From the Department of Clinical Neuroscience
Karolinska Institutet, Stockholm, Sweden

Self-Harm in Youth - Predicting Mental Illness, Social Marginalisation and Suicide

Karin Beckman

Karolinska Institutet

Stockholm, 2018

Published by Karolinska Institutet.
Printed by E-print AB

ISBN 978-91-7676-969-0

Self-Harm in Youth - Predicting Mental Illness, Social Marginalization and Suicide

Thesis for Doctoral Degree (Ph.D.)

by

Karin Beckman

Principal Supervisor
Associate Professor Marie Dahlin
Karolinska Institutet
Department of Clinical Neuroscience
Centre for Psychiatry Research

Co-Supervisors
Professor Bo Runeson
Karolinska Institutet
Department of Clinical Neuroscience
Centre for Psychiatry Research

Associate Professor Ellenor Mittendorfer-Rutz
Karolinska Institutet
Department of Clinical Neuroscience
Division of Insurance Medicine

Opponent
Associate Professor Fotis Papadopoulos
Uppsala University
Department of Neuroscience
Division of Psychiatry

Examination Board
Professor Christina Dalman
Karolinska Institutet
Department of Public Health Sciences
Division of Public Health Epidemiology

Associate Professor Louise Brådvik
Lund University
Department of Clinical Sciences
Division of Psychiatry

Professor Bruno Hägglöf
Umeå University
Department of Clinical Sciences
Division of Child and Adolescent Psychiatry

ABSTRACT

Aims

The aims of this thesis were to study self-harm in young people and to evaluate the risks of adverse outcomes through short- and long-term follow-up. The primary focus was on the risk of suicide, and also on the risk of mental illness and labour market marginalisation in adult life. There was further the intention to explore risk-increasing factors that might signal an elevated risk of an adverse outcome, and thereby help to identify the young people most at risk of suicide.

Methods

Linked national registers were used to identify self-harm events registered in the Swedish National Patient Register (NPR) in studies 1–4. In Study 1, all self-harm events conducted by those aged >10 in 1990-99 were included. In Study 3, all self-harm events conducted by those aged 18-24 in 1990-2003 were included. Both of these studies also used unexposed individuals from the general population, matched by age and sex. In Study 2, all Swedish residents aged 16-30 in 1994 were included, and exposure was defined as a suicide attempt in the NPR in 1992-1994. In Study 4, self-harm events among 10-24 year-olds in 2000-2009 were included. In Study 5, a clinical multicentre cohort of patients who had attempted suicide was examined. Data on previous self-harm, age at self-harm, method of self-harm, mental disorders before or at self-harm, parental educational level, family history of suicide, and the impulsivity of the suicide attempt were collected to explore factors that might be of importance to self-harm and affect the risk of adverse outcomes. The outcomes studied were death by suicide, psychiatric hospitalisation, psychotropic medication and sickness absence, disability pension and unemployment, and fatal or non-fatal suicide attempt within six months. Proportions of outcomes were calculated, and associations between exposures and outcomes were investigated by the use of logistic regression and Cox proportional hazard models, with adjustment for relevant confounders.

Results

Suicide within one year and in long-term follow-up were highly elevated after self-harm compared to those not exposed to self-harm (Study 1, 3). The risk of suicide was lower after self-harm in 10-19 year-olds compared to those who had self-harmed in older age groups (Study 1), but clearly elevated compared to those unexposed to self-harm. After adjustment for relevant confounders, such as mental disorders, the Hazard Ratio (HR) for suicide in long-term follow-up was 16.4 (12.9–20.9) after self-harm among 18-24 year-olds compared to unexposed (Study 3).

The presence of a mental disorder, especially a psychotic disorder, was an indicator of an elevated risk of suicide among those who had self-harmed (Study 3). Among self-harm events that required medical inpatient care in 10-17 year-olds and in 18-24 year-old women, the use of a violent method signalled an elevated risk of suicide, as did cutting that required medical inpatient care in 18-24 year-old women compared to poisoning (Study 4). The risk of

a fatal or-non-fatal repetition within six months was equally high among those who had made an impulsive suicide attempt (ISA) as those with a non-impulsive attempt (Study 4). ISAs were common among young adults and resulted in injuries that were at least as medically severe as more planned suicide attempts.

Out of those who were exposed to self-harm, 20.3% had a psychiatric hospitalisation of more than 5 years after the index event (Study 3). Psychotropic medication had been prescribed to and purchased by 51.1% >5 years after the index event; the most commonly prescribed medications were antidepressants, benzodiazepines and hypnotics (Study 3). After a suicide attempt in youth, the adjusted HR for long-term unemployment was 1.58 (95% CI 1.52 - 1.64), for sickness absence ≥ 90 days 2.16 (2.08 - 2.24), and for disability pension 4.57 (4.34 - 4.81), compared to those unexposed to a suicide attempt (Study 2). After stratification for previous psychiatric inpatient care, the effect of a suicide attempt was still significant for sickness absence and disability pension in both groups, but not for unemployment (Study 2).

Conclusions

Self-harm at a young age highly elevates the risk of suicide, in both the short and long perspective. Assessment of the suicide risk is challenging and highly important. Some of the indicators of a particularly elevated risk of suicide are a mental disorder present at the time of self-harm, especially a psychotic disorder, and a violent method used to self-harm. Suicide attempts that occur without prior planning can result in medically severe injuries and imply a high risk of fatal-or-non-fatal repetition. Upon assessment of young individuals after self-harm, the elevated risk of future mental illness and labour market marginalisation should be kept in mind. The prevention of those adverse outcomes should be a focus in the efforts to help these young individuals in the transition into adult life.

LIST OF SCIENTIFIC PAPERS

I. Tidemalm D, **Beckman K**, Dahlin M., Vaez M, Lichtenstein P, Langstrom N & Runeson B (2015). Age-Specific Suicide Mortality Following Non-Fatal Self-Harm: National Cohort Study in Sweden. *Psychological Medicine*, 45, 1699-1707.

II. Niederkrotenthaler T, Tinghog P, Alexanderson K, Dahlin M, Wang M, **Beckman K**, Gould M & Mittendorfer-Rutz E (2014). Future Risk of Labour Market Marginalization in Young Suicide Attempters - A Population-Based Prospective Cohort Study. *International Journal of Epidemiology*, 43, 1520-1530.

III. **Beckman K**, Mittendorfer-Rutz E, Lichtenstein P, Larsson H, Almqvist C, Runeson B & Dahlin M (2016). Mental Illness and Suicide After Self-Harm Among Young Adults: Long-Term Follow-Up of Self-Harm Patients, Admitted to Hospital Care, in a National Cohort. *Psychological Medicine,* 46**,** 3397-3405.

IV. **Beckman K**, Mittendorfer-Rutz E, Waern M, Larsson H, Almqvist C, Runeson B & Dahlin M. Method of Self-Harm in Adolescents and Young Adults and Risk of a Subsequent Suicide. Accepted for publication on January 15, 2018, in *Journal of Child Psychology and Psychiatry*.

