EPIDEMIOLOGICAL STUDIES OF SUICIDE – CLASSIFICATION BIAS, DRUG USE AND SOCIAL CIRCUMSTANCES

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“A little REBELLION now and then is a good thing”
- Thomas Jefferson
ABSTRACT

Despite the decline in suicide rates in Sweden during the past decades, suicide still constitutes a severe public health problem and is a cause of death that to a large extent could be prevented. In 2008 the Swedish Parliament ratified the Swedish government’s suggestion of a ‘Vision Zero’ policy for suicide.

The overall aim with this dissertation was to increase the knowledge on risk factors for suicide and whether the suicide risk is modified by socioeconomic position.

We examined if different background variables can be helpful in distinguishing deaths classified as suicide from deaths classified as undetermined intent. We selected all suicides and undetermined intents 1987 - 2011. Our results showed differences in most studied background variables where hospitalization for self-inflicted harm was more common among female suicides as was prior psychiatric in-patient care, whereas in-patient for substance abuse was more common in undetermined intents of both sexes. Roughly 50% had a prescription of psychotropics during their last 6 months prior to death. However, this information does not seem to be enough to distinguish between these two deaths modes.

In Study II we examined if initiation with selective serotonin reuptake inhibitors (SSRI) increase the risk of suicide. By using a case cross-over design, we selected all suicides in Sweden between 2007 and 2010 (5 913) and obtained information on prescriptions of SSRI for these individuals. We found a risk increase for suicide during initiation with SSRI with an odds ratio (OR) of 3.7 [95% CI: 2.8-4.9]. Induction time analyses showed the overall highest risk during days 8-11 after SSRI initiation with an overall OR of 9.7 [2.9-31.7]. Regardless of causation issues our findings deserve further attention, especially in the clinical setting and in the monitoring of patients during initiation with SSRI therapy where extra attention to signs of suicidality is called for.

In Study III and in Study IV we used a cohort constituting of Swedish residents born between 1972 and 1981. In Study III we followed this cohort of 898 342 students, graduating from the nine years of compulsory school until December 31st 2006. Students with incomplete grades had highest suicide risk. The risk increased in a gradient fashion, i.e. the lower the grades the higher the suicide risk. Parental educational level did not mediate this relationship.

In Study IV we examined if juvenile delinquency, measured as number of convictions between ages 15 and 19, increased the risk of suicide in young adulthood. Juvenile delinquents had an increased suicide risk where repeated juvenile offenders had highest risk. Parental educational level did not mediate this relationship.

In conclusion, poor school performance and juvenile delinquency seem to be risk factors for suicide in young adulthood. These risk factors were not modified by parental educational level. Our results suggest an increased suicide risk at initiation with SSRI therapy. Regardless of whether the increased risk is due to activation syndrome or more severe depression at initiation with SSRI, this result means that clinicians must closely monitor patients when SSRI therapy is initiated. Despite several differences in background variables, this information does not seem to be enough to distinguish deaths classified as suicide from deaths classified as undetermined intent. The proportion might vary due to validity variations in suicide certification over time and between regions and even between different forensic pathologists.
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<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical Classification System</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<td>DDD</td>
<td>Defined Daily Dose</td>
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<td>DUI</td>
<td>Driving Under the Influence</td>
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<tr>
<td>EU27</td>
<td>The 27 member states of The European Union</td>
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<tr>
<td>GPA</td>
<td>Grade Point Average</td>
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<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
</tr>
<tr>
<td>IRR</td>
<td>Incidence Rate Ration</td>
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<tr>
<td>IQ</td>
<td>Intelligence Quotient</td>
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<tr>
<td>MI</td>
<td>Myocardial Infarction</td>
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<tr>
<td>OR</td>
<td>Odds Ratio</td>
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<td>RD</td>
<td>Risk Difference</td>
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<td>RR</td>
<td>Relative Risk</td>
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<td>SEP</td>
<td>Socioeconomic Position</td>
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<tr>
<td>SSRI</td>
<td>Selective Serotonin Reuptake Inhibitor</td>
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<tr>
<td>SSS</td>
<td>Subjective Social Status</td>
</tr>
<tr>
<td>TCA</td>
<td>Tricyclic Antidepressant Drug</td>
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<td>WHO</td>
<td>World Health Organization</td>
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1 BACKGROUND

1.1 SUICIDE

1.1.1 Introduction

The Swedish Parliament has a vision, a vision of zero suicides in Sweden. In 2008 the Swedish Parliament ratified the Swedish government’s suggestion of a ‘Vision Zero’ policy for suicide. The Swedish National Program for Suicide Prevention was already initiated in 1995 and today the program comprises strategies that incorporate both a public health and a healthcare approach. The ‘Vision Zero’ initiative is to promote the view that suicide is everyone’s responsibility, and first-aid training to help suicidal persons should be provided for every citizen. The plan calls for creating conditions whereby no one finds herself or himself in such a vulnerable position that they see suicide as the only way out.1

Despite the decline in suicide rates in Sweden during the past decades, suicide still constitutes a severe public health problem and is a cause of death that to a large extent could be prevented2. According to the annual official cause of deaths statistics, close to one percent of Swedish women die from suicide and almost two percent of Swedish men3. Worldwide almost one million people commit suicide annually4. The main risk factor for suicide is mental disorders5. Both mental disorders and suicidal behavior aggregates in families. The familial aggregation of suicidality is explained by liability to psychiatric disorder, and liability to impulsive aggression6-8. However, somatic diseases have also been shown to be risk factors for suicide5,10, as has alcohol consumption5,11,12. It is also common with previous suicide attempts among suicide victims12,13. The risk of suicide differs depending on socioeconomic position, where low income and unemployment have been shown to increase the risk of suicide14,15.

1.1.2 Suicide occurrence

The suicide trends have increased globally since the 1950s16. However, reported suicide rates vary considerable between countries. Worldwide, Eastern European countries report the highest annual rates and Latin American and Islamic countries report the lowest rates17. In some parts of the world, like Africa, epidemiological data on suicide is scarce. The view of suicide as a criminal act in many Islamic countries might also affect the registration practices and indirectly the reported suicide rates12. Globally several indigenous populations show higher suicide rates compared to the rest of the population, for example Native Americans in the US, Métis and Inuit in Canada, Aborigines in Australia, and Maori in New Zealand18.

Age standardized suicide death rates (per 100 000 inhabitants) in the European Union (EU27) was 10.2 in the year 2010, 4.3 for women and 16.5 for men. Lithuania displayed the highest rate 28.5 and Greece the lowest 2.9. Sweden was close to the average EU27 rate, 11.1 in total, 5.9 for women and 16.4 for men19. According to the Centers for Disease Control and Prevention statistics, suicide rates in the US is similar to EU27 in women (5.9 per 100 000) but slightly higher in men (22.3 per 100 000)20.

Suicide rates vary according to sex, age, region, time, and ethnic origin. Most probably, practices of death registration contributes to some differences12. Autopsy rates of deceased to establish the cause and mode of death vary between countries, as do the requirements for a
death to be recorded as suicide. Different cultural and social practices and values are therefore likely to have a profound effect on death records and could lead to underreporting of suicides which could affect between country comparisons\textsuperscript{12}.

Since the 8\textsuperscript{th} revision of the International Classification of Diseases (ICD-8) in 1968, deaths where the physician cannot establish the mode of death, i.e. if it was suicide, unintentional or assault, are classified as undetermined intent\textsuperscript{21}. It has been suggested that suicide appears more susceptible than homicide and unintentional injury to misclassification under undetermined intent\textsuperscript{22}. So far in suicide research, there is no true agreement on how to handle deaths with undetermined intent. It is however common to include these deaths when studying suicide in Europe with the argument that the combination of these two is likely to provide the most accurate representation of the “true” suicide rate\textsuperscript{5}. There is also a continuing concern and debate regarding the validity of suicide mortality data\textsuperscript{23-25}.

Men commit suicide in a greater extent than women do in most countries. However, women make more suicide attempts\textsuperscript{26}. This inverse relationship is often referred to as “the gender paradox in suicidal behavior”. In many Asian countries the ratio of male to female is much lower than in Western societies. In Thailand and China women do have a higher suicide rate than men\textsuperscript{12}.

Suicide also varies with age. Data from The World Health Organization (WHO) has shown that the suicide rates increase with age for both sexes with the highest rates among the elderly, 75 years and older\textsuperscript{27}. Despite the fact that suicide rates are highest in elderly people in most countries, the rates have risen among young people over the past 50 years, in particular in men, and decreased in elderly people\textsuperscript{12}.

1.1.3 Suicide trends in Sweden

Figure 1 shows the suicide trends in Sweden between 1911 and 2011. Throughout the period women have a lower suicide rate than men do which is not unique for Sweden\textsuperscript{1}. In 1911 the overall suicide rate was 17.5 per 100 000 inhabitants, 6.5 for women and 29.1 for men, and in 2011 women’s rate was 6.8 and men’s rate was 11.8. The effects of both world wars, 1914-1918 and 1939-1945, are clearly seen in this figure as profound decreases among both women and men. War has been suggested to sometimes bring a greater sense of cohesion and feeling of purpose in society, thus decreasing the suicide rates\textsuperscript{12}. Suicide rates in Sweden, as in many western countries, peaked in the beginning of the seventies followed by a decline in both sexes. At the end of the period women’s rate was almost back at the same level as in the beginning of the twentieth century, whereas the rate for men was much lower in the latest year compared to the rate in the beginning of the period.

One should be aware though that society’s view upon suicide has changed over time. Historically, suicide was no longer seen as a crime since 1864 and in the beginning of the 1900s the separate funeral for people who had committed suicide was no longer in use. Still in the 1930s the bodies from suicide victims were used for anatomic experiments\textsuperscript{28}. These circumstances could of course lead to an underreporting during the earlier part of the period shown in Figure 1.
1.1.4 Suicide among adolescents and young adults

While suicide rates have been reported as stable or falling in many developed countries over the last few decades a stable or rising trend of youth suicide rates has been observed. It is still not established if suicide represents the same phenomenon across the life span or whether it has different meaning and is related to different risk factors in youth in comparison with the elderly. Impulsivity and aggression has been found to be more prevalent among younger suicide victims whereas physical illness is more common among older suicide victims. Suicide attempts (parasuicide) among adolescents and young adults are at least ten times more common than completed suicide. A history of suicide attempt is also a main risk factor for subsequent completed suicide. In a study by Wasserman et al the global suicide rates among adolescents were examined. Data from the time period 1965-1999 showed a marked difference in youth suicide rates between European and non-European countries, where the latter displayed much higher suicide rates. Sri Lanka had an extraordinarily high suicide rate in age group 15-19 with 46.5 per 100 000 inhabitants which was more than six times the global mean rate. A similar pattern is seen in Sweden, where the suicide rates for adolescents and young adults between the ages 15 and 24 do not follow the overall decreasing trend. Instead the rates are fairly stable throughout the last decades 1980-2011 in Sweden (Figure 2a and 2b).
Figure 2a. Suicide death rates per 100,000 women 1980-2011, by age.

Figure 2b. Suicide death rates per 100,000 men 1980-2011, by age.
1.1.5 Methods of suicide

Access to specific methods is essential when a person is contemplating suicide. What means is accessible may also be associated with the possible translation of suicide ideation into suicidal action. If one do not have access to any heights, firearms or poisonous chemicals the risk of making an impulsive suicide attempt decreases\textsuperscript{34} The chosen method may also determine whether the outcome is fatal or not where for instance using firearms increase the risk of fatality. Women in general tend to use less violent methods such as poisoning, whereas men in general tend to choose more violent methods as shooting or hanging\textsuperscript{12}. Worldwide, poisoning is the most common suicide method, foremost through pesticide ingestion which is very common especially in rural areas in Asia\textsuperscript{35}. The use of firearms is most common in the US due to the availability\textsuperscript{12}. Poisoning is the most common method among Swedish women whereas hanging is the most frequent used method among Swedish men. Figure 3a and Figure 3b show percentage of suicide methods used in women and men, respectively, in Sweden 2011.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{suicide_methods_women.png}
\caption{Suicide methods in women in Sweden 2011, percentage.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{suicide_methods_men.png}
\caption{Suicide methods in men in Sweden 2011, percentage.}
\end{figure}
1.1.6 Risk factors for suicide

The reason for suicide is complex and is most likely the result of the interaction of several different factors. Over the last decades, it has become increasingly clear that most people who commit suicide have a certain predisposition that appears to be mediated by a number of factors. Growing interest has focused on the role of personality traits, notably impulsiveness and aggressive behaviors. The effect of impulsive-aggressive traits is often present in child and adolescent suicide but is found to decrease with age.

The most common and well-established risk factor for suicide is mental disorder and mental ill health. A meta-analysis in 1997 concluded that 90% of suicide victims had one or more mental disorders at the time of death. The authors also claimed that if their results could be generalized, virtually all mental disorders would carry an increased risk of suicide except for mental retardation and possibly dementia and agoraphobia. Patients diagnosed with schizophrenia have shown the most elevated suicide risks compared to the general population with a 12 times higher risk. However, most psychiatric patients do not commit suicide, whereupon a psychiatric disorder is generally a necessary but insufficient condition for suicide.

In China, however, a much lower proportion of people who commit suicide seem to have a psychiatric disorder, especially women and girls in rural areas. Suicide in China seems to be a more impulsive act of deliberate self-harm following acute interpersonal crises.

A history of self-inflicted harm and suicide attempt is also a prominent risk factor for later completed suicide. At least 40% of suicide victims have previously attempted suicide and individuals with a history of suicide attempt have overall, an increased suicide risk nearly 40 times that of the general population. Suicide attempters differ from non-attempters with the same psychiatric disorder in so far that attempters experience more subjective depression and hopelessness and see fewer reasons for living. Beastra explicitly compared suicide victims to suicide attempters and found strong etiological overlapping between the two populations. A very similar pattern of risk factors predicted both outcomes such as the presence of current psychiatric disorder, history of previous suicide attempts, previous psychiatric care and contact, social disadvantage and exposure to recent stressful life events. However, some differences were also found. Males with non-affective psychosis were more likely to commit suicide whereas some women with several risk factors were not as likely to commit suicide, such as women with anxiety disorders with poor social support.

The psychological autopsy is a common method for psychiatric assessment of a suicide victim. This method usually includes interviews with relatives as well as the gathering of data from medical records of the deceased. The overall aim of a psychological autopsy is to gather information about the circumstances of an individual’s death to try to understand the reasons for the suicide. This means that a psychiatric diagnosis can be found during the psychological autopsy that have been undiagnosed and untreated. Psychological autopsy studies have also shown a substantial link between clinical depression and suicide in adolescence where depressive disorder at the time of death have been found in up to 60% of adolescent suicide victims. Depression increases the suicide risk among adolescents, however, the majority of depressed adolescents do not develop suicidal ideation, suggesting that additional factors influence vulnerability to suicidal responses.

