psychiatric hospital care)</p> <p>Indicators of social maladjustment (Alcohol abuse, drug abuse, any criminal offence, severe criminal offence, imprisonment)</p>	<p>Family situation (Civil status, number of children)</p> <p>Education</p> <p>Position in the labour market (Unemployment, social welfare)</p> <p>Health problems (Health-related benefits, psychiatric illness, addiction)</p>	<p>Suicide deaths</p> <p>Other avoidable deaths (Deaths related to substance and alcohol abuse, other avoidable natural causes, unintentional injuries, homicide)</p>	<p>Suicide attempt</p> <p>Suicide death</p>	<p>Suicide attempt</p> <p>Psychiatric disorder</p>
Outcome period	<p>1986-95 (suicide death)</p> <p>1986-93 (court sentences)</p> <p>1987-94 (psychiatric illness, suicide attempts, substance abuse)</p>	1997-1999	1991-2000	<p>1987-2002 (suicide attempt)</p> <p>1987-2001 (suicide death)</p>	1990-2000
Ages observed	7-25 years	22-31 years	9-27 years	14-39 years	8(13)-27 years
Study groups	<p>11,320 intercountry adoptees</p> <p>2,343 Swedish-born siblings,</p> <p>4,006 immigrant children</p> <p>853,419 members of the remaining general population</p>	<p>5,942 intercountry adoptees</p> <p>1,884 Swedish-born siblings</p> <p>8,834 European immigrants</p> <p>3,544 non-European immigrants</p> <p>723,154 members of the remaining general population</p>	<p>12,240 intercountry adoptees</p> <p>6,437 foster children</p> <p>15,868 subjected to other forms of child welfare interventions</p> <p>955,326 members of the remaining general population</p>	<p>6,065 international adoptees</p> <p>7,340 national adoptees</p> <p>1,378 siblings of national adoptees</p> <p>3,616 siblings of international adoptees</p> <p>1,269,318 members of the remaining general population</p>	<p>22,305 former child welfare clients (with intervention before their teens)</p> <p>12,240 intercountry adoptees</p> <p>955,326 members of the remaining general population</p>

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5 Manuscript for Submission

Familial Factors and Suicide – an Adoption Study in a Swedish National Cohort

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Background: Research using different approaches has shown that heritable factors contribute to the risk of suicide. A methodological complication when estimating the genetic contribution is that suicide of a parent also implies altered psychological and social conditions for the offspring. Adoption studies provide a good opportunity to address this problem.

Material and Methods: The study population consisted of all Swedish residents in 1986 that were born 1943-1968, a total of 2,942,932 individuals (33,240 adopted). 10,814 individuals (210 adopted) committed suicide during the follow-up period from 1987 until 2002. Hazard ratios for the risk of suicide were calculated in a multivariate analysis using Cox regressions of person time in the study taking childhood household characteristics and psychiatric morbidity of the biological parents into account.

Results: Biological parents' suicide as well as severe psychiatric illness influenced the suicide risk in both groups, adoptees and non-adopted, with HRs of 1.99 (95%CI 1.78-2.23) and 1.51 (1.35-1.70) in the non-adopted and 3.54 (1.67-7.52) and 3.00 (1.36-6.61) in the adopted group. Biological parents' alcohol abuse was a clear risk factor in the non-adopted group (HR 1.88 [1.73-2.94]), but it did not influence the suicide risk in the adopted group (HR 0.85 [0.44-1.65]). Growing up in a single parent household also implied an increased risk, just as urbanicity for women.

Conclusions: Heritable as well as environmental factors contribute to risk of suicide. Further studies are needed that elucidate the interaction between the two. It is notable that alcohol abuse in parents increases the risk of suicide in the offspring only when the offspring is raised in the household of the addicted parent. These results highlight the preventive potential of psychosocial intervention for this exposed group of children.