V. **Beckman K**, Lindh AU, Salander Renberg E, Waern M, Runeson B & Dahlin M. Impulsive vs Planned Suicide Attempts - Clinical Correlates and Prognostic Value in Young Adults. A Clinical Cohort Study. *Manuscript*.

CONTENTS

LIST OF ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
ATC	Anatomical Therapeutical Chemical
CDR	Cause of Death Register
CI	Confidence Interval
C-SSRS	Columbia Suicide Severity Rating Scale
DSM-V	The Fifth Edition of Diagnostic and Statistical Manual of Mental Disorders
ER	Education Register
HR	Hazard Ratio
ICD	International Classification of Disease
IRR	Incidence Rate Ratio
ISA	Impulsive Suicide Attempt
KIVS	Karolinska Interpersonal Violence Scale
LISA	The Longitudinal Integration Database on Social Insurance and Labour market studies
MiDAS	Micro Data for analyses of the Social Insurance database
MGR	Multigenerational Register
NPR	National Patient Register
NSSI	Non-Suicidal Self-Injury
OR	Odds Ratio
PDR	Prescribed Drug Register
SIS	Suicide Intent Scale
SMR	Standardised Mortality Ratio
TPR	Total Population Register

1 INTRODUCTION

Self-harm in young people has been an important topic of research in recent years. As a psychiatrist, I have young patients with experiences of self-harm, suicidal thoughts and behaviour. After examining and treating many of these young individuals, I became interested in the long-term consequences of self-harm at a young age. One of the issues that I wanted to explore was the association of self-harm with mental illness. How strong is the correlation with mental disorder? Could self-harm at a young age be the start of long-term difficulties with mental health? Suicide is always a tragic outcome, and we are perhaps even more affected by a suicidal death when it occurs in a young individual. One of my most important, and challenging, tasks, as a psychiatrist is to predict and prevent suicide. We often try to assess the risk of future suicide in young individuals who have self-harmed. It is a challenge to weigh the risk of a devastating outcome against the wish to transfer comfort, hope and trust in young individuals' own ability to manage their difficulties and to heal. I consider making the effort to gain more knowledge on self-harm, on the prognosis after self-harm, and on the risk of future suicide to be the most responsible way to meet this challenge.

1.1 DEFINITIONS

The phenomenon of self-inflicted injuries, fatal or non-fatal, has been described using different definitions. In European, and especially British, contexts the term deliberate self-harm is mostly used, defined as self-poisoning or self-injuries regardless of the presence or absence of suicidal intent (Hawton et al., 2003b, Hawton, Saunders & O'Connor, 2012b, Madge et al., 2008). However, in a large proportion of current research, especially from the US, suicidal and non-suicidal self-injury are regarded as separate entities. The term "Non-Suicidal Self Injury" (NSSI) is used to describe the deliberate destruction of body tissues without a suicidal intent. This contrasts with "suicidal self-injury", which includes suicide ideation, suicide plans, suicide attempts, and suicide deaths (Nock, 2012). Suicide attempt is sometimes defined as a self-inflicted injury, poisoning or suffocation (or potential self-injurious behaviour) with at least some (non-zero) intention to die (O'Carroll et al., 1996). NSSI was included in section three of DSM-V as a condition for further research. The proposed criteria for the diagnosis include at least five days of engaging in self-injury to body surface, with expectations to fulfil or be relieved of a certain state, or resolve an interpersonal difficulty. Also, the acts of self-injury often appear with an immediate association with interpersonal difficulties, or negative feelings or thoughts. Even though there are clear differences in the definitions of non-suicidal and suicidal behaviours, there is an overlap between them; with both behaviours often occurring in the same individuals (Wilkinson et al., 2011).

In most register-based studies, it is not possible to address suicidal intent due to a lack of information on the intent behind self-harm, which is why the broader term self-harm is perhaps preferable. In the following text, the term self-harm is mostly used, and refers to all self-injuries with or without suicidal intent. If reported studies use a more defined study

population, this is specified in the text.

1.2 EPIDEMIOLOGY

Self-harm is a common phenomenon in adolescence and young adulthood. Suicide is far less common, although self-inflicted injuries are the second most common cause of death among 10-24 year-olds globally (Patton et al., 2009). There is a lack of official statistics on self-harm, but a few studies have tried to compile prevalence numbers from different countries. The WHO/Euro Multicentre Study of Suicidal Behaviour, for which health care facilities from centres in 13 European countries reported suicide attempts during 1989-1992, showed large differences in incidence between European countries. The lowest rates were seen among young men in Ankara, Turkey, 43 per 100,000 and highest among young women in Rennes, France, 832 per 100,000 (Schmidtke et al., 1996).

It is, however, not possible to get a full grip on the issue of self-harm in youth from health care statistics alone. Most self-harm episodes do not come to the attention of the health care system; in the Child & Adolescent Self-harm in Europe (CASE) Study, a multicentre community-based study based on questionnaires to 15-16 year-olds, only 12.4% of the self-harm episodes led to hospital presentation (Madge et al., 2008). In this study, 13.4% of female adolescents and 4.3% of young men had a lifetime history of self-harm, proportions similar to those in other population-based studies where around ten per cent of youth report a history of self-harm (Hawton et al., 2012b, Madge et al., 2008, Hawton, Rodham, Evans & Weatherall, 2002). In a review of the prevalence of NSSI and self-harm from 2012, Muehlenkamp and colleagues found a mean lifetime prevalence of 16.1% in studies of 11-18 year-olds in school or community settings (Muehlenkamp, Claes, Havertape & Plener, 2012). In a Swedish study of self-harm behaviour among 14-year-old school pupils, 40.1% affirmed that they were involved in some form of self-injury according to the Deliberate Self-harm Inventory: Nine-Item Version (DSHI-9). The inventory is wide-ranging, including carving words or pictures on one's skin, preventing wounds from healing, scratching until bleeding, etc. 14.4% had self-harmed on five or more occasions, and 5.4% had made events that required hospitalisation or medical treatment (Bjarehed & Lundh, 2008).

Self-harm occurs at all ages but seems to be particularly prevalent in youth. The prevalence of suicidal thoughts, plans and suicide attempts is significantly higher among young adults (aged 18-29 years) than in older age-groups (Crosby et al., 2011). The debut of self-harm is reported to be increasingly more common after the age of 12 and during the teen years, and peaks, at least in girls, in the mid-teens (Hawton et al., 2012b). According to the National Comorbidity Survey in the United States, the onset of suicidal behaviour is most often in late adolescence or the early twenties (Kessler, Borges & Walters, 1999). The ratio of self-harm to completed suicide is over 200:1 among teenagers, and decreases markedly in older age groups (Hawton & Harriss, 2008). In most centres of the WHO/Euro multicentre study of suicidal behaviour, 15-24 year-olds had the highest prevalence among females, and 25-34 year-olds the highest among men, which is similar to later European studies (Schmidtke et

al., 1996, Hawton et al., 2003a). Females seem to begin to engage in self-harm earlier than males; there is a larger gender difference in the early teenage years than in age groups over age 16 (Hawton et al., 2003a).