Low IQ has also been shown to increase the suicide risk. In a cohort study of 987 308 Swedish men followed for 5-26 years, poor performance in intelligence tests measured at age 18 (at compulsory conscription), was found to be strongly related to subsequent risk of
Lack of self-esteem might also increase the risk of suicide. Bhar et al examined the association between self-esteem and suicide ideation while controlling for depressed mood and hopelessness and found that low self-esteem increase the suicide risk. Suicide rates have been shown to vary by season. Several studies have shown a peak in spring, mainly for men, whereas some studies reported a secondary peak during fall, especially for women. Violent methods also seemed to carry higher degree of seasonality. Gabennesch has presented the “broken promise theory” as explanation for seasonality in suicide. Gabennesch explains life as divided into cycles and every new cycle, be it a new week, a new season, or after holidays, carries expectations for individuals. If these expectations are not met disappointment sets in and the risk of suicide increases.

Suicidal behaviour is partly hereditary, though the familial transmission of suicidal behavior cannot be explained through the transmission by mental disorder alone. One study analyzing relevant genetic traits found aggression/impulsivity, early-onset of major depression, neurocognitive function, and cortisol social stress response to be the most likely endophenotypes. Other studies have found a family history of substance abuse, depression, antisocial and other personality disorders, and assaultive behavior to be linked to suicidal behavior. Brent et al stated that suicidal behavior that begins before 25 years of age is highly familial, and having a greater number of affected family members is associated with an earlier age at appearance of suicidal acts. Evidence from family, twin and adoption studies supports the hypothesis that genetic factors contribute to suicide risk. In a Swedish national cohort study 180 suicides in adopted youth and middle-aged were compared to over 8 000 suicides among non-adopted of similar age and found suicide and severe mental disorder in biological parents to have similar effects in the non-adopted as in the adopted.

Other known risk factors for suicide are being of ethnic minority, alcohol abuse, drug abuse, other sexual orientations than heterosexual, somatic diseases, bullying, change of residence, lone parenthood, low income, and unemployment.

1.1.7 Classification of suicide

To allow comparisons between countries, the statistics used in the comparison must be based on an international standard. The definitions and instructions issued by the World Health Organization in the ICD manuals is the universally accepted standard for mortality statistics. WHO has provided detailed instructions for almost 60 years, and the WHO’s member states pledge themselves to prepare mortality statistics according to these specifications. Sweden follows accordingly these international rules for classifying causes of death.

The underlying cause of death is defined by the WHO as “the disease or injury that initiated the train of morbid events leading directly to death”. The underlying cause of death is used in official cause of death statistics and used in comparisons between as well as within countries.

In the event of a death in Sweden a physician is to establish the cause of death and to submit a death certificate to the National Board of Health and Welfare. At the National Board all diagnoses and injuries reported on the certificate are translated into ICD-codes. A computerized process then selects the underlying cause of death. Information on all deaths is collected in the national Cause of Death Register held at the National Board that is also responsible for publishing the annual official cause of death statistics in Sweden.

When the police suspect an unnatural death, the Forensic Department in Sweden is responsible for performing a forensic examination of the deceased, and most often autopsy. The number of
medico-legal autopsies has remained remarkably constant at about 5 500 cases a year since the early 1990s. Around 97 percent of all suicides have been autopsied by the Forensic Department. Since the introduction of the 8th revision of ICD in 1969 it is also possible to classify death as undetermined intent. This means that the forensic pathologist cannot establish if deaths was due to suicide, accident or assault. Before 1969 a violent death was either classified as suicide, accident, or assault. A certain amount of undetermined deaths are most likely suicide. The problem is that some of these deaths most probably are not. Several studies have aimed at assessing the amount of undetermined intents that are in fact suicides and hence should be included in suicide statistics. In one study from Newcastle they excluded cases in which suicide were considered impossible and found a surprising variation over time in the rate of exclusion, between 14% and 50%. Examples where suicide was considered impossible were a young intoxicated man who fell from a window and an elderly woman with dementia who was found drowned in a small stream. A Swedish study scrutinized a sample of death certificates including forensic reports, police reports, toxicological and histological data to re-evaluate the cause of death. Nine out of 47 cases (20%) officially classified as undetermined intent were re-evaluated as suicide. The authors concluded, taking their results into account, that the true suicide rate probably was even higher. Despite the uncertainty with deaths classified as undetermined intent, it is very common to include undetermined intents when studying suicide in Europe. It is also important to distinguish “mode” of death from the biological “cause” of death. If someone for instance was to commit suicide by jumping from a high place, the biological cause of death would by injuries from jumping whereas the mode of death would be suicide.

In Study I we investigated if information on different background variables can be used to distinguish deaths classified as suicide from deaths classified as undetermined. In Table 1 the ICD-codes for suicide and undetermined intent are presented. Both suicides and deaths classified as undetermined intent are included in the following studies if not otherwise stated.

<table>
<thead>
<tr>
<th>ICD-VERSION</th>
<th>YEAR</th>
<th>SUICIDE</th>
<th>UNDETERMINED INTENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD-6</td>
<td>1952-1957</td>
<td>E970-E979</td>
<td>-</td>
</tr>
<tr>
<td>ICD-7</td>
<td>1958-1968</td>
<td>E970-E979</td>
<td>-</td>
</tr>
<tr>
<td>ICD-10</td>
<td>1997-</td>
<td>X60-X84</td>
<td>Y10-Y34</td>
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1.2 SOCIOECONOMIC POSITION

There are several concepts to describe and categorize individuals according to their status, power, and economical and environmental position in the society. Throughout this dissertation the term socioeconomic position (SEP) is used, defined by Berkman and Kawachi as “the social and economic factors that influence the position(s) individuals and groups hold within the structure of society.”
1.2.1 Measures of socioeconomic position

The following three measures are the most commonly used as a proxy to categorize people into different socioeconomic groups.\(^72\)

- Education
- Occupation
- Income

In this dissertation we have used educational level as a proxy for SEP. We have consistently used the highest educational level to characterize a household with two adults.\(^73\) The reason we chose education is that it is easily understood, it is available for almost all individuals, and it is also easy to categorize.

Occupational categories should be based on prestige, skills, social influence, and power.\(^72\) A commonly used measure in Sweden is the occupation-based socioeconomic classification of Statistics Sweden.\(^74\) This categorization divides the working force into self-employed and employees. The employees are divided into manual and non-manual workers. Manual workers, who are usually affiliated to the Swedish Confederation of Trade Unions (LO) and sell their time for collectively negotiated wages, are sub divided into skilled and un-skilled workers. Non-manual workers, who sell their competence for individual wages, are categorized into lower, intermediate and higher non-manuals based on the average educational requirements of each occupation.

The most complex measure of SEP is income. When considering income you have to take several factors into account as wealth, subsidiaries, and how many individuals the wage should provide for.

Education, occupation and income as measures of SEP, are sometimes believed to be interchangeable which they are not.\(^75\) They overlap to some degree but there are also differences that can be of importance when it comes to health. Socioeconomic factors can also interact with other social characteristics, such as race, ethnicity, and sex, and produce different health effects across groups.\(^76,77\) For example, evident racial/ethnic differences in job status at a given educational level and in income at a given occupational level raise questions about the socioeconomic comparability of individuals who are similar on education or income alone.\(^72\) One should therefore be careful in choosing which measure to use. Some researchers have even argued that one should use and combine as many of the measures as possible instead of selecting only one of them.\(^72\)

Often, very few categories are used (e.g., poor vs. non poor, low education vs. high education), which could obscure important social gradients in health that apply across the entire socioeconomic spectrum.\(^78,79\)

1.2.2 Socioeconomic position and health

Differentials in health and longevity among various groups and by the nature of social relationships have been identified in a large number of studies over the years.\(^76,78,80-84\) Prior research suggest that the onset of health problems is usually postponed until rather late in life among higher SEP persons, while health declines are prevalent in lower SEP groups by middle age.\(^81\)

The classic Whitehall study of British civil servants, showed a steep inverse association between
social classes as assessed by grade of employment, and mortality from a wide range of
diseases. The results also showed clear differences in health related behaviors among different
employment-grade groups. Their results also suggested differences in economic circumstances,
and in social circumstances at work (e.g., monotonous work characterized by low control and
low satisfaction), and in social support.

The absolute level of income is however not as relevant when the individual’s basic needs are
fulfilled. Instead the concept relative deprivation has been introduced and shown to reflect
health outcomes. Having relatively less than your peers might create a stressful situation even
though your basics need are met. Blane et al emphasized that the socioeconomic distribution
is not dichotomous (advantaged vs. the rest) but graded, so that for each change in degree of
advantage or disadvantage generally follows a change in health.

A prominent hypothesis regarding social inequalities in mortality is that the elevated risk among
the socioeconomically disadvantaged is largely due to the higher prevalence of health risk
behaviors. Common health risk behaviors are amongst other, tobacco use, physical
inactivity, excessive alcohol consumption, poor nutrition, and obesity.

In connection to health, patients with higher education might benefit from their already achieved
knowledge, or their ability to obtain new knowledge when it comes to, for instance, conceivable
treatments. They might be better informed on their rights and could also be less intimidated
talking to physicians. Education is also less affected by reverse causation of disease than
income or occupation. Some psychiatric disorders are however exceptions, where a psychiatric
disorder in adolescence might affect the possibility of achieving higher education and thus future
occupation and income. There is however some potential disadvantages in using educational
level. By knowing the number of years of education, you have no information on the quality or
how that particular education is valued socially and economically. Educational level in terms
of number of years might fail to reveal what is important with this measure in relation to health
in different settings. The magnitude hereof is also dependent on the time, and the social and
cultural context. Studying education over time or for different age groups can also be
problematic. Nowadays it is more common to graduate senior high school and to study at
university level than 40 years ago. A comparison between age groups or periods must therefore
be handled carefully.

When using occupation as a measure of SEP one captures both social status and environmental
factors, where different occupations entail different risk factors as noise, dust, physical strain,
exposure to poisonous materials and chemicals. Two models have also been introduced in the
literature to explore how one’s work might affect health the demand-control model and the
effort-reward model. The former refers to the psychological demands put on the working
individual and the degree of control available for her/him and the latter refers to the
balance/imbalance between one’s subjectively perceived contribution to the company and what
you are actually rewarded in terms of wage, career opportunities and self-esteem. If the work
situation brings high demands but no real control it might have a negative effect on health.

Finally, income represents status but also what is perhaps more relevant today, rather than to talk
about “production” we talk about “consumption.” Higher income means that you can afford
living in a more affluent area, have a bigger house, buy a safer car and afford healthier food etc.
Several studies have however suggested that this relationship weakens after age 65. Research
has also suggested less health gain per income unit in the upper end of the income scale. Some
risks are however higher among the more affluent. An example is the tsunami disaster in
Southeast Asia 2004. Few “poor” Swedes could afford travelling that far and hence were not at
risk of experience that disaster\textsuperscript{94}.

An US study has stressed that unhealthy behaviors only contribute in a smaller degree to the inequalities in health\textsuperscript{87}. The authors instead explain some inequalities to be due to differences in exposure to occupational and environmental health hazards, and access to and use of preventive and appropriate therapeutic medical care\textsuperscript{87}. Regardless of measure of SEP, there is strong evidence that the lower the SEP the higher the degree of bad health. There are a couple of exceptions from this though, like breast cancer among women and malignant melanoma where both show an inverse relation i.e. the higher the SEP the higher the cancer risk\textsuperscript{95-97}.

The inverse relationship between SEP and the prevalence of mental disorders is one of the best established in the field of mental health epidemiology\textsuperscript{98}. What remains unsolved is though the causality of this relationship. However, studies in a recent Swedish dissertation support both the social selection and social causation hypothesis\textsuperscript{99}.

Recently, there has been an emerging interest in the relationship between subjective social status (SSS) and health i.e. how people perceive their position in the social hierarchy is significantly associated with health status, independently of objective economic indicators\textsuperscript{100}.

1.2.2.1 Explanations for social inequalities in mental illness

Two main explanations for the observed pattern between low SEP and mental disorder have been suggested and are briefly presented below.

- The selection or reverse causation hypothesis
- The causal hypothesis

Shortly, the selection or reverse causation hypothesis explains the observed pattern as individuals’ mental health status affects their social position. Having poor mental health in youth, for example, can lead to shorter education and less qualified work. The mental health status thus “selects” people into different SEP. In the causal theory on the other hand, lower SEP is believed to increase exposure to risk factors that might cause ill health and mental disorders\textsuperscript{101}. Suggestions have however been made that the two explanations should not be viewed as competing hypothesis rather as complementing each other. The causation theory is relevant when looking at causality issues, whereas none of the hypothesis is relevant when making plans on the societal level.

1.2.3 Social vulnerability

As mentioned above there are three well established and common measures of SEP. However, social differences in health can also be elucidated by studying health outcomes in the most vulnerable groups, for instance social assistance recipients, persons on long term sick leave, individuals living in a deprived neighborhood, lone parents, adolescents involved in juvenile delinquency, children in foster care, and students with low school grades.

Social assistance is foremost seen as a poverty measure but seems also to capture the most marginalized households\textsuperscript{102,103}. Lone parenthood has been shown to be a profound risk factor for children who run a higher risk of several health issues including mortality and delinquency\textsuperscript{104}. Parental educational level is used as proxy for childhood SEP that could affect adult health regardless of own achieved SEP\textsuperscript{72}. Earlier research has also shown international adoptees to
constitute a risk group for suicide\textsuperscript{105}. Children born to teen mothers are at higher risk for both abuse and neglect\textsuperscript{106}. As adolescents they also display higher risk for mental disorders and substance abuse. Regarding foster care, children entering the child welfare services before their adolescent years have in many cases been exposed to abuse and neglect, parental substance abuse or persistent parental mental health problems\textsuperscript{107,108}. Several large cohort studies have found high risks for both suicidal behavior and criminal behavior in this group during late adolescence and young adulthood, compared to majority population peers\textsuperscript{109-111}. Even though Sweden is considered a country with high equality regarding amongst other health care, we find large differences in health throughout the different regions\textsuperscript{112}.

Educational level is often used in public health studies of mortality and morbidity as a marker of SEP, but much less attention has been devoted to the health effects of different levels of school performances. In Study III we explore the association between school grades and suicide risk in young adulthood.

Socioeconomic factors can affect health in individuals differently depending on other factors such as sex, ethnicity, and age\textsuperscript{72}. Different socioeconomic factors can also operate at different levels, on the individual, household or neighborhood level.

### 1.3 SOCIOECONOMIC POSITION AND SUICIDE

Several studies have investigated the relationship between SEP and suicide\textsuperscript{87,113-116}. The most common finding is an inverse relationship where the lower the SEP the higher the risk for suicide. Variations in SEP imply differences in several exposures such as physical, psychosocial, environmental, and occupational factors as well as access to health care and differences in life style. The association between SEP and suicide is however somewhat inconsistent. Even though a majority of studies point in the direction of a negative relationship, studies have shown a positive association in psychiatric patients.