Introduction

Strong evidence from family, twin and adoption studies supports the hypothesis that heritable factors contribute to the risk of suicide (for review see e.g. Brent & Mann 2005). Baldessarini & Hennen (2004) found extensive evidence for a familial transmission of suicidal behaviour, analyzing 21 large family studies, where risks for suicide and severe suicide attempts were calculated for close relatives of index cases with suicidal behaviour. Risks were up to five-fold elevated in families of index cases. However, in family studies effects of gene and environment (nature-nurture) are considerably intertwined, e.g. a suicide in a parent is not only a biological risk factor, but at the same time a traumatic loss for the survivors, thus influencing their psychosocial conditions. Having experienced the suicide of the parent may also hypothetically inspire suicidal behaviour in the offspring. Twin studies offer better possibilities of isolating the effect of these two factors. In several twin studies a significantly greater concordance for both - suicide and suicide attempts - in monozygotic than in dizygotic twins has been demonstrated (e.g. Cho et al. 2006, Roy et al. 1991, Roy et al. 1995, Roy & Segal 2001, Statham et al. 1998). Adoption studies offer even better possibilities to separate genetic effects from effects of the psychosocial loss of someone close. Adopted children who are separated from their biological parents at birth or shortly afterwards share their genes, but not the environmental effects of a parental suicide. This enables the researcher to look at both factors separately. So far, there have been three large adoption studies addressing the topic of familial factors and suicide, all using the same Danish adoption and health registers: Kety et al. (1968), Schulsinger et al. (1979) and Wender et al. (1986). In their classical adoption study from 1979 Schulsinger et al. found a six-fold elevated rate of suicide in the biological relatives of adoptees that had committed suicide compared to relatives of non-suicidal adoptee controls, but no suicidal behaviour among their adoptive parents. However, heritability of major psychiatric risk factors for suicide, as affective and psychotic disorders or substance abuse, was not taken into consideration. Seven years later, Wender and colleagues (1986) carried out an adoption study on affective disorder within the same Danish adoption registry. In biological families of adoptees with affective disorder they identified a 15-fold increased risk of suicide compared to biological families of adoptee controls. One underlying mechanism may be a link between impulsive aggression and suicide (see also Brent & Mann 2005).

It has been well established that suicidal behaviour in men and women differs (Hawton 2000). While men commit more suicides, women have a higher rate of suicide attempts (e.g. Canetto & Sakinofsky 1998, Moscicki 1994, Qin et al. 2000). There are indications that the effect of certain risk factors could differ between men and women (e.g. von Borczyskowski et al. 2006, Motto & Brostrom 1997, Wannan & Fombonne 1998). However, to our knowledge very few studies have specifically addressed the topic of gender differences for heritable factors for suicide. Molecular biological studies have suggested gender specific differences concerning genetic factors, especially for suicide attempts (Baca-Garcia et al. 2002, Tsai et al. 2003). In a large twin study Cho et al. (2006) reported gender differences in the heritability of suicide risk factors, suggesting that genetic contributions for risk factors are, at least partly, gender-specific.

Sweden has national registers of the whole population which can be linked through an individual's unique personal identification number, which follows each resident from birth to death, and provide information on sociodemographic as well as health data. Using linkage to the Multigeneration Register, this data can be identified for adoptees as well as their biological and adoptive parents. As the Swedish Registers cover the whole population large datasets can be created so that even rare outcomes like suicide can be studied in small populations like adoptees.

With the aim of studying and comparing the influence of heritable traits and environmental factors in suicide we address the following research questions in an adoption design:

- 1) To what degree is the risk of suicide influenced by psychiatric morbidity of biological parents in adopted versus non-adopted individuals?
- 2) To what degree is the risk of suicide influenced by childhood household characteristics in adopted versus non-adopted individuals?
- 3) Are these influences equally important for men and women?

Material and Methods

The study population consisted of the entire Swedish population, born between 1943 and 1968, that were resident in Sweden on December 31st 1986 according to the Register of the Total Population (RTP); 2,942,932 individuals. This population was followed prospectively in the Swedish national registers from 1987 until 2001.

Within this population a subgroup of 33,240 national adoptees was identified by records of an adoptive father and an adoptive mother and Sweden as a country of birth. Partner and other family adoptions (adoptions by an older sibling, grandparent, or sibling of the biological parents) were excluded.

5.1.1 Sociodemographic variables

Year of birth, sex and geographic location of the home (residency) of the study population were identified in RTP in 1986.