Self-harm is more common among female than male adolescents although suicide is more prevalent among young men (Hawton et al., 2012b, Madge et al., 2008, Hawton et al., 2002). The high rates of self-harm in women compared to men are seen in all age groups, but seem to be more pronounced in the youngest age groups (Diggins et al., 2017). The high female to male ratio in self-harm as opposed to the high male to female ratio in suicide, sometimes referred to as the gender-paradox in suicide, is valid in all age groups, and is analysed in a review article (Schrijvers, Bollen & Sabbe, 2012). Differences in sociodemographic factors were noted, and men seemed to be more susceptible to separation from partners than women, since higher rates of suicide were seen among men after a separation. Also, there is the issue of the effect of psychopathology in men and women; internalising disorders, e.g. depression and anxiety, which are more common in women, seem to lead to non-fatal suicidal behaviour in women. In men, externalising disorders, e.g. substance-related disorders, personality disorders and attention deficit disorder, increase the risk of suicide, perhaps through aggressiveness and impulsivity. Psychiatric conditions are often undiagnosed in male suicide victims, which may be a sign of a gender difference in help-seeking. Further, a gender difference in attitudes towards antidepressant treatment may add to a worse prognosis for men (Schrijvers et al., 2012). Among suicide victims, men are less likely to have sought mental health care in the year preceding suicide (Schaffer et al., 2016).

Brent and colleagues discuss possible explanations for the gender difference in a study of completed suicide in adolescence. It was found that irreversible methods tended to be used by young men, whereas intoxication, more common in women, was often treatable if brought to medical attention. The authors also found higher rates of conduct disorder in male youth, which was an important risk factor for suicide among males (Brent et al., 1999). In a Finnish analysis of adolescent suicides, some gender differences appeared. More males used a violent method and more females had a history of suicide attempts. The authors speculated that males using a more violent method on their first attempt meant that the attempt was more lethal; by contrast, females more often survived their first attempt (Lahti et al., 2014).

The high incidence of self-harm among female youth has also been analysed. One contributing factor to gender difference may be the higher prevalence of depression among young women than young males. An attempt to explain the difference in the prevalence of depression has been made by Hyde and colleagues, where emotional reactivity, genetic factors and pubertal effect, alongside cognitive style and objectified body consciousness, are discussed (Hyde, Mezulis & Abramson, 2008).

Cutting is the most common method of self-harm in community-based studies (Madge et al., 2008, Hawton et al., 2002), whereas poisoning is the leading method among people who seek hospital care (Olfson et al., 2005, Beckman, Dahlin, Tidemalm & Runeson, 2010). In the CASE study, only 6.9% of cases of self-harm that involved cutting led to hospital care,

whereas 17.9% of multiple methods, 18.1% of overdoses and 22.9% of other single methods led to hospital care (Madge et al., 2008). Cutting is perhaps considered by health care personnel to be less severe than other self-harm methods. In a multicentre study of self-harm presented at hospitals, cutting as a method was associated with a decreased likelihood of a psychosocial assessment after the act of self-harm (Kapur et al., 2008).

There is some evidence that self-harm behaviour in youth has increased in the last decades. The rates of self-harm and suicide attempts seemed to increase in the 1990s in both American and European studies (Hawton et al., 2003a, Brener, Krug & Simon, 2000). In Sweden self-harm episodes resulting in hospital care among 15-24 year-olds increased gradually between 1998 and 2007 (Beckman et al., 2010), but have since decreased, albeit not to the same prevalence rate as in the 1990s (socialstyrelsen.se/statistik/statistikdatabas). Self-reported suicide attempts in Greece doubled between 1984 and 2007 (Kokkevi, Rotsika, Arapaki & Richardson, 2011). In Muehlenkamp and colleagues' review of the prevalence of NSSI and self-harm from 2012, the authors compared studies from 2005 to 2011, and concluded that prevalence rates were relatively stable over these years, although at a high level (Muehlenkamp et al., 2012).

There was an increase in the rate of completed suicides in the United States from the 1970s to the mid-1990s among 15-19 year-olds, which has been attributed to an increase in depression and substance use in youth. Since then, a decrease has been seen (Spirito & Esposito-Smythers, 2006). In many European countries, an increase in adolescent suicides was observed between 1979 and 1996, but prevalence has stabilised since then (Rutz & Wasserman, 2004). Also, there was an increase among adolescents between 2011 and 2014 in the UK, according to a recent study (Morgan et al., 2017).

1.3 RISK FACTORS ASSOCIATED WITH SELF-HARM IN YOUTH

Biological factors, personality factors and cognitive vulnerabilities combined with exposure to negative life events and psychiatric disorders have been proposed as elements in better understanding youth self-harm (Hawton et al., 2012b). A fairly large number of studies have addressed which risk factors are most correlated with youth self-harm and suicidal behaviour. A systematic review of population-based studies of suicidal behaviour among adolescents has highlighted factors associated with suicidal behaviour: depression, hopelessness, low self-esteem, poor body image and unhealthy eating behaviour, poor school achievement, anxiety, anti-social behaviour, smoking, drinking and drug taking, homosexuality, sexual abuse, physical abuse, exposure to suicidal acts in family and especially among friends, living apart from parents, parental divorce, marital conflicts in parents, unsupportive parents, poor general family functioning and poor peer relationships (Evans, Hawton & Rodham, 2004). Many of these factors are intertwined and mediated by each other. Biological factors that have been mentioned include, for example, decreased serotonergic functioning, possibly resulting in increased impulsivity and aggression (Spirito et al., 2006). From a birth cohort in New Zealand several factors were identified as being associated with suicidal behaviour, e.g. low socioeconomic status, family factors especially parental changes, childhood sexual

abuse, parental alcohol problems, and less degree of parental attachment. Also, personality traits assessed at age 16, neuroticism and novelty seeking were associated with suicidal behaviour. Youth reporting adverse life event were also found to be prone to suicidal behaviour (Fergusson, Woodward & Horwood, 2000).