In a comparison of European countries low educational level in men was associated with an increased suicide risk in eight out of ten countries. Smaller socioeconomic inequalities were found among women. The overall result was the greater the socioeconomic disadvantage the higher the risk for suicide.\textsuperscript{114} In a meta-analysis by Li et al the authors found a greater negative association between SEP and suicide for men than for women\textsuperscript{117}, as did a Danish study including 15 648 suicides between the ages 18 and 65\textsuperscript{113}. Low SEP, measured as, low income, unskilled blue-collar work, unspecific wage work and unemployment, increased the risk of suicide more prominently for men than for women. Parenthood with young children lowered on the other hand the risk of suicide, especially among women. The authors concluded that different roles and expectations in women and men, both in society and in the family might affect their suicide risks differently\textsuperscript{113}.

A few Swedish national studies that examined self-inflicted injuries (hospitalized and death cases combined) among 10–19 year olds, found lower parental SEP to be associated with an increased risk of injury\textsuperscript{118,119}. Another Swedish study examined IQ at age 13 and the risk of suicide\textsuperscript{120}. No statistical evidence of an association was found in women, whereas high IQ in men was found to be associated with reduced suicide risk, however though, among men with a history of psychosis, high IQ was instead associated with an increased risk of suicide. Gunnell et al explained the association between low IQ and risk of suicide to be due to the importance of cognitive ability in either the etiology of serious mental disorder or an individual's capacity to solve problems while going through an acute life crisis or suffering from mental disorders\textsuperscript{48}. 

12
There is, however, not always consensus among studies. A Norwegian study that analyzed the association between childhood SEP (parents’ education, parent’s household income and father’s occupation) and suicide in adulthood found a positive relationship where higher childhood SEP increased the risk of suicide\textsuperscript{106}. Controlling for adult education and adult income strengthened the association for females while adult family status attenuated it. Pompili \textit{et al}, who extracted all deaths by suicide and natural causes during the years 2006 to 2008 from the Italian Mortality Database, also found a contrary result. Individuals with higher school attainment, compared to those with only a primary school degree, had significantly increased odds ratios of dying from suicide rather than from natural causes\textsuperscript{121}. The authors concluded that individuals with higher educational achievement and high premorbid functioning might be more prone to suicide risk when facing failures, and public shame. This association was however not as clear among the elderly except for men above age 75. Suicide risk is generally associated with low income, unemployment, educational underachievement, and being single, but some studies suggest that the opposite is true among psychiatric patients\textsuperscript{5,57,122-124}. In a cohort study based on the entire Danish population, Agerbo \textit{et al} investigated the risk of suicide among psychiatric patients and found that higher income and higher education carried higher suicide risks\textsuperscript{57}. Also, occupation has been shown to have little association with suicide among individuals who suffered from a psychiatric illness\textsuperscript{122}.

An inverse finding was seen in a Finnish study where good school performance at age 16 years was associated with increased risk of suicide in individuals who developed psychosis, whereas good school performance was associated with a lower suicide risk in individuals not developing psychosis\textsuperscript{56}.

One possible explanation for the association between SEP and suicide might be the underlying elevated risk for mental disorders in lower SEP\textsuperscript{50,125}. In some cases it seems that mental disorder is a factor on the causal pathway between SEP and suicide\textsuperscript{125}. The question is then if poor socioeconomic circumstances predispose people to mental disorders or if disposition to mental disorder prevent people from achieving higher SEP.

Whilst higher SEP appear to be protective in individuals who do not develop severe mental disorders, these protective effects seem to disappear (or are reversed) in people admitted to psychiatric inpatient care. Earlier research has found an inverse correlation between SEP and mental disorder regardless of causality\textsuperscript{101}. A plausible explanation for the positive relation between SEP and suicide in psychiatric patients is that psychiatric patients with higher SEP are more often employed, well-educated, and married and thus having more to lose, are more prone to anticipate negative reactions from others, and may feel more stigmatized or are ashamed about having a mental disorder. The association between SEP and suicide is thus somewhat inconsistent. Even though a majority of studies point in the direction of a negative relationship, studies have shown a positive association in psychiatric patients.

It has also been suggested that socioeconomic stratification itself may be a social force that has deleterious health effects for those in the lower strata\textsuperscript{86}.
2 AIMS

2.1 OVERALL AIMS

The overall aim of this dissertation is to increase knowledge on risk factors for suicide and whether the suicide risk is modified by socioeconomic position.

2.2 SPECIFIC AIMS

- Can information on different background variables be used to distinguish deaths classified as suicide from deaths classified as undetermined intent?

- Can information on different background variables be used to distinguish poisonings classified as suicide from undetermined intent and from unintentional poisonings?

- Can initiation of drug therapy with Selective Serotonin Reuptake Inhibitors (SSRI) act as a trigger for suicide?

- Is poor school performance from the nine years compulsory school a risk factor for suicide in young adulthood? Is the risk modified by parental educational level?

- Is juvenile delinquency a risk factor for suicide in young adulthood? Is the risk modified by parental educational level?
3 MATERIAL AND METHODS

3.1 BACKGROUND ON REGISTERS

Sweden and the other Nordic countries have a long tradition of collecting data on diseases and deaths. We employ epidemiological registers of high quality covering the whole population and some go as far back as to the 1950s.

Sweden has strict data protection laws which prohibit the collection of sensitive health data and data on social information. Health data that includes identifiers as the personal identity number may be gathered by obtaining informed consent from the patients or clients, or under special legislations. Health data registers constitute an important exception of this general principle. These registers form the basis of health care planning on a community level; they are used for epidemiological descriptive studies on mortality, and they are also used in follow-up studies of different diseases and for analytic studies on risk or survival. Population-based register data are often powerful, useful tools, provided that each registration is complete and valid.

All studies in this dissertation are based on data from health-data registers and other registers covering the entire population of Sweden. Due to the unique personal identity number addressed to all Swedish residents, it is possible to link different national registers and databases and thereby select a great amount of information on health along with different background variables. The national personal identity number system was introduced in Sweden in 1947 as a unique personal identifier. In the 1960’s the population records were computerized and in 1967 the check digit was added to the personal identity number.

In addition to health data registers and the Cause of Death Register, other registers held by Statistics Sweden, The National School Service Administration and The Swedish National Council for Crime Prevention were used in this dissertation. All registers used are presented below.

3.2 REGISTERS USED IN THIS DISSERTATION

3.2.1 The Cause of Death Register and Health Data Registers

The Cause of Death Register

Swedish statistics on causes of deaths are among the oldest in the world. They go back to 1749 when a nationwide report system was first introduced. At the beginning this responsibility lay with the clergy until 1860 when doctors were entrusted with the task of filling out death certificates, especially in cities with medical officers of their own.

In 1951 after various changes over the years the registration was adapted to the standards of the World Health Organization (WHO). WHO has since then included detailed instructions on collection, classification and dissemination of mortality data in the International Classification of Diseases (ICD), and WHO member states pledge themselves to prepare mortality statistics according to these specifications.

In 1961 the cause of death statistics was computerized in Sweden and data between the years 1952 to 1960 was also digitally registered in a “historical” register. For statistical purposes on an aggregated level this register is still useful, in spite of some personal identity numbers being missing or erroneous.
Today, the Cause of Death register is held by the National Board of Health and Welfare and comprises all deaths due to Swedish residents since 1952. The basis for the register is the death certificates executed in each case by a physician. During the last couple of decades a fully 90,000 deaths are reported annually. Only deceased who at the time of death were residents in Sweden are included in the register. This is regardless of citizenship and irrespective of where death occurred, in Sweden or abroad, although there seems to be an underreporting of deaths occurring abroad129. Hence, the register does not include stillborn, persons who died on a temporarily visit to Sweden, or asylum seekers who had not yet obtained residence permit.

In general the younger the deceased and the more violent death, the better the accuracy of the death certification. A majority of death occurs in older people who more often suffer from multiple conditions that can lead to more difficulties in establishing what finally caused death. The autopsy frequency has declined profoundly since the seventies. However, this does not suggest that the precision in establishing the cause of death has declined to the same degree. Provided that cases where a distinct clinical diagnosis is missing are further investigated, refined diagnostic methods along with higher probability of correct diagnosis prior death can make the decline in autopsies less crucial66.

Figure 4 shows the trend of autopsy rates in Sweden for all-cause mortality, suicides, and deaths with undetermined intent, in Sweden between the years 1980 and 2011.

Figure 4. Autopsy rates for all-cause mortality, suicides and undetermined intents in Sweden 1980-2011, percentage.

Despite the legislation that states that it is compulsory to within three weeks following death send in the death certificate to the National Board of Health and Welfare, a certain amount of certificates are annually missing. Figure 5 shows the numbers of certificates missing since 1975.
### Table: Number of certificates missing per year

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of certificates</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1975</td>
<td>5</td>
<td>0.006</td>
</tr>
<tr>
<td>1985</td>
<td>&lt;5</td>
<td>0.005</td>
</tr>
<tr>
<td>1995</td>
<td>329</td>
<td>0.300</td>
</tr>
<tr>
<td>2000</td>
<td>539</td>
<td>0.600</td>
</tr>
<tr>
<td>2005</td>
<td>687</td>
<td>0.700</td>
</tr>
<tr>
<td>2006</td>
<td>638</td>
<td>0.700</td>
</tr>
<tr>
<td>2007</td>
<td>773</td>
<td>0.800</td>
</tr>
<tr>
<td>2008</td>
<td>762</td>
<td>0.800</td>
</tr>
<tr>
<td>2009</td>
<td>1066</td>
<td>1.180</td>
</tr>
<tr>
<td>2010</td>
<td>1715</td>
<td>1.890</td>
</tr>
<tr>
<td>2011</td>
<td>1656</td>
<td>1.840</td>
</tr>
</tbody>
</table>

*Figure 5. Number of death certificates missing per year.*

The Cause of Death Register is used in all studies in this dissertation to obtain information on suicides including deaths classified as undetermined intent and also as an endpoint of follow-up.

**The Patient Register**

The Patient Register, also held by the National Board of Health and Welfare, contains psychiatric in-patient care from some regions since 1964 and on a national level since 1973, all in-patient care since 1987, and outpatient care (primary care excluded) since 2001. The purpose of this register is to follow the development of health in the population, to obtain information on health care consumption, to improve the abilities of prevention and treatment of disease and to contribute to the progress of health care.

This register was used in Study I to compare the level of psychiatric in-patient care prior to death between deaths classified as suicide and deaths classified as undetermined intent. In Study II the Patient Register was used to exclude patients with recent psychiatric hospitalizations (ICD-10: F00-F99), i.e. hospitalizations within one month before the dispensed prescription during both the case- and the control period since they could have initiated SSRI therapy at the hospital. In Study III and in Study IV the Patient Register was used to obtain information on hospitalization for mental disorders and substance abuse as indicators of mental illness and substance abuse.

**The Prescribed Drug Register**

The Prescribed Drug Register contains information on all dispensed prescribed drugs to the entire Swedish population from 1999 and onwards. The personal identity number is available since July 2005. The quality is regarded as very good where only 0.3% of the records lack information on personal identity number[^33]. All drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system. Measurement units of utilization are prescriptions, Defined Daily Doses (DDDs) and expenditures. Updates are carried out monthly.

This register is essential in Study II to obtain information on initiation with SSRI therapy (according to the ATC classification: N06AB). It is also used in Study I where we obtained prescriptions of neuroleptics, antidepressants and sedatives (ATC: N05A, N05B, N05C and N06A).
3.2.2 Socio demographic registers

The Total Population Register was established in 1968 and is held by Statistics Sweden. Statistics Sweden is the central government authority for official statistics and other governmental statistics and in this capacity also has the responsibility for coordinating and supporting the Swedish system for official statistics. The Total Population Register is an excerpt from the national registration of all Swedish residents at the Tax Agency. The Total Population Register is foremost used as a source for producing statistics on population basis by sex, age, marital status, and region etc. In this dissertation this register was used as basis for Study III and IV where all birth cohorts between 1972 and 1981 were selected.

The Swedish Population and Housing censuses of 1985 and 1990 were conducted at and are held by Statistics Sweden. Sweden has a long census history, the first being performed as early as in 1749. During the years 1860 to 1930, population censuses took place every tenth year, and from 1930 until 1990 every fifth year with the exception of 1955. No census has however been carried out since 1990. The purpose of these censuses was to describe the society from different perspectives such as the occupational situation, the households’ compositions, and the residents living conditions. This register was used in Study III and IV to obtain information on lone parenthood.

The Total Enumeration Income Survey, held by Statistics Sweden, contains data on all governmental benefits provided to Swedish residents as well as on all incomes and taxes. This register was used in Study III and in Study IV to collect information on social assistance recipiency and disability pension.

The Multi-Generation Register held by Statistics Sweden, is destined for linking together children, the so-called “index persons” and parents (both biological and adoptive). Also siblings and cousins can be linked to the index persons. This register is limited to index persons born 1932 or later with parents who have been registered in Sweden at some time since 1961. There are about 10 million index persons in this register. The Multi-Generation Register covers, for the most part, all index persons who have been registered since 1968. For those who were only registered between 1961 and 1967, coverage is good but not as comprehensive. Around 2 800, of those who emigrated between 1961 and 1967 and who did not return are missing in the register. This register was used in Study III and in Study IV to obtain information on adoption.

The Longitudinal Integrated Database Predestined for Labor Market and Similar Studies (LISA), contains several demographic variables such as; marital status, immigration and emigration, place of housing and family variables as number of children at home and their age, further it also contains information on education and employment, income and social assistance, and early retirement. This register is held by Statistics Sweden and was used in Study I, in Study III and in Study IV to obtain information on educational level.

3.2.3 Other registers

The National School Register, which is administered jointly by the Swedish National School Administration and Statistics Sweden, encompasses information on each individual’s educational achievement, i.e. grades by subject as well as grade point average (GPA), for all students graduating in Sweden since 1988. This register was used in Study III to obtain exposure information on GPA from the nine years compulsory school.
The Crime Register, held at the Swedish National Council for Crime Prevention, contains information on all convictions in Sweden from age 15 and has very good coverage, only 0.05% of the convictions between 1988 and 2000 have incomplete personal identity numbers. This register was used in Study IV to obtain exposure information on convictions between ages 15 and 19.

The Swedish Register of Children and Young Persons Subjected to Child Welfare Measures was established in 1968 at Statistics Sweden but is held by the National Board of Health and Welfare since 1994. The purpose is to supply local authorities with statistics on child welfare interventions for evaluation and follow-up. Former information has been updated as far as possible according to new regulations. This register was used in Study III and in Study IV to retrieve information on foster care.

### 3.3 EXPOSURES

In Study I we examined if information on different background variables can be used to distinguish deaths classified as suicide from deaths classified as undetermined intent. All suicides and undetermined intents between the years 1987 and 2011 were included. We analyzed the following background factors; age, sex, country of birth, method used, marital status, educational level, prior in-patient care for self-inflicted harm, prior in-patient care for alcohol and/or drug abuse, prior psychiatric in-patient care, and recent prescriptions of anti-depressants, sedatives and anti-psychotics.

In Study II we selected all suicides and all deaths classified as undetermined intent between 2007 and 2010 from the Cause of Death Register. We then linked the cases to the Prescribed Drug Register to obtain exposure information on prescriptions of SSRI (according to the Anatomical Therapeutic Chemical (ATC) classification: N06AB). Prescriptions were obtained during the case period that took place during 28 days prior suicide and during the corresponding control period (of 28 days) 364 days earlier.