Data on the families' socioeconomic background was derived from the latest Swedish Population and Housing Census before the study subjects turned 18. For those born 1943-52 it was the 1960 census, for those born 1953-62 it was the 1970 census, for those born 1963-68 it was the 1980 census, and for those born 1968 it was the 1985 census. Variables that were identified for the childhood household socioeconomic background were socioeconomic status (SES), residency, housing, single parenthood and maternal age (the mother's age at the time of the child's birth). For the adoptees these variables refer to their adoptive families unless stated otherwise.

Socioeconomic groups were defined according to a classification used by Statistics Sweden, which is based on occupation but also takes educational level of occupation, type of production and position at work of the head of the household into account (Statistics Sweden 1982). In this study a simplified categorization identifying blue collar, white collar and unclassified (including missing, unemployed and other that do not fit into the first two categories e.g. self employed) was used.

Parental morbidity

Data on parental risk factors were obtained through individual record linkage to the Swedish Hospital Discharge Register (SHDR) for the years 1987-2002 and the National Cause of Death Register (NCDR) from 1960-2002. The variables were defined according to the 6th and 7th (1960-68), 8th (1969-86), 9th (1987-96) and 10th (1997-2002) revision of the WHO International Classification of Diagnosis (ICD 6-10):

Suicide death (an underlying cause of death of code E970-979 [ICD6-7], E950-959, E980-989 [ICD8-9] or X60-X84, Y10-Y34 [ICD10]);

Suicide attempt (a main or contributory diagnosis of code E970-979 [ICD6-7], E950-959, E980-989 [ICD8-9] or X60-X84, Y10-Y34 [ICD10]);

Severe psychiatric disorder (a main or contributory diagnosis of code 300-303 [ICD6-7], 295-298 [ICD8-9] or F20-F39 [ICD10]);

Alcohol Abuse (a main or contributory diagnosis of code 322 [ICD6-7], 291, 303, 571.0, E860, E980, N980 [ICD8], 291, 303, 305.0, 357.5, 425.5, 353.3, 571.0-571.3, E860, E980+980 [ICD9], F10, G312, G621, G721, I426, K292, K700-709, K860, O3554, P043, Q869, T510-519, Y901-Y909, Z502 or Z714 [ICD10]);

Illicit drug abuse (a main or contributory diagnosis of code 323 [ICD6-7], 304, N965.0, N969, N970.9, N971 [ICD8], 304.0-304.9, 305.2-305.7, 305.9, 965.0, 968.5, 969.6, 969.7 [ICD9] F11, F12, F14, F15, F16, F18, F19, O35.5, P04.4, T40.0-T40.3, T40.5-T40.9, T43.6, Z50.3 or Z71.5 [ICD10]).

For the adoptees these variables were available for biological as well as adoptive parents.

Outcome variable

The outcome variable suicide death was created with data from the NCDR and defined according to ICD-9 for outcomes taking place in the years 1987-96: an underlying cause of death of E950-E959 or E980-E989 and ICD-10 in 1997-2001; X60-X84 or Y10-Y34, thus including certain and uncertain suicides.

Statistical analysis

In the multivariate analysis Hazard Ratios (HR) were calculated using Cox regressions of person days with suicide death as dichotomized outcome variable (definition above). Person time in the study was calculated with data on death from the NCDR and data on immigration during 1987-89 and the Total Enumeration Income Survey during 1990-2001.

Several different regression models were created: One general model (*Model I*) for the total population was fitted and adjusted for year of birth, sex and sociodemographic indicators. Birth year was entered as a continuous variable, since the outcome variable tended to decrease by year of birth in a linear fashion. Other sociodemographic variables were entered as category variables (using dummy variables) into the models. A second model (*Model II*) was created adjusted for year of birth, sex and biological parents' psychiatric morbidity entering biological parents' suicide, severe psychiatric illness and alcohol abuse as dichotomized variables into the model. Within a third model (*Model III*) all factors – childhood household characteristics as well as biological parents' psychiatric morbidity – were considered in one model.