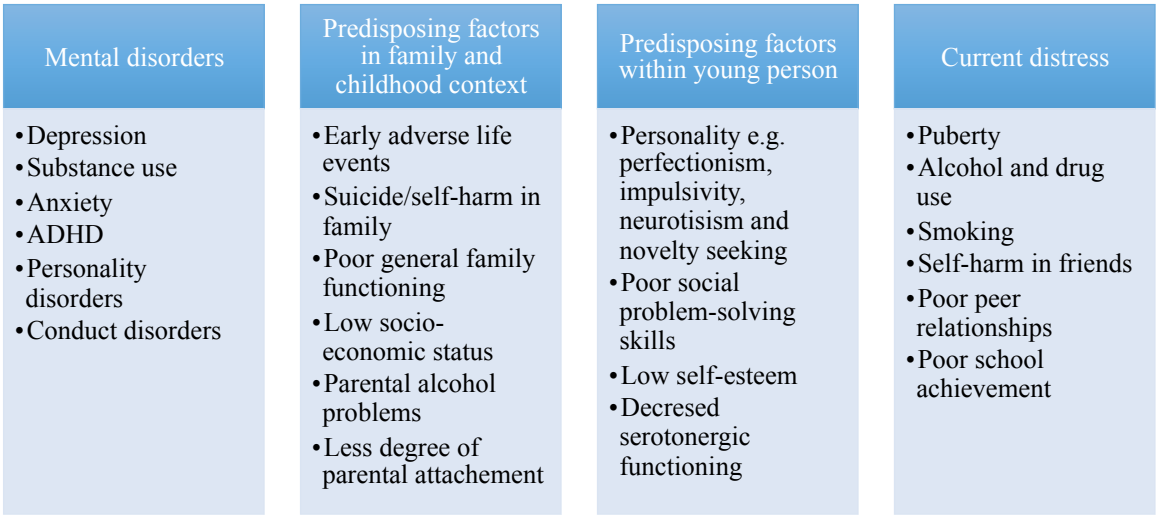

Figure 1. **Risk factors for self-harm in youth.**

1.3.1 Mental illness and self-harm

Mental disorders have been in focus in studies of the explanatory factors behind self-harm. In a systematic review, a mental disorder was recorded in 81.2% of young self-harm patients (Hawton, Saunders, Topiwala & Haw, 2013). Depression, or mood disorders, seem to be the disorder most commonly reported (Hawton et al., 2013, Fergusson et al., 2000, Goldston et al., 1996). In a systematic review of mental disorders in self-harm patients, depression was found in half of the patients. ADHD, substance use, adjustment disorder and anxiety were seen in around one quarter, but with large variations between studies (Hawton et al., 2013). Another review highlights three disorders – affective disorders, substance use, and antisocial behaviours – in suicidal behaviour in youth; (Beautrais, 2000). Attention deficit disorder (ADHD) has been found to be common among those with suicidal ideation, suicide attempts and completed suicide, often together with other conditions e.g. substance use and mood disorders (Impey & Heun, 2012). The roles of depression, anxiety and hopelessness in suicidal behaviour have been scrutinized among high-school drop-outs, and it is suggested that the role of anxiety is mediated by depression and hopelessness in males and by hopelessness in females (Thompson et al., 2005). Hopelessness is often referred to as being of high importance in adult self-harm, and has also been highlighted in studies of young people (Boergers, Spirito & Donaldson, 1998, Mazza & Reynolds, 1998).

1.3.1.1 Impulsivity

Impulsivity is a well-known risk factor for self-harm (Auerbach, Stewart & Johnson, 2017, Gvion & Apter, 2011). In a review of the role of impulsivity in adolescent self-harm, its importance in both non-suicidal and suicidal self-harm was highlighted, and an attempt was made to differentiate between its different aspects (Lockwood, Daley, Townsend & Sayal, 2016). In short, mood-based impulsivity was said to be associated with the initiation of self-harm, and cognitive impulsivity traits with the continuance of self-harm. Impulsive suicide attempts (ISA) are common at all ages, and many studies that evaluate the frequency of ISA find that more than 50% of attempts can be regarded as impulsive (Rimkeviciene, O'Gorman & De Leo, 2015). Some studies suggest that young age increases the risk of higher impulsivity in suicidal behaviour (Conner et al., 2005, Conwell et al., 1998, Hawton et al., 2005). These results are, however, contradicted by other studies (Baca-Garcia et al., 2001, Conner et al., 2007, Deisenhammer et al., 2009).

1.3.2 Risk factors correlating self-harm to young age

The incidence of self-harm among adolescents and young adults is thus higher than in older age groups and it is of interest to understand why self-harm behaviour occurs more often at this specific age. Some of the risk factors described in the previous paragraphs are perhaps particularly important at a young age, e.g. the onset of depressive symptoms often occur in adolescence and high prevalence rates of depression are seen in late adolescence and young adulthood (Costello et al., 2002).

In his article on emerging adulthood, JJ Arnett argues that the age 18-25 is a distinct developmental time period in most parts of the world. This time period is important for becoming self-sufficient, described as taking responsibility for oneself and making independent decisions. It is also the time for identity exploration, mainly in three areas: love, work, and worldviews (Arnett, 2000). There are perhaps reasons to consider this time of change as unstable, and emerging adults may possibly be more susceptible to stressors. Also, it is possible that self-harm at this identity-forming age has more long-term consequences for future life than self-harm in adult life.

The brain undergoes functional and structural changes during adolescence, and attempts have been made to correlate these changes, together with behavioural changes, to psychopathology in this life phase. The importance of changes in social behaviour in adolescence is sometimes highlighted (Nelson, Leibenluft, McClure & Pine, 2005, Blakemore, 2008, Guyer, Silk & Nelson, 2016). Different brain areas are involved in social information processing, and mature in different phases of life. Affective reactivity to social stimuli is heightened during adolescence whereas the cognitive regulatory functions develop in late adolescents or early twenties. New social challenges occur in relations to peers as well as to parents, and appear in forms not previously experienced. The social support network, which is important in resistance to stress and other difficulties, shifts from parents to peers. It is suggested that psychopathology in adolescence, e.g. depression and anxiety, is related to hyper-reactivity to

negative social stimuli together with difficulties in modulating or contextualising these elevated emotions. Pubertal hormones are involved in the maturation of certain brain areas important to emotional processing (Guyer et al., 2016, Nelson et al., 2005). Pubertal stage and the effect of puberty on self-harm may partly explain its prevalence among youth, especially among girls (Hawton et al., 2012b). In a study of adolescents in Victoria, Australia, the prevalence of self-harm seemed to be better correlated with late pubertal stage than age. The effect of puberty is largely mediated by the effect of puberty on depressive symptoms, alcohol use and sexual activity, all of which are elevated in late puberty or after puberty, and are known risk factors for self-harm (Patton et al., 2007, Hawton et al., 2012b).

1.4 MODELS FOR UNDERSTANDING SELF-HARM AND SUICIDE

As well as identifying factors that might increase the risks of self-harm and suicide, it is relevant to try to understand the psychological processes involved in these behaviours. Models have been proposed to conceptualise the onset of both non-suicidal self-harm and suicidal behaviour.

1.4.1 Non-suicidal self-injury

Nock and colleagues have presented a functional model for understanding self-harm without a suicidal intent (Nock & Prinstein, 2004). The model includes automatically reinforcing motives (e.g. affect regulation) and socially reinforcing motives (e.g. attention seeking and avoidance). Accordingly, the authors suggest directed treatment based on the individual's motives. Escaping from difficult emotions is also emphasized in the Experiential Avoidance Model, which also addresses the functions of self-harm where there is no intent to die (Chapman, Gratz & Brown, 2006). In a review article from 2007, Klonsky summarized 18 studies that addressed the functions of self-injury, and he concluded that an affect-regulated function had the strongest support. There was also support for self-injury being used for self-punishment, and some support for the functions of anti-dissociation, interpersonal-influence, sensation-seeking, anti-suicide, and interpersonal boundaries (Klonsky, 2007).