Exposure in Study III was grade point average (GPA) from the nine years compulsory school, equivalent to junior high school. During these years (1988-1997) the Swedish school system used a grade scale that was normally distributed ranging from 1 (lowest grade) to 5 (highest grade), where 3 was defined as the national average. We categorized all subjects into five different exposure groups according to their GPAs and created one separate group for students with incomplete grades. Students with highest grades were placed in grade group 5. Consequently students with lowest grades were categorized into group 1 and students with average grades were placed in group 3. Students with highest grades (Group 5) were used as the reference group.

In Study IV the exposure was number of convictions between ages 15 and 19. We summarized all convictions, categorizing our cohort into four groups; Group 1 consisted of individuals with one conviction, Group 2 included individuals with two to four convictions, Group 3 consisted of individuals with five or more convictions or individuals with less than five convictions but with more severe penalties, i.e. probation or imprisonment, and finally Group 0 comprised those who had not been convicted of a crime between ages 15 and 19.
3.4 SENSITIVITY AND SPECIFICITY

The concepts of sensitivity and specificity have to do with accurateness in assessing if an ill individual is diagnosed as ill (positive) and whether a healthy individual is correctly diagnosed as healthy (negative). Sensitivity measures the proportion of actual positives that are correctly identified as such whereas specificity measures the proportion of negatives that are correctly identified as negatives.

The predictive positive value is also referred to as precision rate, and is the proportion of positive test results that are true positives. The predictive negative value is accordingly the proportion of negative test results that are true negatives. This is illustrated in Figure 6.

<table>
<thead>
<tr>
<th>Test result</th>
<th>Disease</th>
<th>No disease</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>a</td>
<td>b</td>
<td>a+b</td>
</tr>
<tr>
<td>Negative</td>
<td>c</td>
<td>d</td>
<td>c+d</td>
</tr>
<tr>
<td>Total</td>
<td>a+c</td>
<td>b+d</td>
<td>a+b+c+d</td>
</tr>
</tbody>
</table>

Sensitivity test: \( \frac{a}{a+c} \)  
Predictive value positive of test: \( \frac{a}{a+b} \)

Specificity test: \( \frac{d}{b+d} \)  
Predictive value negative of test: \( \frac{d}{c+d} \)

Figure 6. Illustration of sensitivity, specificity, predictive value positive, and predictive value negative

Most literature in suicide research has focused on the sensitivity of suicide certification, which is a measure of the degree to which true suicides are certified correctly, or classified, as such. The other side, specificity, has mostly been ignored, since it is not believed that other modes of death are misclassified as suicides. To illustrate the concepts of sensitivity and specificity in a suicide setting an example of 100 cases referred to medical examiners in Los Angeles county California is shown in Figure 7.

<table>
<thead>
<tr>
<th>Death certification</th>
<th>Suicide</th>
<th>Not suicide</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suicide</td>
<td>44</td>
<td>8</td>
<td>52</td>
</tr>
<tr>
<td>Not suicide</td>
<td>11</td>
<td>37</td>
<td>48</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>45</td>
<td>100</td>
</tr>
</tbody>
</table>

Sensitivity test: \( \frac{44}{11+44} = 80.0\% \)  
Specificity test: \( \frac{37}{8+37} = 82.2\% \)

Predictive value (+) \( \frac{44}{8+44} = 84.6\% \)  
Predictive value (-) \( \frac{37}{11+37} = 77.1\% \)

Note: Data source: Litman, Curphey, Shneidman, Farberow, & Tabachnick (1963) Los Angeles County, California

Figure 7. Example of sensitivity and specificity in certification of suicides

In the above example the certification of suicide would have been incorrect in 8 cases (15.4%), and the certification of non-suicides would have been incorrect in 11 cases (22.9%).
3.5 CONFOUNDERS, MEDIATORS, AND ADHERENCE

Failure to distinguish a presumed confounder from a mediator is one of the most common errors in epidemiology. These two kinds of variables cannot be distinguished on statistical grounds; they can only be separated from each other based on an understanding of the disease process.

A confounder is an extraneous variable that correlates (positively or negatively) with both the independent and the dependent variable, i.e., the exposure and the outcome. Importantly, a confounder is not on the causal pathway between the outcome and the exposure. When confounding is present, the true association between the exposure and outcome is blurred due to the effect of the confounding factor. A common example is the spurious correlation between alcohol consumption and lung cancer. At first one might be tempted to regard this as a “true” association, i.e. interpreted as alcohol consumption increase the risk of lung cancer. When examining the data one will however find that a third variable, smoking is correlated to both alcohol consumption and to lung cancer. Thus, smoking is called a confounder.

![Figure 8. Scheme of the relation between exposure, outcome and a confounder](image)

The effects of a confounder can be handled in several ways, for example by matching, stratification or by adjusting in a regression model. In Study III and IV we handled confounding by using multi adjusting regression models.

A mediator has an effect by itself and is part of a causal chain from the exposure to the outcome, thus creating a spurious association. Schizophrenic patients have for instance higher risk of lung cancer. However, smoking is more common in schizophrenic patients and when you remove the effect of smoking the association between schizophrenic patients and lung cancer disappears.

![Figure 9. Scheme of the relation between exposure, mediator, and outcome](image)

The concept confounding by indication is often used in pharmacoepidemiology in evaluation of pharmacologic therapy where the preferred design is a controlled clinical trial. When results from a clinical trial are not available, the alternative design is observational epidemiological studies of drug effects where confounding by indication is frequently encountered. Confounding by indication is a bias that stems from inherent differences in prognosis between patient groups given different therapies. The more ill are more likely to get a prescription. Confounding by indication is our main limitation in Study II.

Adherence is a common concept in medicine and refers to what extent a patient follows (adheres to) medical advices/instructions. Adherence can vary from an occasional missed dose of
medicine to chronic defaulting on medication regimens. The patient and physician may or may not know when this happens, and there may be any number of contributing factors or explanations. Some patients may be unsure about their medication and need clarification, while others who are well informed may actively resist complying with their prescribed treatment. Adherence is of immediate importance in Study II where we study prescriptions of SSRI and presume initiation at the same day as dispensation.

### 3.6 STUDY DESIGNS

#### 3.6.1 Cohort studies

A cohort is defined as a designated group of subjects who are followed or traced over time. In its simplest form the cohort is divided into two groups, the exposed and the unexposed. Ideally the exposed and unexposed groups are similar in all aspects except one, which is the one we want to study, i.e. the exposure.

Another crucial criterion is that all subjects, both exposed and unexposed, have to be “at risk” of developing the outcome. If the outcome of study is death there is normally not a problem since all people alive are at risk of dying. But if you for example want to study first time myocardial infarction (MI), only people without a history of MI can be included. Individuals who already experience a myocardial infarction might be at risk of experience theirs second or third, but not their first and must hence be excluded. The cohort is sometimes also referred to as the population at risk.

When you define your exposure you have to be cautious. It must be absolutely clear who is regarded as exposed and who is regarded as unexposed. What does it take to be classified as exposed? If cigarette smoking is your exposure, who should be regarded as exposed? Are you exposed if you smoke just once a month? If you just quit smoking? These questions deal with two concepts that are important to consider in assessing the exposure and they are duration and intensity. It might also be of value to quantify the exposure by degree instead of using only a binary “yes” and a “no” group. The purpose of a cohort study is to measure the occurrence of a specific outcome, usually disease or death, and compare the outcome occurrence between the exposed and the unexposed groups. It is therefore important to have access to exposure information for the whole cohort. You have to be certain who is exposed and who is unexposed.

In this dissertation we used clearly defined groups as exposures; in Study III school grades categorized into five distinct groups due to grade point average (and a sixth group for incomplete grades) and in Study IV the number of convictions between ages 15 and 19 categorized into four groups; no convictions, 1 conviction, 2-4 convictions and 5 or more including individuals with less number of convictions but with more severe penalties such as probation or imprisonment.

It is also important that the outcome is well defined, that it is specific and of course, measurable. Failure to assess objective and measurable outcomes can lead to non-interpretable results. In some studies the outcome can occur several times, like migraine. In this dissertation the outcome is suicide and can therefore only occur once.

Two main types of data collection are available, prospective and retrospective. In the former type of study you select your exposed and unexposed groups and then track your subjects forward in time from exposure to outcome. In a retrospective study you use already existing data (which is less costly) and you can for instance identify your subjects from already available
register data. The time they are at risk then actually occurred before the study began. However, the study still moves from exposure to outcome. Retrospective cohort studies were performed in Study III and in Study IV.

In Study III we selected all Swedish residents born between 1972 and 1981 (N=1 073 684) from the Total Population Register. At least one parent had to be born in Sweden (904 300 individuals). We excluded students who had been inpatient treated for substance abuse and psychiatric inpatient care before graduation (n=4 234, 0.4 %). After excluding also those who died before age 15 (n=1 724, 0.2 %), our final cohort consisted of 898 342 individuals.

Study IV also included all birth cohorts between 1972 and 1981 (n=1 067 202) in Sweden. We excluded children who had been diagnosed with mental retardation up until age 17 (n=1 834) as well as children who died before the age of 20 (n=4 443). Only individuals alive at age 20 and who had been Swedish residents between ages 7-19 were included (excluding n=68 328). Finally 992 881 individuals were included in our cohort.

### 3.6.2 Case cross-over studies

The case-crossover design was introduced in the 1990’s by Maclure and was first used to study triggers of myocardial infarction. The original study aim was to use a case-control approach to investigate why the incidence of myocardial infarction peaks in the morning. And the question was who should be in the control group? The researchers came up with the idea of the cases being their own controls but at a different time point. After the initial myocardial infarction studies researchers started to use this method in analyzing injuries.

The case-crossover design is very similar to a matched case-control study with the important difference that the cases serve as their own controls, but at a different point in time. The purpose with this design is to study if some outcome was triggered by another event happening just before the outcome in time. Time is therefore very crucial in this design.

This method is preferably used when exposure causes a transient change in risk of a disease with acute onset. The induction time, that is, the time between exposure and the outcome, is assumed to be short, hours or days rather than years.

If an exposure has a triggering effect, it should be more frequent in the period prior outcome, than in the more distant control period without outcome. The exposure frequency during the a priori time period before the event i.e. the case period is compared to the exposure frequency during one or more control periods for the same individual.

The case cross-over design was used in Study II where we analyzed whether initiation with SSRI therapy can act as a short-term trigger for suicide.

### 3.7 STATISTICAL METHODS

#### 3.7.1 Descriptive analyses

In Study I we compared systematic differences in background information between deaths classified as suicides and deaths classified as undetermined intent. The aim was to investigate if information on different background variables can be used to distinguish deaths classified as suicide from deaths classified as undetermined intent.
We presented trends of death rates per 100,000 inhabitants. We also calculated different ratios where we have divided number of undetermined deaths with the number of suicides i.e. a ratio of 1 equals the same number of suicides as undetermined intents whereas a ratio below 1 equals fewer undetermined intents and a ratio above 1 equals more undetermined intents than suicides.

\[
\text{Ratio} = \frac{\text{Undetermined intents}}{\text{Suicides}}
\]

All deaths classified as either suicide or undetermined intent between 1987 and 2011 were included. Since a majority of deaths classified as undetermined intent are poisonings and it is often difficult to establish intent in these deaths, we chose to study poisonings separately in a sub analysis. In this analysis we also selected all deaths classified as unintentional poisonings (ICD-10: X40-X49) as either the underlying cause or as contributing cause between 1997 and 2011. Because of new regulations on classifying unintentional poisonings between ICD-9 and ICD-10 we only analyzed the years classified according to ICD-10.

3.7.2 Case cross-over analyses

In case cross-over studies one can use two different approaches. The frequency approach (comparing exposure frequency during the case period with the control period(s)) using logistic regression to obtain odds ratios (OR), the matched-pair interval approach (using control information based on the matched-pair control period(s)) where you use conditional logistic regression and also obtain OR. The OR reflects the odds of exposure in the case period compared to the odds of exposure in the control period.

In Study II we used a case-crossover design with the matched-pair interval approach analyzed by conditional logistic regression. We used conditional logistic regression since we wanted to estimate association of a within-strata exposure (drug exposure) and outcome. Conditional logistic regression works in nearly the same way as regular logistic regression, except we needed to specify which individuals belonged to which matched set (e.g., which pair) or stratum. We compared frequency of initiation with SSRI therapy in the case period, that was defined as 28 days prior suicide, to the frequency during the control period (one year earlier), which is represented by the OR with 95% CI.

3.7.3 Survival analysis

Contrary to the intuitive understanding of this concept, survival analysis does not only have to deal with survival. Another commonly used name is time to event analysis. The ability to censor study subjects is what is unique with this method. Survival analysis is used when you compare two groups with regard to a specific outcome. The outcome can be time to: disease, disease recurrence, and recovery to health. One group of subjects are exposed to a factor (exposure) that you believe could be contributing to the outcome (increase the risk) or protective (decrease the risk), and the other group is not exposed. One count and add up time after the exposure when the subjects are “at risk” for the outcome in question. The time “at risk” is referred to as the follow-up time. The purpose is to compare if the exposed group experience the outcome more often than the unexposed group per unit of time or vice versa.

The ideal way of performing survival analysis is to have two identical groups who only differ with regard to the studied exposure. In reality and when you study human beings this is of course not possible. However, you should as a researcher aim at having as similar groups as
possible.

A study subject may be censored before the end of follow-up. This means that for some reason you can no longer follow this subject. This could be due to emigration, loss of contact, or death (if death is not the studied outcome). When a subject is censored she or he still contributes with the amount of time she has been “at risk”.

In survival analysis one always need both a starting point, from when you start counting follow-up time and an ending point when you stop counting follow-up time. It is very common for subjects to enter the study continuously throughout the length of the study. Meaning, in reality in calendar time, both the entry and the exit time of the subjects are staggered and can occur at any time throughout the course of the study. One commonly used measure in survival analysis is the incidence rate ratios (IRR). To calculate IRR you add up the time units (e.g. hours, days, months or years) when the subjects are “at risk” for the outcome in question, the follow-up time. Total time for the exposed and the unexposed constitute the nominators. The denominators are the total number of outcomes occurred during the follow-up time.

In epidemiology effects can be measured either on the absolute or the relative scale. The most commonly used effect measures are the relative risk (RR), and the risk difference (RD), both comparing the risk or incidence rate in two groups, in relative and absolute terms, respectively. Only relying on relative differences without taking the underlying risks into account can lead to inaccurate conclusions. An example hereof is a study comparing mortality in male manual and non-manual workers in Europe. The results showed highest RR in the Nordic countries; however, the baseline mortality in non-manual workers was lower in the Nordic countries, and comparisons between relative risks is not accurate. This is because it is easier to get a high relative risk when the baseline is low. The RD always expresses the absolute difference between two studied groups, whereas the magnitude of the RR will depend on the baseline level of the reference group. A high relative risk will thus not necessarily affect large groups of individuals. And on the contrary a relative small relative risk, might affect a substantial amount of people and generate a real public health problem. An important feature of relative risk is that it tells you nothing about the actual risk. This can be very important for evaluating how substantial a relative risk increase might be. A small increase in risk in a large population can result in many deaths. And opposite, a high risk does not necessarily affect large groups of individuals.