The major multivariate analysis was separate for the adopted and non-adopted group. However, the whole study population (adopted and non-adopted) was used for the interaction analysis for childhood household characteristics, psychiatric morbidity of the biological parents and adoptions status. Three models were created corresponding to the above described models I-III containing an additional variable defining adoption status.

The SPSS 14.0 for Windows software package was used in all statistical analyses (SPSS Inc 2004).

Results

The study population consisted of a total of 2,942,932 individuals (33,240 adopted) out of which 10,814 [0.4%] individuals (210 [0.6%] of adopted individuals) committed suicide within the course of the study period. 72.6% of all suicides were committed by men.

The risk of suicide in general differed between adopted and non-adopted individuals (Table 1). Adoptees had a higher risk of suicide (HR 1.7 [95%CI 1.5-1.9] in a Cox regression model

adjusted for sex and age). This risk tended to increase when additionally adjusting for childhood household characteristics (1.9 [1.6-2.1]) and tended to decrease when considering psychiatric morbidity of the biological parents (1.6 [1.2-2.0]) (results not presented in table).

Suicide risk varied considerably for all demographic and childhood household factors investigated in the study (Table 1). The most important risk factors were male gender (HR 2.6) and growing up in a single parent household (HR 1.5), while parental SES, housing and maternal age contributed less (HR 1.1-1.2). When men and women were considered separately, several gender differences were noticed (results not presented in table). For men, parental low SES was a clear risk factor, while it did not contribute to the risk for suicide in women (HR 1.2 [95%CI 1.1-1.3] and 1.0 [0.9-1.1] respectively; $p < 0.001$). Looking at residency, the highest rate of suicides for women could be found in metropolitan regions, falling with decreasing degree of urbanicity (HR 1.39 [95%CI 1.23-1.56] for metropolitan areas, HR 1.19 [1.06-1.33] for smaller cities and 1 for rural areas). This pattern was not present in the men ($p < 0.001$; in an interaction analysis for gender and residency).

In an interaction analysis that included adopted as well as non-adopted individuals there were no significant interactions between adoption and sociodemographic characteristics, apart from single parent household where a strong trend was observed: single parent household did not influence the risk for suicide in the adopted group, contrary to the non-adopted group ($p = 0.05$).

Biological parents' suicide as well as severe psychiatric illness influenced the suicide risk in both groups, adoptees and non-adopted, similarly (Tables 2a and 2b). The effect tended to be even stronger in the adopted group (HR 3.54 and 3.00) than in the non-adopted group (HR 1.99 and 1.51). Biological parents' alcohol abuse presented with a different pattern. While it was a clear risk factor in the non-adopted group (HR 1.88), it did not influence the suicide risk in the adopted group. This difference between adopted and non-adopted concerning biological parents' alcohol abuse is underlined by the interaction effect between adoption status and alcohol abuse in biological parents ($p = 0.03$).

Discussion

Childhood household characteristics, biological parents' suicide and biological parents' severe psychiatric disorder were important risk factors for both, adopted and non-adopted. Biological parents' alcohol abuse, however, was only a risk factor for suicide for non-adopted individuals. Thus, the results indicate that both, hereditary and environmental factors contribute to the risk of suicide. However, with HRs of two to three-fold, hereditary factors showed only medium high risk increases unlike in other highly genetically influenced conditions like schizophrenia where ORs as high as around five to nine-fold can be found (Cannon et al. 1998, Cardno et al. 1999, Cardno & Gottesman 2000, Lichtenstein et al. 2006, Wicks et al. 2005). While heritable traits seemed to influence men and women equally, there were marked differences for childhood household characteristics.

The absence of an increased risk for suicide in children born by parents with alcohol problems but raised by adoptive parents contributes to further nuances of the knowledge about the genetics of suicide; although there is strong support for the genetic contribution also by studies indicating that genes of the serotonergic systems are involved in susceptibility to suicidal behaviour (Mann et al. 1999, Mann et al. 2001, Roy et al. 1997, Roy et al. 1999, Souery et al. 2003, Turecki 2001), there is also a contribution from the psychosocial environment. We believe that the gene-by-environment interaction model (see e.g. Caspi et al. 2003) fits well with our results on the effects of parental alcohol abuse in cases where the offspring is raised/not raised in the household of the addicted parent.