1.4.2 Suicide

Several models have been suggested for the understanding of suicide and suicidal behaviour. Among others, John Mann has described a stress-diathesis model to explain the interplay between pre-dispositional vulnerability and current stress (Mann, 2003). In the following paragraphs, a few other models are briefly explained.

1.4.2.1 The suicidal process by Paykel and O´Connell

An early mapping of different steps in the suicidal process was made by Paykel and colleagues when exploring suicidal thoughts and behaviour in the general population (Paykel, Myers, Lindenthal & Tanner, 1974). The authors created a step-based model with the first steps including thoughts of life being not worth living and the last steps resulting in the making of a suicide attempt (*Figure* 2). The concept of a continuum of steps was based on the idea that people who had experiences of the last steps also had experiences of the earlier

steps. This model was further developed for elderly people by O´Connell and colleagues (O'Connell, Chin, Cunningham & Lawlor, 2004). And it was also explored in young suicide victims in Sweden, where two main two pathways to suicide were identified (Runeson, Beskow & Waern, 1996). A process of short duration was seen in people with adjustment disorder and depression, whereas patients with long-standing disorders, such as schizophrenia and borderline personality disorder, underwent a longer process with more communication.

Figure 2. **The suicidal process, based on Paykel et al., 1974.**

1.4.2.2 The interpersonal theory of suicide

In the interpersonal theory developed by Joiner and colleagues, suicidal behaviour develops from three main constructs: thwarted belongingness, perceived burdensomeness (both of which give rise to suicidal desire), and the acquired capability to engage in potentially lethal behaviour (Van Orden et al., 2010). Thwarted belongingness (e.g. social isolation, loneliness, loss of partner) acts in relation to perceived burdensomeness (illustrated by the importance of unemployment, family conflicts, and physical illness for the risk of suicide). These are not enough to actually act on desire. The capability to act is enabled through reduction of fear of death and through physical pain tolerance. This can be acquired through repeated exposure to experiences that are physically painful and induce a fear of death. By acts of self-harm, a certain habituation occurs via which there is an increased possibility that one might really act on a suicidal desire.

1.4.2.3 Integrated motivational-volitional model of suicidal behaviour

In this model major components from several other models are integrated into one and the transition from suicidal ideation to suicidal behaviour is theorized (O`Connor R, 2016). O´Connor describes three phases of the suicidal process. The premotivational phase can be said to offer a broader context for how suicidal thinking/ behaviour might occur. It involves a combination of diathesis, environmental factors and life events (*Figure 2*). The motivational phase is where suicidal ideation/ intention is formed. A pathway from an experience of defeat/humiliation is transferred into feelings of entrapment and then further into suicidal ideation. Specific moderators enhance each step. The transference of ideation into behaviour, the volitional phase, depends on moderators such as having the access to means, the

capability to attempt suicide, knowing others who have attempted suicide, and impulsivity. Impulsivity as well as self-harm in the family or among friends may be important among adolescents in order to distinguish those who have suicidal ideation only from those who act on their thoughts (O'Connor, Rasmussen & Hawton, 2012).

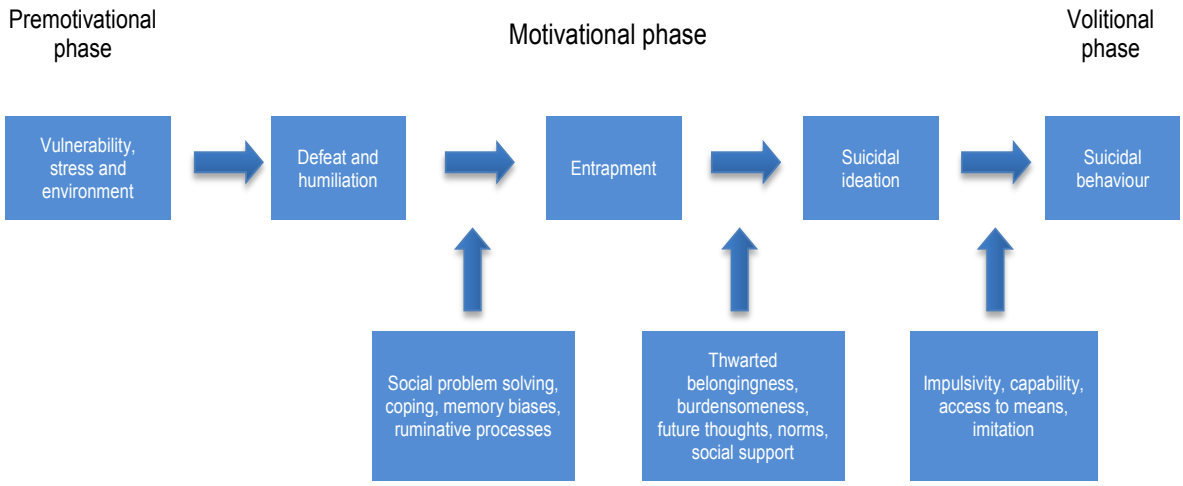

Figure 3. **The Integrated Motivational- Volitional Theory of Suicide. Modified version from O´Connor**

1.5 PROGNOSIS AFTER SELF-HARM

The risk of negative outcomes later in life after self-harm in youth, such as morbidity and early death, has been one focus of research in recent years. Some of the studies have included assessments of whether the adverse outcomes are attributable to preceding mental disorders/social disadvantages/cognitive and emotional difficulties.

Moran and colleagues studied the course of self-harm from adolescence to young adulthood (14 to 29 years of age) and found that self-harm tends to subside in adulthood (Moran et al., 2012). This seems to be the path for most young people who self-harm, and attempts have been made to understand who are most at risk of repeated self-harm, long-term difficulties and early death.

1.5.1 Repeated self-harm and suicide

Most studies of the long-term consequences of self-harm at a young age have focused on the risk of suicide after self-harm or the risk of repetition of self-harm episodes.

In large cohorts of age-mixed populations, the risk of suicide after self-harm seems to be lower in younger age groups compared to older (Haukka, Suominen, Partonen & Lonnqvist, 2008, Cooper et al., 2005, Hawton et al., 2015). Even so, the risk is vastly increased compared to the general population (Hawton & Harriss, 2007). In studies that have examined completed suicide as outcome, self-harm is an important risk factor (Fortune, Stewart, Yadav & Hawton, 2007). Previous suicide attempts and mood disorders are major risk factors for adolescent suicides; 33% were found to have made a previous attempt in a psychological autopsy study (Shaffer et al., 1996). In another study, 66% had made a previous attempt before suicide, and among women as many as 81% (Runeson et al., 1996). Young male suicide victims who had a family history of suicide more often had a history of suicide attempts, an early debut of suicidal behaviour, and a longer duration of the suicidal process (Runeson, 1998).