In this dissertation survival analysis is used in Study III and Study IV and the outcome in both studies is suicide. Exposure in Study III is final school grades from the nine years compulsory school. We followed our cohort from the 1st of July the year of graduation until the 31st of December 2006. Hence, the follow-up period spanned from 9 to 18 years, or until age 25 for the youngest born in 1982 and up to age 34 at most for the oldest, those born in 1971.

Exposure in Study IV was number of convictions between ages 15 and 19. We followed our cohort from age 20 until the 31st of December 2006. The follow-up period spanned from 5 to 14 years, or until age 25 for the youngest up to age 34 at most for the oldest.

3.7.3.1 Effect modification and stratified analyses

When a variable (positively and negatively) modifies the observed effect of a risk factor on the outcome, it is known as an effect modifier. This means that different groups have different risk estimates when effect modification is present. Identifying effect modifiers can be of immense value in health prevention. A common example is the campaign against driving under
the influence (DUI) where driving in itself is a risk factor for accidents as is drinking, but the two combined profoundly increase the risk.

One cannot speak in general terms of presence or absence of effect measure modification. One has to specify if you refer to the risk difference (RD) or the relative risk (RR). The existence of effect modifiers requires measuring an effect in subgroups (strata) of the study population called stratified analysis.

Stratified analyses were performed in Study III and in Study IV. In Study III we examined if parental SEP (measured as highest attained educational level) was an effect modifier. Hence we analyzed effect modification from parental education by dichotomizing this variable with 12 years of education or more in the highest category and below 12 years in the low category. Grade point average was merged into three groups 1-2, 3, and 4-5. In Study IV we also wanted to further examine whether social background modified the relationship between delinquency and suicide. We established six mutually exclusive groups based on parental education, and conviction group. The four groups for parental education were reduced to two groups: 9-12 years of education, and more than 12 years of education. We merged the four convictions groups into three groups: conviction Group 0, conviction Group 1+2, and conviction Group 3.

### 3.7.4 Risk and Odds

In general settings the terms ‘risk’ and ‘odds’ are often used interchangeably as if they described the same quantity. In statistics, however, risk and odds have particular meanings and are calculated in different ways. Ignoring the difference between them might result in misinterpretations of the results.

A risk describes the probability of a certain (health) outcome and is commonly expressed as a decimal number between 0 and 1, but can also be expressed in percent. A more common way to express risk is as number of cases per 1 000, or if the risk is 0.1 it is usually expressed as one out of ten. It is also of importance to bear in mind that the magnitude of the RR will depend on the baseline level of the reference group.

Odds are the ratio of the probability that an outcome will occur to the probability that the outcome will not occur. It is commonly used in gambling and can be expressed as for instance 1:3 (0.33). The interpretation of odds is less intuitive than for risk, but is usually interpreted as being equivalent to the relative risk. However the odds ratios do not approximate well to the relative risk when the prevalence of the outcome is high. When the outcome is rare, the difference between risks and odds is small, and an approximation is adequate.

Odds can nevertheless be converted into risks and vice versa:

\[
\text{Risk} = \frac{\text{Odds}}{1 + \text{Odds}}
\]

\[
\text{Odds} = \frac{\text{Risk}}{1 - \text{Risk}}
\]

In Study II we calculated odds ratios by a matched pair approach. The odds ratio (OR) represents the odds of SSRI initiation during the period prior to suicide compared to the odds of SSRI initiation in the control period (one year earlier). In this study we considered the ORs as estimates of the incidence rate ratio comparing the risk of suicide in exposed time-periods to the suicide risk in unexposed time periods.
3.7.5 Precision

When we calculate effects in epidemiology we talk about point estimates i.e. a risk or an odds. The precision of the point estimate is measured by using a confidence interval (CI), which shows the range within which the true point estimate is likely to lie with a specified probability. The purpose with CI is to indicate the amount of random error. Commonly the significance level is arbitrary set to 95%. If the interval contains the null value many researchers are prone to state non-significance and if not, the estimate is seen as significant. However, according to Rothman it is inadequate to use a confidence interval to determine significance.\(^\text{134}\)

3.7.6 Ethical approvals

The studies are approved by the ethical committee at Karolinska Institutet, Stockholm, Sweden. Study I and Study II, registration number: 2011/295 -31/4 and Study III and Study IV registration number: 60-5075/2007.
4 RESULTS

4.1 STUDY I: SUICIDE OR UNDETERMINED INTENT? - A REGISTER-BASED STUDY OF SIGNS OF MISCLASSIFICATION

Objective: To investigate if information on different background variables can be used to distinguish deaths classified as suicide from deaths classified as undetermined intent.

We selected 46,909 deaths that occurred in Sweden during the studied period 1987-2011 of which 31,883 (68%) classified as suicides, 9,196 (20%) classified as deaths with undetermined intent, and 5,830 (12%) classified as unintentional poisonings (ICD-10: X40-X49, used in a sub analysis on poisonings between 1997-2011). Since a majority of deaths classified as undetermined intent are poisonings and as it is often difficult to establish intent in these deaths, we chose to study poisonings separately. In this sub analysis we also selected all deaths classified as unintentional poisonings as either the underlying cause or a contributing cause. Because of changes in the regulations of classifying unintentional poisonings between ICD-9 and ICD-10 we did not include the years coded according to ICD-9 (1987-1996). Due to changes in the regulation we also included unintentional poisonings both as the underlying and as the contributing cause of death.

It was more common with prior hospitalization for self-inflicted harm among female suicides 21.1% [95% CI: 20.1-22.1] compared to 14.3% [95% CI: 12.8-15.8] in undetermined intents. Prior psychiatric hospitalization showed similar difference with 38.1% [95% CI: 36.9-39.3] among female suicides and 26.7% [95% CI: 24.8-28.6] among female undetermined intents. Male suicides and male undetermined intents showed equal proportion of prior in-patient care for self-inflicted harm 9.6% [95% CI: 9.1-10.1] in suicides and 9.2% [95% CI: 8.3-10.1] in undetermined intents. Prior hospitalization for substance abuse was in contrary more common among undetermined intents in both sexes, 27.1% [95% CI: 26.0-28.2] among undetermined intents and 9.6% [95% CI: 9.2-10.0] among suicides altogether.

In another sub analysis containing 9,779 deaths during 2006 - 2010 we also obtained information on prescriptions of neuroleptics, antidepressants and sedatives during their last years prior to death. Prescription was also categorized according to elapsed time between last dispensation and death into five mutually exclusive groups (1 month, 6 months, 1 year, 2 years, and no prescription). Among all suicide victims 5,870, 62% (75% in women and 60% in men) had at least one prescription and the corresponding number for undetermined intent was also 62% (86% in women and 55% in men). When we calculated elapsed time between dispensation and death different patterns emerged among women and men. More than half, 51.4% [95% CI: 47.0-55.8] of female undetermined intents had a prescription during the last month compared to 32.8% [95% CI: 30.6-35.0] of female suicides. However, during the last six months around 60% in both groups had at least one prescription. Among male suicides 32.1% [95% CI: 30.7-33.5] had a prescription during the last month compared to 18.1% [95% CI: 15.7-20.5] among undetermined intent. A gradient in prescription of psychotropics during their last six months of life was found among poisonings where it was most common among suicides (73.3% in women and 60.4% in men) followed by undetermined intent (62.2% in women and 50.5% in men), and unintentional poisonings (55.7 in women and 41.3% in men).
4.2 STUDY II: INITIATION WITH SELECTIVE SEROTONIN REUPTAKE INHIBITORS AS TRIGGER OF SUICIDE - A NATIONWIDE REGISTER-BASED CASE-CROSSOVER STUDY

Objective: To investigate if initiation with selective serotonin reuptake inhibitors (SSRI) therapy can act as a trigger for suicide.

The analyses included 5 913 suicides between 2006 and 2010, 1 711 (29 %) women and 4 202 (71 %) men. With a case-control design, we set the case period to take place 28 days prior to suicide with a previously prescription free time window (wash-out period) of four months. The corresponding control period took place 364 days earlier so the index day occurred on the same weekday.

We calculated number of initiations with SSRI therapy during the case- and control period respectively. During the 28-day case period 59 women and 169 men were exposed to SSRI initiation while 22 women and 41 men were exposed during the control period one year earlier.

Our results showed an overall increased suicide risk during the first 28-days of initiation of SSRI therapy with an OR of 2.7 [1.6-4.4] for women, and 4.3 [3.0-6.1] for men. Induction time analyses showed the highest overall risk to take place during days 8-11 after SSRI initiation with an overall OR of 9.7 [2.9-31.7] and with sex specific OR for women of 7.0 [0.9-56.8] and for men 11.0 [2.6-46.8]. Women showed the highest OR during days 12-15 with OR 8.00 [95% CI: 1.0-63.7]. When we extended the wash-out period from 4 to 6 months, we found similar results as the main analysis.

The odds ratios of suicide during the first 28 days of initiation with SSRI therapy seemed to slightly increase with age. We had however too few cases to study adolescents separately so the youngest age group included individuals aged 13-24.

When we restricted our analysis to cases classified as violent suicides, the overall OR for suicide during the first 28 days of initiation of SSRI therapy was 4.8 [95% CI: 3.2-7.2] for men and 3.2 [95% CI: 1.6-6.3] for women. For women and men combined the OR for violent suicide during the 8-11 day period after SSRI initiation was 19.0 [95% CI: 2.5-141.5].

In a further sub analysis we looked exclusively at certain suicides and got OR 4.1 [95% CI: 3.0-5.7] for women and men combined during the 28 days period. When we solely studied undetermined intents as outcome we obtained OR 1.5 [95% CI: 0.8-7.7].

4.3 STUDY III: SCHOOL GRADES, PARENTAL EDUCATION AND SUICIDE - A NATIONAL REGISTER-BASED COHORT STUDY

Objective: To investigate if final school grades from the nine years compulsory school are correlated with the risk of suicide in young adulthood and if so, to what extent intergenerational effects of parental educational level can explain this.

This cohort study included 436 293 women and 462 049 men. During the follow-up period 1 490 suicides occurred, 414 in women and 1 076 in men (20% were undetermined intents). The suicide rate was 7.7 per 100 000 females and 18.7 per 100 000 men. Mean age at suicide was 23.8 for both sexes. The average grade point average (GPA) among females was 3.38 and 3.09 among males. Students from households with higher education had higher school grades and
tended to have slightly lower rates of suicide. Adopted children had more than twice the suicide rate compared with non-adopted children.

We calculated incidence rate ratios (IRR) with 95% CI and presented four different models. The crude relative risks (adjusted only for year of graduation) displayed a gradual risk increase with decreasing levels of grades in both women and men (model I). When we adjusted for family living conditions, i.e. parental education, lone parent status, receipt of social welfare or disability pension, place of schooling, adoption and maternal age in (model II) we ended up with slightly attenuated risk estimates. Adjustment for parental in-patient care due to psychiatric disorders (model III), generated very similar results as model I. Students who had been treated as inpatients for substance abuse and psychiatric inpatient care before graduation were excluded.

In the fully adjusted model (model IV) we obtained a gradient among women ranging from IRR: 1.36 [95% CI 0.84-2.20] for group 4 (second highest grades) down to IRR: 2.67 [95% CI 1.42-5.01] for group 1 and finally IRR: 4.99 [95% CI 2.85-8.72] in the group with incomplete grades. A similar gradient was found among men where IRR ranged from 1.52 [95% CI 0.94-2.45] in group 4 to 6.12 [95% CI 3.71-10.11] in the group with incomplete grades. We also performed the same analysis with only certain suicide as outcome and obtained similar risks estimates and gradients.

In a restricted analysis we followed our cohort only to age twenty. This resulted in similar relative risks for men but slightly lower risk estimates for women.

In a stratified analysis we analyzed the effect modification from parental educational level. We dichotomized parental education into one “high” category defined as 12 years of education or more and up to 11 years as the “low” category. GPA was categorized into three groups; “low GPA” (consisting of incomplete grades, grade group 1 and group2), “average GPA” (grade group 3), and “high GPA” (grade groups 4 and 5). In this analysis we found that the effect of having low grades was not modified by parental educational level.

4.4 STUDY IV: JUVENILE DELINQUENCY, SOCIOECONOMIC BACKGROUND AND SUICIDE - A SWEDISH NATIONAL COHORT STUDY OF 992 881 YOUNG ADULTS

Objective: To investigate if juvenile delinquency measured as number of convictions between ages 15 and 19, increase the risk of suicide in young adulthood. In addition, we wanted to examine whether the risk increased with increasing numbers or severity of convictions and finally also to see if socioeconomic background modified the relationship.

A total of 992 881 women and men were included and followed with respect to suicide. We found that 5.9 % of women and 17.9% of men had at least one conviction between ages 15 and 19. Of the 226 women in the conviction group 3, 31.1% had more severe penalties and 69.0 % had five convictions or more. Nearly 12 % of the men had one conviction, and 4.9% had between two and four convictions. Of the 1.2 % in conviction group 3, 4 % had more severe penalties, thus 61.0 % had five convictions or more.

Compared to adolescents with no convictions, those with higher numbers of convictions had more often been treated in psychiatric in-patient care, as well as for substance abuse disorders. Their parents had more often received social welfare benefits or disability pensions, and had suffered more from psychiatric disorders or substance abuse compared to parents of adolescents.
with no convictions. The most convicted adolescents were also more often raised in foster homes.

We calculated IRR in four different models where the non-convicted group was used as the reference group. The crude IRRs (adjusted only for year of birth) displayed a gradual increase of suicide risk, i.e. the risk increased as the number of convictions increased (model I). Women with one conviction had 2.6 times higher IRR [95% CI 1.9 - 3.6] compared to non-convicted. The corresponding IRR for men was 2.2 [95% CI 1.9 - 2.6].

In the fully adjusted model women with one conviction had IRR 1.7 [95% CI: 1.2-2.4] and men 2.0 [95% CI: 1.7-2.4] meanwhile the heaviest convicted women had IRR 5.7 [95% CI 2.5-13.1] and the corresponding risk for men was 6.6 [95% CI: 5.2-8.3]. Analyses restricted to only certain suicides as outcome generated similar results. Analyzes that were restricted to only certain suicides as outcome generated similar results. Further on, when looking at age group 20-24 and 25-34 separately, we also received similar results.

In a sub analysis we studied violent crimes separately. Violent crime was defined according to Fazel et al., as homicide, assault, robbery, arson, sexual offence (rape, sexual coercion, child molestation, indecent exposure or sexual harassment), illegal threats or intimidation. Hence, burglary and other property offences, traffic offences and drug offences were excluded. An adolescent with both violent and non-violent convictions was placed in the ‘violent’ group.

Table 2. Suicide risks for violent and non-violent offenders, IRR by sex.