Our results on the relation between parental alcohol abuse and offspring suicide is supported by previous studies. In their study about the long term consequences of parental alcohol abuse on children in Denmark, Christoffersen & Sothill (2003) demonstrated that parental alcohol abuse has long-term developmental effects for the offspring, such as increased risk of self-destructive behaviour like attempted suicide. However, when factors like unemployment, mental illness, suicidal behaviour and domestic violence were taken into account, the impact of parental alcohol abuse became less clear. In a recent children-of-twins study Glowinsky et al. (2004) found a relationship between paternal alcoholism and suicidal behaviour in the offspring, but their data spoke against a purely genetic relationship. They concluded that

without a high risk environment, even a group at high or intermediate genetic risk was not at higher risk for suicide attempts than a group with low genetic risk.

The generally higher risk for suicidal behaviour in the group of national adoptees has been shown in previous studies (von Borczyskowski et al. 2006). The increase of those risks with adjustment for childhood sociodemographic factors is an indication of the better-situated background of the adoptive parents as a positively selected group. On the other hand psychiatric morbidity in the biological parents is more common in adoptees than among the majority population, which leads to decreasing risk ratios for suicide in the adoptees when those factors are controlled for.

Biological parents' psychiatric morbidity tended to have a stronger influence on the suicide risk for the adoptees than in the non-adopted group. The large confidence intervals in the adopted group warrant caution in interpreting this tendency, but it may be a sign of certain genetic traits showing a greater influence in population segments with more advantaged childhood environments (e.g. Raine 2002, Rutter et al. 2006, Rutter 2006). Adoptive parents tend to provide "better than average" socioeconomic rearing conditions for their children, and they also have lower than average rates of psychopathology (e.g. Hjern et al. 2002). An alternative explanation is that more adoptees than non-adopted peers may have clusters of genetic risk factors - interacting with each other - that we have not been able to detect in the register data. These risk factors may have been inherited from *two birth* parents with severe psychopathology through the process of assortative mating (Rutter 2006). A third possibility is that genetic vulnerability among adoptees may interact with adoption-specific negative psychological experiences, resulting in an increased risk of suicide. Our register data do not enable us to test any of these alternative hypotheses.

Having grown up in a single parent household stood out as a risk factor within the childhood household socioeconomic circumstances. Similar results have been shown in previous studies by Weitoft et al. (2002 and 2003). Behind this could be an accumulation of risk factors as well as a higher incidence of psychiatric morbidity in single parents, which in turn has a negative influence on the children. In our study this is supported by the fact that the HR decreases when not only sociodemographic factors, but also parental morbidity are considered (1.46 respective 1.33). Partially this can be explained by selection mechanisms (people with increased

psychiatric morbidity might have lesser chances of a stable long-term relationship), partly by the greater strains that single parents are exposed to in their daily lives (Weitoft et al. 2002 and 2003).

While we did not find any major gender differences for the influence of psychiatric morbidity of the biological parents on the risk of suicide in the offspring, childhood household characteristics seemed to have gender-specific effects.

Some of the most striking gender differences were observed for residency where the risk of suicide decreased with decreasing degree of urbanicity for women only. Similar patterns (although for the place of residence at the time of suicide) have been described by Qin et al. (2003) and Qin (2005) in large register based studies from Denmark. The author suggests that men (especially young men) may benefit from the advantages of a big city while women may be more vulnerable to the accumulation of risk factors in an urban environment. Certainly, the gender differences thus brought up in two different Scandinavian studies may be explained by a large variety of factors and it is beyond the scope of this article to bring out knowledge about this complex interplay. Few studies have investigated the influence of childhood socioeconomic status on suicide. Trends that low parental SES is a risk factor for men, while risks are not influenced for women (Galobardes et al. 2004), as found in this study, or even increased with increasing parental SES (Strand & Kunst 2006) have been found in previous studies. Gender specific patterns that lead women to be more susceptible to stress from trying (or failing) to meet demands from their parents (Strand & Kunst 2006) or the risk of decreasing SES with the transition into adulthood (Blane et al. 1999, Pensola & Martikainen 2003) have been suggested as explanations.