Risk factors for suicide among youth with self-harm have been studied. Long-term follow-up (median follow-up of 11 years) of 15-24 year-olds with a hospital presentation following self-harm showed an all-cause mortality rate of 2.9%, and at least half of the deaths were suicides. The risk factors associated with suicide among these people were male gender, previous deliberate self-harm, prior psychiatric history (females), and high suicide intent (Hawton et al., 2007). In a case-control study of young patients (15-24 year-olds) with an act of self-harm, substance misuse and prior inpatient psychiatric treatment best discriminated between cases (completed suicides) and controls (Hawton, Fagg, Platt & Hawkins, 1993). Among adolescents, aged under 18, with an act of self-harm, male gender, cutting as a method and previous psychiatric treatment were associated with suicide (Hawton et al., 2012a).

Repetition of self-harm has been explored in several studies. Repetition seems to be more common among younger age groups who self-harm than among older (Haukka et al., 2008). In another study of self-harm in all age groups, the effect of repetition on suicide risk was greatest among young women; having multiple episodes implied a seven-fold relative risk compared to a single self-harm episode in this age group. Hence, repetition seems to be an important marker of severity among young women (Zahl & Hawton, 2004).

Risk factors for repeated self-harm have been investigated. In a large international community-based study of 15-16 year-olds, more than half reported more than one episode during their lifetime. Cutting or multiple methods used at the most proximal event was associated with repeated self-harm (Madge et al., 2008). A prior suicide attempt increases the risk of a new attempt more than five-fold in adolescents (Lewinsohn, Rohde & Seeley, 1994). In a sample of 228 teenagers, participants were grouped as suicide ideators, single attempters or multiple attempters. They were assessed for psychiatric disorders, and information about the attempts was gathered. Adolescents with repeated suicide attempt were more likely to have a mental disorder (mood disorder, anxiety or substance use), had a stronger intent to die at first attempt, planned less for a possible intervention to occur, and were more prone to repeat further than single attempters (Miranda et al., 2008). Features of the first attempt that predict repetition are a wish to die, isolation, and planning (Miranda, De Jaegere, Restifo &

Shaffer, 2014). In a cohort of 10-18 year-olds who presented to hospital care with self-harm, 27.3% repeated self-harm. History of psychiatric treatment, previous self-harm, older age at initial presentation, and cutting compared to self-poisoning were associated with an increased risk of repetition of self-harm. (Hawton et al., 2012a).

1.5.2 Social outcomes

Only a few studies have focused on social outcomes after self-harm at a young age. In a follow-up study of a birth cohort in New Zealand, people who attempted suicide up to age 24 were twice as likely to be convicted of a violent crime or be abusive towards an intimate partner. Also, they were more likely to be in need of social welfare, and to be a victim of partner abuse. These findings remained significant after adjustment for previous mental disorder (Goldman-Mellor et al., 2013). Adolescents in UK who had self-poisoned between 11 and 16 years of age were more likely than community controls to experience problems such as dependence on welfare benefits, disrupted education, leaving home early, and difficulties with marital/partner relationships (Harrington et al., 2006). Adolescent men who made suicide attempts were more likely to experience relationship problems and be aggressive toward partners (Kerr & Capaldi, 2011). A follow-up study of adolescent suicide attempters in adult life showed a negative effect of attempt on several social and psychiatric outcomes. However, after adjustment for relevant confounders that were present in adolescence only, the effects on social adjustment and global functioning remained significant. The authors conclude that there is long-standing impairment in adult life but that this reflects other social, familial or individual vulnerabilities in adolescence (Briere et al., 2015).

1.5.3 Mental illness

Future mental health after self-harm behaviours in adolescence and young adulthood have been explored in some studies, most of them with limited numbers of participants with self-harm. Both population-based studies (Goldman-Mellor et al., 2013, Briere et al., 2015, Moran et al., 2015, Mars et al., 2014b, Fergusson, Horwood, Ridder & Beautrais, 2005) and studies in clinical settings (Harrington et al., 2006, Groholt & Ekeberg, 2009) have been published. Some studies have differentiated between acts with and without suicidal intent (Mars et al., 2014b), and also between suicidal ideators and enactors (Fergusson et al., 2005).

In clinical settings, a high risk of psychopathology in adult life has been noted after self-harm or suicide attempts at a young age. In a follow-up of 156 adolescents, aged 11-16 years, psychiatric disorders were prevalent six years after episodes of self-poisoning; depression was especially common. More than half of the youths had used medication or services for a psychiatric condition during follow-up (Harrington et al., 2006). A follow-up study of 92 adolescents admitted to hospital after a suicide attempt; 79% had at least one psychiatric diagnosis on interview after 8-10 years. The most common disorders were depression, personality disorder and anxiety disorder (Groholt et al., 2009).

A few studies have tried to differentiate between aspects of suicidal behaviours and thoughts and the risk of long-term consequences. A history of suicidal thoughts and behaviours, respectively, were examined among 1,025 18 year-olds who were followed regarding suicidal behaviour, depression, anxiety and substance use up to the age of 25. The highest frequency of suicidal behaviour, mental disorder and treatment-seeking for mental disorders were seen among those who had made a suicide attempt in adolescence and an intermediate risk was noted among suicidal ideators (Fergusson et al., 2005). In a recent follow-up of a population-based cohort by Mars and colleagues, adolescents were asked about their history of self-harm before age 16 while mental disorders were assessed at age 18. There was a strong association between early self-harm and later mental disorders even after adjustment for previous depressive symptoms and socioeconomic position. The authors tried to examine whether there was a difference in outcome between self-harm with and without suicidal intent. Later mental disorders were more common among those who self-harmed with suicidal intent. However, suicide attempts often occur in the context of a mental disorder, hence the difference in association was weak after adjusting for mental disorder at baseline (Mars et al., 2014b).

Several studies have tried to assess possible confounding factors at time of self-harm that also increase the risk of psychiatric morbidity. Known factors in youth that predispose people to mental disorders in adult life have been included, especially the symptoms of early mental disorders that are prevalent at self-harm. Efforts have been made to examine the specific association of self-harm with future mental health problems.

Some studies were able to find an independent association between self-harm in youth and later psychiatric morbidity. Goldman-Mellor and colleagues found, in the follow-up of a New Zealand birth cohort, that young people who had made a suicide attempt before age 24 were twice as likely to report depression and substance dependence up to age 38. They were also more likely to seek help for psychiatric problems, to use psychiatric medication, and to be hospitalised for a psychiatric condition. After the authors adjusted for a history of depression, anxiety and conduct disorder, the association between suicide attempt in youth and mental outcome in adult life remained significant (Goldman-Mellor et al., 2013).