<table>
<thead>
<tr>
<th>Conviction group</th>
<th>Number of suicides</th>
<th>Suicide Rate (No/100 000 person years)</th>
<th>Adjusted IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Model I *</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never convicted</td>
<td>321</td>
<td>6.9</td>
<td>1 (REF)</td>
</tr>
<tr>
<td>Convicted (no violent crime)</td>
<td>37</td>
<td>14.8</td>
<td>2.2 (1.6-3.1)</td>
</tr>
<tr>
<td>Convicted for violent crime</td>
<td>38</td>
<td>87.3</td>
<td>12.9 (9.2-18.0)</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never convicted</td>
<td>563</td>
<td>13.4</td>
<td>1 (REF)</td>
</tr>
<tr>
<td>Convicted (no violent crime)</td>
<td>238</td>
<td>33.9</td>
<td>2.5 (2.2-3.0)</td>
</tr>
<tr>
<td>Convicted for violent crime</td>
<td>285</td>
<td>82.1</td>
<td>6.1 (5.3-7.1)</td>
</tr>
</tbody>
</table>

As seen in Table 2 female non-violent offenders had, in the fully adjusted model 50% greater risk of suicide and among violent offenders the risk increase was 4 times that of never convicted. The IRRs for men were 2.2 [95% CI 1.9–2.6] for non-violent and 4.2 [95% CI 3.6–4.9] for violent offenders, respectively.

To further investigate whether social background modified the relationship between delinquency and suicide we performed a stratified analysis. We established six mutually exclusive groups based on parental education and conviction group. The four groups for parental education were reduced to two groups: 9-12 years of education, and more than 12 years of education. We merged the four conviction groups into three groups: conviction Group 0, conviction Group 1+2, and conviction Group 3. We found a slight increase in suicide risk for those whose parents had fewer years of education. However, after adjusting for a range of other social background factors and mental health factors, this association was eliminated.
5 DISCUSSION

5.1 MAIN FINDINGS

The main findings in this dissertation are that low school grades increase the risk of suicide in young adulthood as do juvenile delinquency. Also, initiation with selective serotonin reuptake inhibitors (SSRI) therapy seems to trigger a short-term increased suicide risk. Despite several differences in background variables between deaths classified as suicide and deaths classified as undetermined intent, this information does not seem to be enough to distinguish between these two modes of death.

Our stratified analyses (Study III and IV) did not indicate any differences in suicide risk with regard to socioeconomic position. This means that the suicide risk was similar when we looked at students in the same grade group and compared students whose parents had long education (university) with students whose parents had less years of education. So as for convicted adolescents, their suicide risk did not differ between adolescents whose parents had university education and adolescents whose parents had less years of education. However, several risk factors were more common among individuals whose parents had less years of education. We found a gradient in grade point average (GPA) where children whose parents had shortest education (9 years) had lowest GPA in average and consequently, children whose parents had more than 13 years of education had highest GPA. Students growing up with a lone parent or in a household receiving social assistance had lower GPA and higher suicide rates. As did students whose parents had experienced psychiatric in-patient care. Delinquent behavior was more common among adolescents whose parents had lower SEP. Adolescents from lower SEP families were also more likely to experience risk factors like social assistance, lone parenthood, heritage of mental disorders and drug abuse. Youths, regardless of their parents educational level, who do not engage in school-based instructional and social activities might be of risk of decreased academic achievement and increased adjustment problems (delinquency). They might not only miss the opportunity to acquire an education but they are also at risk of being exposed to risky activities141. In line with our results we emphasize the importance of prevention through early targeting of students with poor school performance and youths with a troublesome home environment.

5.1.1 Possible misclassification of deaths classified as suicide and deaths classified as undetermined intent (Study I)

Suicide is the outcome in all studies included in this dissertation. In Study I we investigated if information on background variables such as; educational level, marital status and previous psychiatric in-patient care among others, can be helpful in distinguishing deaths classified as suicide from deaths classified as undetermined intent. Earlier in-patient care for self-inflicted harm and psychiatric in-patient care were more common among female suicides than among female deaths classified as undetermined intent. Mental disorder is the most common risk factor for suicide2,117,142,143. As history of mental disorder was more common among suicide deaths than deaths classified as undetermined intent this may indicate that a certain proportion of undetermined intent probably are accidental and not suicides. Or it could mirror the pathologists’ prejudices to rather classify a certain death as undetermined if there is no known mental disorder. Our result differ from Linsley et al who
found no significant differences in previous psychiatric treatment between the two modes of death.69

Prior in-patient care for substance abuse was on the other hand more frequent among undetermined intents. Around 50% had a prescription of psychotropics prior to death was common in both groups, although displayed in a gradient fashion (most common among suicides followed by undetermined, and unintentional). Higher educational level was more common among deaths classified as suicide compared to undetermined intents.

When we restricted our analysis to poisonings as outcome, higher education was less common in undetermined intents and unintentional poisonings compared to suicides. This result could imply a higher degree of uncertainty among lower educated groups due to more substance abuse, including alcohol, in these groups.144 Especially alcohol misuse and dependence is strongly associated with suicidality where the disorders’ severity, aggression, impulsivity, and hopelessness seem to predispose to suicide.12 Also in the sub analysis of poisonings as outcome we found in-patient care for substance abuse to be more frequent among undetermined intent and unintentional poisonings than among suicides. This could indicate more uncertainty among deaths in known drug abusers with over dose, which is in line with the results of an American study from 2006.145 Their study showed a somewhat surprising result, where several known risk factors for suicide were more frequently reported as present in unintentional poisoning deaths than in deaths classified as suicide poisoning.145 Also, drug users who die of a drug overdose are unlikely to be classified a suicide verdict. This despite the known fact that drug abusers often suffer from depression and other severe mental disorders including suicidal ideation.25

A Finnish study concluded that deaths classified as undetermined intent appeared to reduce the suicide rate with 10%. A 10% underreporting of suicides was also estimated in a study from Utah.146 Further on, when they solely looked at suicide rates related to poisonings they found an underestimation of suicide with 30%. During the observation period in Study I the mortality from undetermined intent in Sweden constituted around one third of the suicide mortality among women and around one fourth among men.

Our results from Study I indicated some differences due to sex, where young women (ages 15-24) displayed the lowest ratio of undetermined intent (fluctuating over the years between 10% and 30%) whereas the opposite was seen among men where the oldest (65+) had the lowest ratio of undetermined intent (around 20%). Hanging was the most common method among deaths classified as suicide in young women in contrast to all other age groups where poisoning was the most common method. Poisonings constituted slightly more than 50% of deaths classified as undetermined intent in young women (ages 15-24), compared to more than 66% in the other age groups. The percentage of poisonings was also lower among the elderly men (65+) than among the other age groups. If this lower proportion of poisonings explains, or partly explains this finding is however not known. Our study did not stipulate why we saw this difference between the sexes.

Current guidelines from The World Health Organization (WHO) states that it must be beyond reasonable doubt for a forensic pathologist to establish suicide as the mode of death, otherwise the pathologist is to classify death as undetermined intent.69 If these guidelines are followed, there should be very few non-suicides incorrectly certified as suicides.25 However, we cannot fully exclude the existence of misclassification of true suicides as unintentional, undetermined intent or homicide deaths. It would be valuable to analyze this in a future study to grasp both the sensitivity and specificity of suicide classification.
It is easy to theoretically define a suicide. The injury must have been self-inflicted and with the intention to die. In practice, however, it is not always this straightforward. Self-infliction can be very difficult to determine in some cases, whereas deciding if the intent was to die or not can be close to impossible. Suicides also occur in a continuum of concealment\textsuperscript{70}. Some people want to inflict pain, shame and guilt on their families through their suicide act whereas others want to spare their family from trouble. They might even want to facilitate for their families to receive life insurance payment etc. These different conditions can have an impact on the work of the forensic pathologist who is to certify that particular death\textsuperscript{70}.

The main concern is whether the degree of misclassification of suicides is sufficient to threaten the validity of suicide research. It might therefore be of value, whenever it is possible, to conduct analyses with only certain suicides as well as with suicides and undetermined intents combined. Our results also showed a similar relative decline in both suicides and undetermined intents over the studied time period of 40\% to 50\%.

Finally, analyzing background variables does not seem to be enough to distinguish deaths classified as suicide from deaths classified as undetermined intent. It might also be inappropriate to generalize these results to other settings and time periods, as there are so many factors affecting the likelihood that a real suicide is correctly certified as such. It might also be a good idea to follow the suggestions from Mohler \textit{et al}, who stressed that it might be a good idea to continuously scrutinize official suicide data with regard to misclassification, especially in populations with high proportions of undetermined intents and accidents\textsuperscript{147}.

\subsection*{5.1.2 Initiation with SRRI therapy and the risk of suicide (Study II)}

It is by now well established that treatment with selective serotonin reuptake inhibitors (SSRI) reduces the risk of suicide in depressive patients\textsuperscript{148-150}. However, it has been widely debated whether initiation of SSRI therapy might provide an activation syndrome among depressed patients or not in the beginning of therapy\textsuperscript{151-153}. Of course, this arises a bit controversy since SSRI therapy is supposed to be one of the most effective tools in treating depression\textsuperscript{150}.

In Study II including 5\,913 suicides in Sweden 2007-2010, initiation with SSRI therapy seemed to carry a short-term increased suicide risk. However, we had no access to indications for treatment. Other indications than depression such as; anxiety, insomnia, irritability, and panic attacks, which are also treated with SSRI, might carry lower underlying suicide risks whereupon our lack of information on the indication of treatment is unfortunate. Also, we have no information on the severity of depression among the depressed. We can therefore not exclude that our results could be due to confounding by indication, which means that the severity of the underlying illness might differ between the case and control period, and being more severe during the former. If so, indicating a spurious association.

Our induction time analysis showed a peak during days 8-11 after initiation, which is in accordance with the results of Jick \textit{et al} who also studied initiation with antidepressant and found an elevated risk during the first month with a peak during days 1-9\textsuperscript{154}.

Depression has been shown to play a key role in suicidality. Every attempt to treat depression is therefore essential in a suicide prevention perspective. The use of anti-depressants has played a key role in the recent decline in suicide rates in many Western countries\textsuperscript{148,155}. Although the causality has been questioned\textsuperscript{156}. Most typical antidepressants have a delayed onset of action (2–6 weeks). During this time window physicians and health care personnel, together with family members, should pay extra attention to depressed patients.
In a meta-analysis the effect of anti-depressants on suicide risk was substantially lower in trials for non-psychiatric indications\textsuperscript{157}. But just as in our study the authors of the meta-analysis stated that just because suicidal thinking, feeling, and behavior are core symptoms of depression, there is no way to know whether suicidal symptoms that develop during treatment are due to the underlying illness or the medication.

Because suicidality to a large extent is a symptom of major depression it could be expected to occur during treatment of depression and perhaps more so during the first stages of treatment. One explanation for this is the phenomenon called activation syndrome or jitteriness syndrome. This is explained as antidepressant treatment gives depressed patients the energy to follow through on suicidal impulses before the mood improvement takes effect\textsuperscript{148,149}.

Harada\textit{et al} studied the incidence of activation syndrome and found a significant association for only one diagnosis, personality disorder (OR: 4.20, P=0.002). Further they found no significant association with sex, age, or class of antidepressant\textsuperscript{155}. Another study showed a lack of activation syndrome\textsuperscript{151}, so there is yet no consensus regarding the existence or magnitude of this syndrome.

Prior research has linked the often coexisting of impulsivity and aggression with suicidality to biological mechanisms where SSRI therapy more specifically might trigger suicide in some individuals\textsuperscript{158,159}. For instance, significantly reduced serotonin transporter availability in individuals with impulsive aggression compared with healthy subjects was found in a case control study\textsuperscript{160}. This personality trait could be crucial when it comes to the development of activation syndrome or not, and could possibly contribute to our results. Impulsivity and aggression have also been shown to be risk factors for suicide whereupon these traits could also play a role in our results. Since we performed a register study we had no access to personality traits, however this might be valuable in future studies.

Our results did not display a particular risk increase in young adults. Young women aged 13-24 had OR 1.3 [95\% CI: 0.3-6.0] whereas young men had OR 3.6 [95\% CI: 0.9-12.1]. Their OR was slightly lower than the average 2.7 [95\% CI: 1.6-4.4] in women and 4.3 [95\% CI: 3.0-6.1] in men. However, we had too few subjects to study adolescents separately, which is unfortunate since earlier studies have shown a suicide risk increase among adolescents during initiation with SSRI therapy\textsuperscript{152,161,162}. A matched case control study in the US showed no risk increase among adults but found increased risks among adolescents for suicide attempts as well as for suicide\textsuperscript{162}. Another study concluded however, that it was common with an under prescription of SSRI to adolescents. The authors investigated six different studies where only nine out of 574 (1.6\%) young persons who died by suicide had had recent exposure to SSRI\textsuperscript{163}. The authors concluded that physicians should be more confident in prescribing SSRI to young people with moderate to severe clinical depression. This naturally requires the same youths to actually seek help, which might not always be the case. It is too common for adolescents to hide feelings of depression from their parents and other adults\textsuperscript{71}. Other studies have also found neither parents nor teachers to be able to accurately judge depression in children and adolescents\textsuperscript{164}.

Previous studies have been limited by the rare occurrence of suicide, and have often used data drawn from clinical trials, which may capture the experience of a more selected and highly monitored group relative to those using the drug outside of this setting. In our register study we excluded patients who had been in-patient treated prior to death, thus our finding primarily applies to patients who have initiated SSRI as outpatients.

It is important to stress that our results do not dissuade from prescribing SSRI. There is on the
contrary evidence that this medication is helpful in depressed patients. Nevertheless there is still controversy regarding the existence of a so-called activation syndrome. Regardless of causation, our results stress the importance of clinicians to carefully monitor their depressed patients’ initiation of SSRI treatment.

5.1.3 School grades and the risk of suicide (Study III)

Study III demonstrated an inverse gradient between school grades and risk of suicide in young adulthood. It is probably fair to say that poor grades do not per se increase the suicide risk. It is more complex than that. The benefits of education and the opportunities it provides have shown to be instrumental to both physical and mental health. Educational achievement also affects future employment opportunities and earnings potential that are detrimental contributors to health. Adult socioeconomic position (SEP) is therefore to some extent dependent on school performance.

According to Baumeister, people are at risk of developing suicidal ideation when they set unattainable goals and then blame themselves for their failure to achieve these goals. These negative self-attributions provide a context for the emergence of suicidal intent and desire. This may very well apply to students with low and incomplete grades. Low self-esteem might contribute to a range of negative life outcomes, including mental illness, substance abuse, and dissatisfaction with relationships and life in general. Poor school performance might therefore act as a mediating factor between low self-esteem and later problems and increased suicide risk.