The presence of heritable factors that, apart from increasing the risk of a specific event such as suicide, also may influence the interaction of the individual with the labour market creates the possibility of a “social drift” over generations (Goldberg & Morrison, 1963; Timms, 1998). An advantage of the adoption-design is that it eliminates the influence of social drift. As no major interaction between adoption and childhood household socioeconomic determinants could be found, we conclude that socioeconomic factors influence suicide risks even after having considered the possibility of social drift due to psychiatric vulnerability.

Limitations

One problematic aspect of using register data for the study of suicide is that official mortality data will not include all suicides, but only those registered. However, previous studies have shown a good validity of these data in western countries (e.g. Moscicki 1997). Furthermore, in our definition of suicide undetermined deaths were included herewith improving number of cases detected (Linsley et al. 2001). On the other hand, an advantage of a register design in this respect is that it reaches beyond the scope of smaller case-control studies with a selected population and therefore does not only give information about the risk factors in the affected groups, but provides a larger reflection of the general population.

A specific problem of this study is that we did not have any information on parental morbidity before 1960. This is a problem that effects the older part of the study population on a larger scale than the younger. However, when we split the total population into two smaller cohorts (one older, born 1943-1955, and one younger, born 1956-1968) and analyzed them separately, no major differences between the two groups could be found. This implies that the possible influence of missing data on early manifestations of parental risk factors with death of those parents before 1960 in effect is quite limited.

No data was available about age at adoption and the actual environmental circumstances of the children prior to adoption (e.g. time in infant residential care).

The quality of the indicators for parental morbidity differs considerably. Parental suicide is a more reliable and comprehensive indicator than parental severe psychiatric illness which could lead to a possible underestimation of psychiatric risk factors. This in turn might provide an explanation why parental suicide seems to have more influence on the suicide risk than parental psychiatric illness. In general, dealing with hospital care implies that only a smaller fraction of the total morbidity will be recorded (the most extreme fraction). However, in this respect parental alcohol abuse is a better indicator in a middle aged and older population, since chronic alcohol abuse tends to cause physical morbidity that often leads to hospital admissions and is easily recognized in a post-mortem examination.

Conclusions and implications for practice

Both genetic and parental related environmental factors influence the risk of suicide. It is notable that alcohol abuse in parents increased the risk of suicide in the offspring only when the offspring had been raised in the household of the addicted parent. These results highlight the preventive potential of psychosocial intervention for this exposed group of children.

Further studies, both molecular biological and epidemiological, are needed to determine especially the interaction between genetic and environmental factors.

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Tables

Table 1 - Incidence for suicide death in the total population by adoption status and childhood household characteristics

		Men		Women	
		Number of suicides	Incidence per 1000	Number of suicides	Incidence per 1000
Adoption-status	adopted	147	8.5	63	3.9
	non-adopted	7706	5.2	2898	2.0
Parental SES	white collar	2438	4.5	1050	2.0
	blue collar	3493	5.6	1203	2.0
	missing or other	1922	5.6	708	2.2
Residency	metropolitan regions	2315	5.1	1078	2.4
	smaller city	3969	5.2	1431	2.0
	rural area	1569	5.3	452	1.7
Housing	multifamily residence	3244	5.9	1311	2.4
	single occupancy house	4553	4.8	1610	1.8
Single parent household	yes	1573	7.1	554	2.6
	no	6229	4.9	2370	2.0
Maternal age	<25	2580	5.3	932	2.0
	25-34	3473	4.5	1314	1.8
	>34	1307	5.2	504	2.1
TOTAL		7853	5.2	2961	2.1

Table 2a - Cox Regression for suicide in relation to sex, childhood household characteristics and psychiatric morbidity of biological parents in the NON-ADOPTED group