Other studies have had difficulties finding a clear association between self-harm and later psychiatric morbidity above the effect of symptoms of a mental disorder at the time of self-harm. Most of the mental disorders later in life have been explained by earlier psychopathology. A population-based cohort study examined the association between self-harm in adolescence and substance use in young adulthood. An increased risk of substance use disorder in young adulthood after self-harm in adolescence was seen, but the risk was partly explained by depression, anxiety and substance use disorder in adolescence. Self-harm remained as an independent risk factor only for multiple dependence syndromes in young adulthood (Moran et al., 2015). Suicide attempts in adolescence (mean age 17) predicted psychopathology in adult life (mean age 30), e.g. anxiety disorder, and antisocial and borderline personality disorder. Other psychopathological states, such as depression, were

present among those with a suicide attempt in adolescence but were largely explained by other factors present among young suicide attempters, in particular psychopathology and family background (Briere et al., 2015). Some of the longitudinal associations between suicidal thoughts and behaviour in adolescence and mental health problems in young adulthood have been explained by other known risk factors, e.g. social, family and related life-history measures, individual characteristics and behaviour, and mental disorder at ages 14–18 years (Fergusson et al., 2005).

In summary, self-harm in youth is more common than in other age groups, and is also more common among females than males. Mental disorders, e.g. depressive disorders and substance use, impulsivity, low familial socioeconomic status and suicidal acts among family members or friends are some of the studied risk factors for self-harm. Suicidal acts sometimes occur without previous planning, and there are indications that impulsive suicide attempts are made more often by young people than older. The risk of suicide is elevated after self-harm but the risk seems to vary with age at self-harm, although this has not been extensively explored in large epidemiological studies. Some indicators of elevated risk of suicide among people who self-harm have been identified, e.g. previous self-harm and a history of psychiatric treatment. More knowledge is needed in order to help risk assessment after self-harm. It has been suggested that self-harm behaviour at a young age impairs both social and financial functioning in adult life, and also implies a higher degree of mental illness in long-term follow-up. More knowledge of adverse outcomes in a long-term perspective is needed.

2 AIMS

The overall aim of this thesis was to understand the significance of self-harm at a young age and its effect on future mental illness, social marginalisation and death by suicide. Further, we aimed to identify the individuals most at risk of adverse outcomes after self-harm at a young age.

The main research questions were:

1. Suicide risk after self-harm at a young age
   1.1. What is the risk of suicide after self-harm at a young age compared to the general population? (*Study 1 and 3*)
   1.2. Is the risk of suicide lower after self-harm at a young age compared to older age? (*Study 1*)
   1.3. Which clinical factors predict an elevated risk of suicide among young people who self-harm? (*Study 1, 3, 4, 5*)

2. Adult life after self-harm at a young age
   2.1. What is the long-term prognosis regarding mental illness? (*Study 3*)
   2.2. What is the effect of self-harm on labour market participation in adult life? (*Study 2*)

3. Significance of the impulsiveness of a suicide attempt among young adults
   3.1. Are impulsive suicide attempts (ISA) more common among young people than older? (*Study 5*)
   3.2. Among young people, who makes impulsive and who makes more planned suicide attempts? (*Study 5*)
   3.3. Do ISAs result in less medically severe injuries? (*Study 5*)

3 METHODS

	Study 1	Study 2	Study 3	Study 4	Study 5
Overall research focus	Suicide risk after self-harm in different age groups	Labour market marginalisation after youth suicide attempt	Suicide risk and psychiatric prognosis after self-harm in young adulthood	Suicide risk after self-harm according to method used by youth	Impulsive suicide attempt in youth and clinical correlates, medical severity and risk of repetition
Study design	Cohort study (matched)	Cohort study	Cohort study (matched)	Cohort study	Cohort study
Study population	Individuals with self-harm leading to in-patient care, 1990-1999 + 10 population controls	Swedish residents aged 16-30 on 31 Dec 1994	Individuals with self-harm leading to in-patient care, 1990-2003 + 10 population controls	Events of self-harm leading to in-patient or outpatient care, 2000-2009	Individuals with suicide attempts in a multicenter study, 2012-2016
Data source	National Registers	National Registers	National Registers	National Registers	Patient interviews and medical records
Size of study population (n)	592 236	1 613 816	151 041	38 673 events (24 072 ind)	666
Follow-up time	9-19 years	15 years	6-20 years	< 10 years	6 months
Explanatory variable	Age at self-harm	Suicide attempt	Self-harm	Method at self-harm	Impulsive suicide attempt
Age at exposure	≥ 10	14-30	18-24	10-24	18-25
Main outcome variables	Suicide	Unemployment, sickness absence and disability pension	Suicide, psychiatric hospitalisation and psychotropic medication	Suicide	Medical severity and fatal and non-fatal repetition
Statistical analyses	Pearson's Chi^2 test, Cox regression models	Cox regression models	Pearson's Chi^2 test, Cox regression models	Cox regression models, Logistic regression models	Pearson's correlations, Cox regression models, Logistic regression

3.1 DATA SOURCES

3.1.1 National registers

Four out of the five studies are based on Swedish national registers. The personal identification number, which has been assigned to every Swedish resident since 1947 (Ludvigsson, Otterblad-Olausson, Pettersson & Ekbom, 2009), links the registers, and the data are de-identified before being made available to the researchers. The following registers have been used:

3.1.1.1 National Patient Register (NPR)

The NPR covers 99% of all in-patient episodes in Swedish hospitals (Ludvigsson et al., 2011). It has been in use since 1964, and for psychiatric admissions since 1973, but did not reach its present coverage until 1987. Information in the register includes main diagnosis and multiple secondary diagnoses, according to ICD-8, -9, and-10. The positive predictive value of in-patient diagnoses set in the NPR is 85-95% (Ludvigsson et al., 2011). Since 2001, outpatient events have been included in the register, with coverage of around 80%, but reports on visits from private caregivers are mainly lacking (Forsberg, 2009). The data also include date of admission, length of stay, and type of department. The National Board of Health and Welfare holds the register.

3.1.1.2 The Cause of Death Register (CDR)

The CDR includes information on all deaths of individuals registered in Sweden, even if the death occurred abroad. It was founded in 1952 and has almost complete coverage (Brooke et al., 2017). Causes of death are recorded according to the ICD system. The National Board of Health and Welfare holds the register.

3.1.1.3 The Prescribed Drug Register (PDR)

Information on all drugs prescribed and dispensed in Sweden since July 2005 (Wettermark et al., 2007) is included in the PDR. It includes data on age, sex, the drug prescribed, amount and dosage, prescriber's profession and practice, and date of dispensation. It does not include drugs sold over the counter, or drugs dispensed in hospitals, in ambulatory care or nursing homes, or vaccines. The National Board of Health and Welfare holds the register.

3.1.1.4 The Total Population Register (TPR)

The TPR contains information on sex, date and place of birth and civil status (Ludvigsson et al., 2016). The register is held by Statistics Sweden and was established in 1968.

3.1.1.5 The Multi-Generation Register (MGR)

The MGR contains information on the link between biological or adoptive parents and their children (Ekbom, 2011). All individuals born after 1932 who have been residents of Sweden after 1961 are included. The MGR is held by Statistics Sweden.

3.1.1.6 The Swedish Educational Register (ER)

The ER was founded in 1985 and contains information on the highest level of education, from elementary to post-graduate level, of all individuals registered in Sweden from 1985. It also contains data from the national censuses of 1970 and 1990. The register is held by Statistics Sweden.