School grades could also be interpreted as proxy for IQ and cognitive ability. Several studies have presented a negative relationship between cognitive ability, often measured as IQ, and suicide risk, i.e. the lower the IQ the higher the risk for suicide. A Swedish study aimed at exploring the underlying mechanisms in the association between IQ and subsequent completed and attempted suicide in men, and found a strong negative association. The association was however attenuated by 45% after controlling for risk factors measured over the life course. Psychiatric diagnosis, maladjustment and aspects of personality in young adulthood, and social circumstances in later adulthood, contributed in attenuating the associations, although a negative association was still there. However, there is not a complete consensus regarding the relation between IQ and suicide since other studies have found inconsistent and attenuated results when controlling for mental disorders. Other factors than cognitive ability also affect school performance like motivation and commitment from parents, something that is not possible to analyze in register studies.

Although we excluded the most severe hospitalized psychiatric patients with an onset during childhood and the early school years, we could not control for all mental ill health. Depression has been found to be associated with heritable traits and adversity in early childhood, and also with deteriorated school performance during the school years and self-harm in youth and young adulthood. It is therefore unfortunate that we could not grasp these conditions and hence missed valuable information with importance for our study. If we had been able to control for all mental disorders the effects of school grades might have weakened.

Other psychiatric conditions, such as anxiety disorder and ADHD Combined Type, that have been found to be associated with educational problems as well as suicidal behavior, can be expected to have similar complex interaction patterns with self-harm and school performance. Low school performance has also been found to be associated with behavioral problems. The causality hereof is however not clear. Students with somatic and psychiatric diseases have also
higher risk of low school performance.

A broad scope of literature has linked family discord with suicidal behavior among adolescents. Bad relations with parents along with neglect, violence, substance abuse, alcohol misuse, physical-, verbal- and sexual abuse have been shown to be more common among suicidal youths. The descriptive table shows the suicide rates were higher for students with a lone parent, among those who lived in a household that received social welfare or disability pension, those who were adopted, and had parents who had been in-patient treated for mental disorder.

Low sense of mastery seems to account for much of the association between low educational level and psychological distress. Thus providing a potential explanation for the association found, since psychological stress can contribute to the development of suicidal ideations. It would be incorrect to talk about causality, rather school grades acting as a mediator affecting the next steps into establishing behaviors and habits in young adulthood. Similar results were found in a Norwegian study where a sense of mastery emerged as a strong mediating variable between level of education and psychological distress. This same mechanism might possibly explain some of the association found in Study III.

Sense of mastery is related to self-esteem, where lack thereof has been shown to increase suicide risk. In a study on self-esteem and suicide ideation in psychiatric outpatients, self-esteem was conceptualized as two dimensions; the individuals’ beliefs about themselves and also their beliefs about how other people perceive them. Both dimensions of self-esteem predicted suicide ideation beyond the effects of depression and hopelessness.

Study III showed a negative gradient regarding school grades and suicide risk among both females and males. Males displayed a slightly more distinct gradient than females and males had also lower GPA on average. These findings emphasize the importance of further research to clarify the association shown here between low school performance and risk for suicide.

5.1.4 Juvenile delinquency and the risk of suicide (Study IV)

In Study IV with 992,881 adolescents we found juvenile delinquency to be a risk factor for suicide in young adulthood. Among adolescents who later committed suicide, 37% had been convicted for at least one crime during ages 15-19. This result is in line with previous research that has stressed juvenile delinquency as a risk behavior, where adolescents involved in either the juvenile justice or child welfare systems have higher risks of suicidal behavior compared to the general adolescent population.

Even after controlling for several confounders, we found a gradient in suicide risk, where those in the most severe delinquency group had highest risks. Thompson et al examined associations between delinquency and suicidal behaviors in a nationally representative sample of 14-17 year olds in the US. Their results indicated that delinquent adolescents were more likely to seriously have considered suicide (OR 5.44) and attempted suicide (OR 10.08).

In our study we controlled for psychiatric inpatient care, including drug and alcohol abuse, up until age 19. The association between delinquency and suicide also decreased when we controlled for mental disorders and substance abuse. However, as only a handful of adolescents who misuse alcohol and drugs are treated in inpatient care, we could not control for all drug abuse, which is a limitation.

Drug and alcohol abuse is part of delinquency. There is, however, no clear evidence of a causality pathway. In an American study the prevalence of delinquency and, amongst other,
drug abuse was examined in three urban settings. The percentage drug abusers among delinquent youths were reported between 7.25% and 29.0%. The corresponding percentage delinquency among drug abusers was between 93.6% and 97.9%. These results indicate that delinquency is more common among drug abusers than drug abuse is among delinquent youths. However, the generalizability to Swedish conditions is not known.

When we dichotomized offences into violent and non-violent, we found violent offenders to have substantially higher suicide risks. This is in line with Web et al, who examined the suicide risk among people with a criminal justice history and found that violent offenders had particularly high suicide risk. One possible explanation for violent offenders’ higher suicide risk is the possibility of shared common biological mechanisms for homicidal and suicidal behavior through serotonin dysfunction, which is related to several impulse disorders. In a meta-analysis by Fazel et al including 16 750 incarcerated youths, the prevalence of conduct disorders was a little more than 50 % This finding is not surprising as considerable symptom overlap between conduct disorder and antisocial behavior is well known.

Behavioral problems are intertwined with different forms of mental disorders that are known risk factors for delinquency as well as for suicide. Higher levels of impulsivity, a lifetime history of aggression, and novelty seeking have been found to be associated with youths’ suicides. It is also highly likely that aggression and novelty seeking is a common trait among delinquent youths. Juvenile delinquency might therefore be seen as a mediating factor between behavioural problems and later suicide.

Our results in Study IV showed that female adolescents were convicted to a much lesser extent than their male counterparts 5.9% compared to 17.9%. Nevertheless, it is clear in our study that the small group of females who repeatedly commit offences constitute a more highly selected, poor resource group, than the corresponding group of males. This is also indicated in previous research. A higher percentage of delinquent women reported psychological consultation, one-third compared to one-fifth among men in another study. A key finding in a meta-analysis by Foy et al was that female offenders often had experienced both family-based violence (childhood physical and sexual abuse i.e. domestic violence), as well as various incidents of community violence.

A recent American study reported greater experiences of prior victimization among women prisoners as well as more mental illnesses such as serious depression, and high rates of involvement with illicit substance use where all factors are seemingly connected and might contribute to the risk of offending. One possible reason for the marginalization among these women could be that non-normative behavior is more stigmatizing for women.

Though it was not a primary aim in our study to analyze the marginalizing of the most convicted women, when looking at the cohort characteristics we see that psychiatric in-patient care including substance abuse, being adopted, living in foster care, parents receiving social assistance, and lone parenthood was more common among females who repeatedly had committed offences. Regardless of the question of causality, professionals in health, social and correctional services that come in contact with delinquent youths should regard repeated juvenile offenders as a high-risk group for suicide. Generally this knowledge should guide mental health services targeting juvenile delinquents.
5.1.5 Social inequalities in the risk of suicide

The results in this dissertation indicate that there are social inequalities in the risk of suicide. The fact that lower socioeconomic groups in society are more susceptible to mental ill health and carries a higher risk for overall mortality as well as for suicide is however of no news value. Even the Whitehall findings suggested that the debate should not be whether those in poverty are at greater risk of ill health, since they in fact are. Instead not just the poor should be involved but the entire social spectrum, and the question should be whether the relative position in society is an important determinant of morbidity and mortality\(^79\).

Throughout this dissertation we have used education as a proxy for SEP. Although our stratified analyses in Study III and IV did not indicate any clear effect modification by parental SEP, many risk factors were more common in adolescents’ with lower SEP parents. In another Swedish cohort study the authors concluded poor school performance to be an important mediator through which parental SEP translated into a risk increase for non-fatal suicidal behavior\(^80\). Further on, Agerbo found considerable variation in suicide risk across occupations and explained those by socioeconomic factors such as marital status and income\(^122\). With lower SEP, regardless of measure, followed higher suicide risks, except for doctors and nurses, who showed the highest overall suicide risks.

In another Danish study of 15 648 suicides with matched population controls they investigated several measures of SEP such as low income, unskilled blue-collar work, non-specific wage work and unemployment and the risk of suicide\(^113\). The authors found a negative association between the whole range of SEP measures and suicide risk although the risk was more pronounced in men than in women. It has also been suggested that common SEP measures such as education, occupation and housing standard predict all-cause mortality in a similar way, but when broken down to cause-specific mortality the association differs, indicating different causal pathways\(^88\).

In Study III we observed not only that students with low and incomplete grades had higher risk for suicide, we also found an inverse relation between GPA and suicide. A gradient was also found in Study IV where more convictions led to higher suicide risk. This might be interpreted as if relative position does matter also when it comes to school grades and delinquency.

Wilkinson stressed the importance of the relative-income hypothesis that indicates that an individual’s relative- rather than absolute income affects her health\(^189\). Wilkinson writes

“... poor people in the United States often have death rates comparable with people in Bangladesh. Their high death rates are not so much a product of their absolute living standards but reflect their low relative incomes and social status. ... Mortality is associated with relative income.”

In Study III and IV adolescents and young adults who have not yet achieved their own adult SEP were included; still both studies indicate that relative position could be of importance. Relative deprivation could also apply to other aspects than income, such as occupation and education where both evident and more subtle levels could appear. For example, could similar educations from two different universities be valued differently because of the status of the University. Systematic variation by employment grade in several potential biological, behavioral, and psychosocial risk factors was also shown in the Whitehall studies where adverse factors clustering in the lower grades\(^79\).
Differences in life style might explain some of the observed inequalities in health outcomes. In some part life style factors can contribute to increased suicide risk like excess gambling, alcohol consumption and drug abuse. Other predisposed factors might be difficult to control for the individual such as; growing up in a stressed home environment, growing up with a lone parent, if the household receives social welfare assistance, adoption or foster care, heritage of mental disorders, and heritage of drug- and alcohol abuse. Differences in life style might be of importance in both Study III and IV where we did not capture all mental disorders and substance- and alcohol abuse. However, the important question from a preventive perspective is what explains differences in life style habits, and whether, and to what extent, they are determined by an individual’s own choices or that of an individual’s surroundings and living conditions while growing up.

Kawachi et al studied crime, variations in health and well-being, and relative deprivation. They found that places where social relations are strained also have increased rates of crime, as well as unhealthier and unhappier citizens. Reducing social inequalities could therefore also be a way of reducing crime and delinquency.

Neither low school grades nor juvenile delinquency should be seen as an acute risk factor for suicide. In Study IV we only included individuals who were still alive at age 20, thus we have no information on suicides that could have occurred as an immediate result of the conviction. Even so both poor school performance and juvenile delinquency should be regarded as indicators of future increased suicide risk. Prevention is therefore crucial in these groups. It would, however, be better if high-risk individuals could be targeted at as young age as possible, before too much harm have been done to them and to diminish as large part of ill health as possible. This would preferably take place during the first school years where resources should be available to give extra help and attention to students with learning and concentration difficulties. In a preventive perspective the schools should play a big part in detecting troubled youths.

5.1.6 Implications of the results

Based on our findings in Study I we cannot draw any conclusions about the amount of undetermined intents that are misclassified suicides. The similarity in the rate of the recent declines both suicides and undetermined intents might speak in favor of a larger amount of undetermined intents being misclassified suicides. However, differences in prior hospitalization were found where suicides had slightly higher share of prior hospitalization for self-inflicted harm and other mental disorders and undetermined intents had a higher share of hospitalization for drug and alcohol abuse. The latter findings would speak in favour of some real differences between these two modes of death. To fully elucidate the relation between suicide and undetermined intent one would have to go through all medical records, police reports and other relevant facts concerning these deaths which were not possible within the scope of our study.

The inverse trends in poisoning classified as suicides and undetermined intents on one hand and as unintentional on the other could imply a real difference between these modes. Although, we also included contributing accidental poisonings, which might have been spurious for our interpretation since only underlying suicides and undetermined deaths were included. Further research is needed to get a fully understanding of the sensitivity of suicide classification. It could also be that in some fatal cases neither the deceased was absolutely certain whether the intent was to die. This has been shown to be true among substance abusers that survived “unintentional” overdoses where they had an ambivalent attitude towards their own potential
The increased suicide risk found at initiation with SSRI therapy in Study II, whether due to activation syndrome or to severity of the underlying depression, emphasizes the importance of careful monitoring of these patients. As important is to provide adequate information to the patient and people closest to her or him.

In Study III we did not only find that students with lowest and incomplete GPA had higher suicide risk than students with highest GPA, we also found a gradient, meaning that the risk slightly increased by each decrease in grade.

Similarly to Study III we also found a gradient in Study IV. Suicide ideation and suicide attempts are not only important risk factors for suicide among adolescents, they are also serious problems in their own right. Both suicide ideation and attempts in adolescents have been found to predict mental disorders and mental ill health as well as psychosocial problems and further adult suicidal behavior. Specifically suicide attempts among young people have been shown to be associated with significant morbidity.

The findings in this dissertation should not be interpreted as alarming of highly elevated suicide risk among all adolescents who do not graduate at the top of their class. Instead these results should be considered in a larger public health perspective. What can society do to promote overall health in lower socioeconomic groups? How do we best promote healthy behavior in all socioeconomic groups? Since we still have inequalities in health including suicide risk, society has obviously not succeeded. Let us not stop at that, let us look forward. Since in a democratic society this would most probably not be accepted, neither by the politicians nor by the average citizen, we have to find other solutions to eliminate inequality in health. Schools are the natural basis for supplying the next generation with information as well as targeting individuals who are regarded as belonging to a high risk group, not only to suicide, but also for an unhealthy lifestyle in general and alienation and delinquency in particular. I therefore want to stress the importance that all adults (and peers as well) who come into contact with youths who in some way are troubled, regardless of what the problems might be, behavioral problems, depression, drugs, not fitting in, bullying, poor school performance, or a negative psychosocial home environment, take action and help out.

5.1.7 Social inequalities

Disparities in health due to socioeconomic position result from numerous risk factors and differences in access to a broad range of resources. Several negative health outcomes including elevated mortality risks are associated with lower socioeconomic position. To some extent this is due to the higher prevalence of health risk behaviors among persons who are poor and/or have low educational attainment. Despite the presence of significant socioeconomic differentials in health behaviors, these differences account for only a modest proportion of social inequalities in overall mortality. It has also been suggested that socioeconomic stratification itself may be a social force that has deleterious health effects for those in the lower strata.

Although reducing the prevalence of health risk behaviors in low-income populations is an important public health goal, socioeconomic differences in mortality are due to a wider array of factors and, therefore, would persist even with improved health behaviors among the disadvantaged.
Bourdieu proposed in 1984 that social position affects everything in our lives from home décor, to taste in food and music, to opinions on arts and desirable vacations, diets, exercise and other behaviors. According to Bourdieu, reducing social inequality in health is thus a real challenge. In a study of Pampel et al they recognized that socioeconomic disparities in health behavior involved more than lifestyle factors chosen by free will. To the contrary, they suggested that unhealthy behaviors result from the vast differences in the social circumstances of low- and high- socioeconomic groups.

A large body of scientific literature has also shown that more equal societies with less social stratification have smaller health inequalities. It also seems that socioeconomic position throughout the entire life course affects health. But being in adversity in some periods in life may be more important than others for the risk of developing disease and health-damaging behaviors.