		Model I*		Model II**		Model III***	
		RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
Sex	male	2.59	(2.47 - 2.70)	2.60	(2.48 - 2.73)	2.62	(2.50 - 2.75)
	female	1		1		1	
<i>Childhood household characteristics</i>							
Parental SES	white collar	1		-- ----		1	
	blue collar	1.15	(1.10 - 1.21)	-- ----		1.13	(1.08 - 1.19)
	missing or other	1.14	(1.08 - 1.21)	-- ----		1.12	(1.06 - 1.19)
Residency	Metropolitan regions	1.05	(0.99 - 1.11)	-- ----		1.04	(0.98 - 1.11)
	Smaller city	1.02	(0.97 - 1.08)	-- ----		1.03	(0.97 - 1.09)
	Rural area	1		-- ----		1	
Housing	multifamily Res.	1.16	(1.11 - 1.21)	-- ----		1.13	(1.07 - 1.18)
	single occupancy house	1		-- ----		1	
Single parent household	yes	1.46	(1.39 - 1.54)	-- ----		1.33	(1.25 - 1.42)
	no	1		-- ----		1	
Maternal age	<25	1.16	(1.11 - 1.21)	-- ----		1.13	(1.07 - 1.19)
	25-34	1		-- ----		1	
	>34	1.11	(1.05 - 1.17)	-- ----		1.14	(1.07 - 1.21)
<i>Psychiatric morbidity of biological parents</i>							
Suicide		-- ----		1.99	(1.78 - 2.23)	1.88	(1.68 - 2.10)
Severe psychiatric disorder		-- ----		1.51	(1.35 - 1.70)	1.50	(1.33 - 1.69)
Alcohol abuse		-- ----		1.88	(1.73 - 2.04)	1.71	(1.57 - 1.86)

* Adjusted for age, sex and childhood household sociodemographic indicators

** Adjusted for age, sex and biological parents' morbidity

*** Adjusted for all factors in Model I and II

Table 2b - Cox Regression for suicide in relation to sex, childhood household characteristics and psychiatric morbidity of biological parents in the ADOPTED group

		Model I*		Model II**		Model III***	
		RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
Sex	male	2.15	(1.59 - 2.90)	2.68	(1.57 - 4.59)	2.67	(1.56 - 4.57)
	female	1		1		1	
<i>Childhood household characteristics</i>							
Parental SES	white collar	1		--	----	1	
	blue collar	1.20	(0.87 - 1.66)	--	----	1.10	(0.61 - 2.00)
	missing or other	1.20	(0.83 - 1.74)	--	----	2.01	(1.12 - 3.60)
Residency	metropolitan regions	0.99	(0.65 - 1.52)	--	----	1.11	(0.54 - 2.27)
	smaller city	1.04	(0.71 - 1.52)	--	----	1.04	(0.55 - 1.97)
	rural area	1		--	----	1	
Housing	multifamily residence	1.45	(1.07 - 1.95)	--	----	1.82	(1.09 - 3.06)
	single occupancy house	1		--	----	1	
Single parent household	yes	0.92	(0.57 - 1.47)	--	----	0.78	(0.35 - 1.75)
	no	1		--	----	1	
Maternal age	<25	1.56	(1.05 - 2.30)	--	----	1.21	(0.63 - 2.32)
	25-34	1		--	----	1	
	>34	1.10	(0.80 - 1.49)	--	----	0.92	(0.54 - 1.56)
<i>Psychiatric morbidity of biological parents</i>							
Suicide		--	----	3.54	(1.67 - 7.52)	3.45	(1.62 - 7.33)
Severe psychiatric disorder		--	----	3.00	(1.36 - 6.61)	2.98	(1.35 - 6.56)
Alcohol abuse		--	----	0.85	(0.44 - 1.65)	0.85	(0.44 - 1.63)

* Adjusted for age, sex and childhood household sociodemographic indicators

** Adjusted for age, sex and biological parents' morbidity

*** Adjusted for all factors in Model I and II

6 Eidesstattliche Erklärung

Ich versichere, dass ich die vorliegende Arbeit ohne fremde Hilfe selbständig verfasst und nur die angegebenen Hilfsmittel benutzt habe. Wörtlich oder dem Sinn nach aus anderen Werken entnommene Stellen sind unter Angabe der Quelle kenntlich gemacht.

Hamburg, den 13.Oktober 2006

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(Annika von Borczyskowski)