5.1.8 Vision zero for suicide

Thanks to the extensive scientific basis on suicide research in Sweden and the consensus among suicide researchers that suicide needs to be prevented, the Swedish government announced a ‘Vision Zero’ policy for suicide in spring of 2008. This vision poses the requirements for action to be taken by several different professions and institutions. The aim with this vision is to increase awareness and knowledge about suicide attempts and suicide, i.e. the whole suicide process. Another goal is to eliminate the fear and the taboos that still surround suicide and mental disorders. The lack of knowledge could lead to avoidance to intervene when fellow human beings are contemplating suicide.

Pharmacological treatment and cognitive behavioral therapy are evidence-based methods to reduce suicidal risk. Another effective prevention method is educating health workers in suicide prevention. The Gotland study is one example where a significant decrease in suicide was found compared to other regions after education had been given to the health workers. However, the evidence regarding effective suicide preventions for adolescents and young adults is extremely limited. Many more methodologically rigorous studies are required. Since depression and other mental disorder in youths and approximately 90 % of suicide attempters are shown to suffer from a mental disorder, early detection is of great importance. Another target group is adolescents attempting suicide. The after-care they receive might have profound impact on their future and on their future suicide risk. Intensive follow-up and treatment are therefore warranted. Since humans to a large degree have a free will, it might be close to impossible to completely eradicate suicide. However the vision zero is of great importance as it stresses the goal to continuously try to reduce the number of suicides. A goal in every civilized society should be to eliminate as many suicides as possible.

5.2 METHODOLOGICAL CONSIDERATIONS

Some methodological considerations are of similar kind since all four studies are based on register data. The limitations with using population-based register data include the shortcomings of collecting data without advanced specified diagnostic criteria, the limited number of variables collected, and sometimes the crudeness of the available variables. The variables might hence be a little broad and rough and might not always capture the underlying mechanisms.

Cohort studies are often time-consuming and expensive, since only a minority of those who are
at risk actually experience the outcome. This argument does, however, not apply to retrospective cohort studies using population-based registers. In two of the studies (Study III and IV) in this dissertation we used a retrospective cohort design.

In Study III as well as in Study IV we were only able to control for psychiatric in-patient care and in-patient care related to alcohol and drug abuse, thus not capturing all mental health problems, including drug abuse. We had no information about those with problems treated in primary health care, or about those who were never treated at all by the health care services. This is a limitation in both Study III and in Study IV, since mental health problems are well-known risk factors for suicide. Criminal behavior and drug use are also often intertwined. There is however no consensus on the causality\(^\text{180}\). Mental ill health is also related to school failure, behavioral problems and delinquency. Accordingly the risk estimates decreased when we controlled for psychiatric in-patient care in Study IV. In a future analysis it would be valuable to add psychiatric outpatient care and prescription of psychotropics as confounders as an attempt to refine the association between delinquency and suicide.

5.2.1 Random and systematic errors

Random errors occur because of sampling variability, and causes results to fluctuate around the true value. Random error is just that: random. It can occur during data collection, coding, or during data transfer. Random errors are assumed to be normally distributed with zero mean and a constant variance. Precision in epidemiological studies is a measure of the size of the random error. Precision is consequently inversely related to random error, so that to reduce random errors is synonymous to increase the precision.

In this dissertation we have calculated confidence intervals to present the degree of uncertainty to which the point estimates are measured. Another way to measure random errors is through calculating p-values.

Systematic errors (bias) on the other hand affect the validity. A systematic error occurs when there is a difference between the true value (in the population) and the observed value (in the study) from any cause other than random sampling variability. Systematic errors can also occur, just as random errors, during the collection, coding, and transfer phase of the study. There are different types of systematic errors and usually three main types are mentioned: misclassification, selection bias, and confounding.

Misclassification of outcome

Misclassification of outcome occurs when there is risk for either a healthy subject to be classified as having the outcome or for a diseased (or deceased) subject to erroneously be classified as healthy. There are two different forms of misclassification of outcome, non-differential (when it is unrelated to the exposure) and differential (when it is related to the exposure). If it is non-differential and there is an under diagnosis (i.e. we miss some cases) this should not affect the risk estimate. On the other hand, if there is an over diagnosis (i.e. too many cases are included) this will bias the effect towards null, which means diluting the difference between the exposed and the unexposed cases.

Differential misclassification of outcome occurs when the degree of measurement error is different in the exposed and the non-exposed group and becomes a systematic form of bias. In other words, outcome misclassification is differential if the misclassification differs between the
exposed and unexposed subjects, and introduces a bias towards an under- or an over-estimation of the true exposure effect.

Suicide is the outcome in all studies included in this dissertation. As described earlier, since ICD-8 (introduced in the Swedish cause of death register 1969) codes for undetermined intent were introduced. To study misclassification of suicide by exploring deaths classified as suicide and deaths classified, as undetermined intent was the main purpose in Study I. Most background factors differed between the two modes of death. Prior hospitalization for self-inflicted harm and other mental disorders was slightly more common among suicide victims, while prior hospitalization for drug and alcohol abuse was somewhat more frequent among undetermined intents. On the other hand percentage of psychotropics as well as of prior psychiatric hospitalization were high in both groups. We could not assess the extent of misclassification of suicides, in some part due to the restrictions of register data. In a future attempt it would be of value to go through all medical records, police reports and other relevant facts around these deaths but this were not possible within the scope of this study.

In a sub analysis we examined poisonings specifically, including poisonings classified as unintentional. We included poisoning as both the underlying cause as well as the contributing cause to avoid differences in trend due to changes in the classification rules. The downside to this is that we obtain too many unintentional poisonings because all drug related deaths are included. This means the number becomes too high, but the trend will be more accurate and easier to interpret as well. However, this is a limitation.

In Study II we included both deaths classified as suicide and deaths classified as undetermined intent but performed a sub analysis on the outcomes separately. These results indicated a distinction between deaths classified as suicide OR 4.13 [95% CI: 2.99-5.70] and deaths classified as undetermined intent OR 1.50 [95% CI: 0.83-7.72]. If deaths classified as undetermined intent to a large degree hide actual suicides, the separate ORs would most probably be more similar. There could however have been other differences associated with death that contributed to the established mode of death that we could not capture within the scope of our study.

In addition to the main analyses in Study III and IV we also performed the analyses with only certain suicide as outcome and obtained similar risks and gradients. However, misclassification of suicide still constitutes a problem and brings uncertainty to suicide statistics.

Misclassification of exposure

Just as misclassification of disease, misclassification of exposure can also be non-differential or differential. If we have a differential misclassification of exposure, the exposure is misclassified differently according to the individual’s outcome status. When the misclassification of exposure is non-differential, the misclassification does not depend on the individual’s outcome status. Non-differential misclassification of exposure influences the effect towards the null. An example of this is in Study IV where only convicted youth were seen as exposed leading to the possible risk of non-differential misclassification of exposure, i.e. some youth engaged in delinquent behavior were not registered and convicted and hence misclassified as non-delinquent. And if so, the consequence would be dilution of our results, i.e. the obtained risk estimates might be lower than they otherwise would have been.

Several background factors were compared between suicides and deaths with undetermined intent in Study I. Couple cohabitating without being married were misclassified as unmarried
due to restrictions of data availability.

The Patient Register carries high quality whereupon the measures of in-patient care for self-inflicted harm, substance abuse and other mental disorders may be regarded as more or less accurate. However, some diagnoses could still be erroneous, but most likely we missed some patients whose information was not accessible in the Patient Register, hence leading to misclassification of hospitalized patients as not hospitalized. Also, only self-inflicted harm that led to in-patient care was accounted for, whereupon we possibly missed some cases of self-inflicted harm.

To reduce exposure misclassification in Study II we excluded patients with recent psychiatric hospitalizations (ICD-10: F00-F99) i.e. hospitalizations within one month prior the dispensed prescription during both the case and the control period, since they might have initiated SSRI therapy at the hospital. Thus, our results refer foremost to out-patients.

Since a prescription in Sweden is intended to last for no more than three months, we chose a four-months wash-out period in an attempt to ensure that patients were not on SSRI prior to initiation. In a sensitive analysis we extended the wash-out period to six months, which generated similar results as the main analysis.

In Study III where the exposure was GPA from the nine years compulsory school, erroneous GPA is most likely to be scarce and most likely random, and should thus not constitute a major limitation.

5.2.2 Confounding by indication

Confounding by indication is a type of bias introduced when prognostic factors influence treatment decisions. This is a common limitation for example in observational studies on treatment effects where comparisons between outcomes among patients who have taken a specific drug or not are carried out. The dilemma arises from the fact that the two patient groups may differ with regard to the medical indication of drug prescription, i.e. type of treatment is not randomized. Even though patients might suffer from the same disease, the severity of the disease may differ and those who receive the drug and those who do not may differ according to other risk factors. Thus, this produces an imbalance in prognostic factors between the compared patient groups. This creates a bias in the comparison that is referred to as confounding by indication. In contrast to confounding there are no standard methods to control for confounding by indication. The best way of handling this source of error is to control for as many known confounders as possible and if possible perform sub analyses based on severity. This bias constitutes the main limitation in Study II where we studied if initiation with SSRI therapy can act as a trigger for a short-term increased risk for suicide. The possible depression dependent differences in level of suicidality between the compared time periods might differ. It was not possible to establish to what extent confounding by indication affected our overall risk estimates. However, in an attempt to try to explore this confounder we analyzed the effect of tricyclic antidepressant drugs (TCAs), which may be less likely to produce an "activation syndrome." This analysis suggested no significant short-term risk increase at initiation with TCA.

Another limitation is the lack of information on indication for SSRI. A meta-analysis on the effect of anti-depressants on suicide risk found substantially lower risk increase in trials for non-psychiatric indications and, hence, concluded depression to play a key role in suicidality and that antidepressants themselves did not generate additional suicidal symptoms. If our study includes several cases where indication for SSRI therapy was another diagnosis than depression,
our results might underestimate the true risk. However, we do not know if this is the case or not.

5.2.3 Adherence

Adherence is a common concept in medicine and refers to what extent a patient follows (adheres to) medical advices/instructions. Adherence is of immediate importance in Study II. Unfortunately, we had no way in knowing whether patients prescribed SSRI actually took their medication or not and, if so, we did not know when they started their therapy. The exact day of initiation is important in this case since time is measured in days. In this study we however assumed adherence and we also presumed their therapy to start at the day of prescription. This potential lack of adherence is of course a limitation. If patients we assumed initiated their therapy on the day of dispensation did not, we would overestimate the risks.

5.3 IMPLICATIONS FOR FUTURE RESEARCH

To fully evaluate the validity of suicide statistics, future studies on misclassification of suicide would benefit from a design that allows the collection of additional information on the deceased and on the circumstances surrounding the death. It would also be of value to go through all medical records, police reports and other relevant facts including interviewing family members and those close to the deceased. Moreover, to perform a study comparing classification routines and traditions between the different forensic departments in Sweden would also be of value.

Our finding indicates that SSRI initiation can cause a short-term increased suicide risk. This calls for extra attention in the clinical setting and in the monitoring of patients during initiation of SSRI. However, due to the possibility of confounding by indication, there is still need for more research to explore this relation.

We found an increased suicide risk in individuals with poor school grades and adolescents being involved in delinquent behavior. However, as most youths who experience these risk factors still do not commit suicide future research would benefit from qualitative studies that more in depth could investigate the mechanisms behind the pathways leading up to suicides among young adults.
6 CONCLUSIONS

The overall aim of the studies comprising this dissertation was to increase knowledge on risk factors for suicide and whether the suicide risk is modified by socioeconomic position. Another aim was to examine if information on different background variables can be used to distinguish deaths classified as suicide from deaths classified as undetermined intent.

- Comparing background information between deaths classified as suicides and deaths classified as undetermined intent do not seem to be enough to distinguish between these two modes of deaths.

- Our results suggest a suicide risk at initiation with SSRI therapy. The descriptive question whether there is an increased risk of suicide in the early phase of SSRI treatment, is not confounded by indication. This bias only interferes with our understanding of the causation of this increased risk. Regardless of whether the increased risk is due to activation syndrome or more severe depression at initiation with SSRI, this result is of great clinical importance, which means that clinicians must closely monitor patients when an antidepressant is initiated.

- We can not state that the risk elevation is specific to SSRIs, it may also be present with other treatments for depression, and therefore the specificity of this effect should be studied further.

- Poor school performance and juvenile delinquency seems to be a risk factor for suicide in young adulthood.

- Even if mental health problems and drug abuse explained a large part of the observed increased suicide risk in convicted youths, as well as in students with low or incomplete grades, these findings are still of value from a preventive perspective. It is important that school professionals as well as professionals in social and correctional services are aware of this group being a high risk group for suicide.

- Aspects not fully considered in this dissertation that are likely to be important contributors between delinquent or otherwise troubled adolescents and future suicide risk should be incorporated into further studies, especially mental disorders and alcohol and drug abuse.
7 POPULÄRVETENSKAPLIG SAMMANFATTNING

Den här avhandlingen syftar till att öka kunskapen om olika riskfaktorer för självmord. Vi har också tittat på om riskerna ser olika ut beroende på föräldrars utbildningsnivå, d.v.s. om barn till föräldrar med kortare utbildning har högre risk för självmord än barn vars föräldrar har längre utbildning.

I den första studien undersökte vi om man med hjälp av bakgrundsvariabler kan skilja ut faktiska självmord bland dödsfall klassifierade som "oklart uppsåt" (oklart uppsåt" ska väljas som dödsorsak när patologen inte säkert kan fastställa om syftet bakom ett dödsfall var självmord, övergrepp av annan person eller olycka). Vi jämförde alla dödsfall klassifierade som självmord med alla "oklart uppsåt" mellan 1987 och 2011. Tidigare slutenvård för självillfogad skada och psykiatrisk slutenvård visade sig vara vanligare bland dödsfall klassade som självmord medan tidigare slutenvård för missbruk var vanligare bland oklart uppsåt. I bågge grupperna hade ca 50% fått en förskrivning av antidepressiva läkemedel under de sista sex månaderna i livet. Trots att vi fann skillnader i nästan alla bakgrundsfaktorer var det inte tillräckligt för att skilja ut faktiska självmord från dödsfallen klassade som "oklart uppsåt"

Behandling med SSRI har blivit allt vanligare, både vid depression men även vid andra tillstånd som ångest, panikattacker och tvångssyndrom. En hel del diskussioner har förts huruvida insättning av SSRI kan medföra s.k. aktiveringssyndrom. Detta syndrom innebär att patienten får kraft att "ta tag i saker" innan känslostämningen blir bättre. I Studie II tittade vi på om insättning av SSRI skulle kunna innebära en kortsiktigt förhöjd självmordsrisk. Vi fann en förhöjd risk under de närmaste 28 dagarna efter påbörjad SSRI-behandling, främst under dag 8 till 11. Den främsta begränsningen var dock att vi inte vet om våra resultat beror på att den underliggande depressionen är som väst vid insättning av medicin eller om det är medicinen i sig som bidrar till riskökningen. Oavsett vad riskökningen beror på är det viktigt ur ett preventivt perspektiv att vara medveten om denna.


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