3.1.1.7 The Micro Data for Analyses of the Social Insurance Database (MiDAS)

The MiDAS contains information on the sickness absence and disability pension of Swedish residents since 2005 and 1994, respectively. The Social Insurance Agency holds the register.

3.1.1.8 The Longitudinal Integration Database on Social Insurance and Labour market studies (LISA)

LISA contains sociodemographic data on all Swedish residents above the age of 16 since 1990, and is held by Statistics Sweden. It contains information on, for example, family situation, employment status and educational level (scb.se/lisa-en).

3.1.2 The Multicentre Study on Self-harm

A multicentre cohort study was conducted in three Swedish psychiatric university departments, Norra Stockholms psychiatry in Stockholm (affiliated with Karolinska Institutet), Umeå University Hospital, and Sahlgrenska University Hospital in Göteborg, between April 2012 and March 2016. Patients above age 18 presenting for psychiatric evaluation within one week of an event of self-harm, with or without suicidal intent, were considered for inclusion in the study. Specially trained mental health staff (psychiatric nurses, psychologists and psychiatrists) performed an interview that lasted around 1.5 hours, including various assessment instruments. Among other data, the Suicide Intent Scale (SIS) (Beck, Morris & Beck, 1974), the Columbia Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2011) and the Karolinska Interpersonal Violence Scale (KIVS) (Jokinen et al., 2010) were included, along with directed items on sociodemographics data and past-week symptoms of distress. Follow-up was conducted in medical records, where psychologists, psychiatric nurses, medical students and psychiatrists collected data on possible new events of fatal or non-fatal self-harm.

3.2 STUDY DESIGNS AND STUDY POPULATIONS

3.2.1 Cohort studies

Cohort studies are longitudinal observational studies. In a cohort study, a defined population is followed from a starting point until an outcome occurs or there is censoring due to other causes. The population may or may not be exposed to a certain variable of interest. This variable is investigated to establish whether it affects the probability of the occurrence of a particular outcome. The data might be collected prospectively or retrospectively. The population should be free of the outcome at the time of the exposure; hence, the cohort is studied prospectively with regard to the effect of the exposure on the outcome. Therefore, the

design offers a possibility to study the relationship between the exposure and the outcome prospectively. The absolute risk of an outcome among exposed and non-exposed can be calculated as well as relative risks among exposed compared to non-exposed. Rare exposures are preferably studied with this design.

In this thesis, a few variations in cohort designs were applied in the different studies. In Study 1 and Study 3, the population was selected based on the individuals with a self-harm event (exposed), registered in the Swedish National Patient Register, and 10 controls from the general population (non-exposed), matched on age and sex, among correspondingly exposed individuals. The cohort was open; hence, the inclusion date varied according to the time of exposure. The cohort was followed up to the time of the outcome, migration or death by other causes. This design can be referred to as a matched case-cohort study.

The cohort in Study 2 consisted of a study population of all individuals, defined by age and country of residence, alive at a certain time point. The cohort in Study 4 consisted of all events of self-harm in the National Patient Register in a certain period of time, and was evaluated based on the exposure of a certain method used at self-harm. Both Study 2 and Study 4 can be regarded as using open cohorts. The clinical cohort in Study 5 consisted of patients who were included upon presentation at hospitals after an event of self-harm.

3.2.2 Outcome variables

3.2.2.1 Suicide and suicidal behaviour

In studies 1, 3, 4 and 5, the outcome was suicide as recorded in the Cause of Death Register. We included deaths with the underlying cause of death as intentional self-harm (X60-84), and also undetermined intent (Y10-34), in order to avoid underestimation of the number of suicides (Neeleman & Wessely, 1997, Linsley, Schapira & Kelly, 2001). In Study 5, the outcome of suicidal behaviour was retrieved from medical records and categorized as a fatal or non-fatal suicide attempt within 6 months.

3.2.2.2 Unemployment, sickness absence and disability pension

In Study 2 we used several outcomes to capture labour market marginalisation. Long-term unemployment was defined as unemployment in the LISA database of more than 180 days. Data for the variables long-term sickness absence (more than 90 days) and disability pension were taken from MiDAS,.

3.2.2.3 Psychiatric hospitalization and psychotropic medication

In Study 3 two different outcomes were used to evaluate future mental illness. Psychiatric hospitalisation at short-term follow-up was defined as having a hospitalisation at a psychiatric department with a psychiatric diagnosis at discharge at least once, as registered in the NPR, 1-5 years after inclusion. Psychiatric hospitalisation at long-term follow-up was defined as a hospitalisation episode occurring more than 5 years after inclusion. Data on psychotropic medication was collected from the PDR and grouped according to the Anatomical

Therapeutical Chemical (ATC) classification system into antidepressants, antipsychotics and mood stabilizers, benzodiazepines and hypnotics, Attention Deficit Hyperactivity Disorder (ADHD) medication and medication for alcohol and opioid use disorder.

3.2.2.4 Medical severity of suicide attempt

In Study 5 we calculated the correlation between impulsive suicide attempts and the medical severity of the attempts. We used item CS21a from the rater/clinician-administered version of the Columbia Suicide Severity Rating Scale (C-SSRS), which refers to the medical severity of the latest attempt scored from 0 (no physical damage or very minor physical damage) to 5 (death). The item was dichotomised and *high medical severity* was defined as a rating of 3 or 4 on CS21a (requiring medical hospitalisation/intensive care).

3.2.3 Explanatory variables

3.2.3.1 Self-harm

Slightly different constructs of self-harm were used in the included studies. In the register-based studies of self-harm events (studies 1-4) we used ICD-10 codes X 60-84 and ICD- 9 codes E 950-9 (intentional self-harm), and in studies 1-3 also Y 10-34 and ICD-9 codes E980-9 (events of undetermined intent). For Study 2 the group of authors decided that, since the self-harm events required hospital care, there was a strong possibility of a high degree of suicidal intent in the events, and therefore the term "suicide attempt" was used. In studies 1, 3 and 4 we used the term "self-harm" to stress the fact that there is no possibility of determining the presence of suicidal intent from register data; therefore, it is possible that both suicidal and non-suicidal acts of self-harm are included. In the clinical multicentre cohort study, Study 5, only self-harm events with a suicidal intent were included. The suicide attempters were defined as having a non-zero intent to die (O'Carroll et al., 1996)

Repetition of self-harm is a well-known risk factor for even further repetition of self-harm as well as suicide (Haw, Bergen, Casey & Hawton, 2007, Zahl et al., 2004). Previous self-harm was included as a covariate in the analyses in studies 1, 2, 4 and 5..

3.2.3.2 Impulsive suicide attempt

To determine the impulsivity of each attempt, we used Beck's Suicidal Intent Scale (SIS), specifically the items that concern active preparation for the attempt and degree of premeditation (items 6 and 15). Impulsive suicide attempt was defined as 0 = no preparation and 0 = no premeditation/impulsive. The same definition has been used in a number of previous studies (Baca-Garcia et al., 2001, Brown, Overholser, Spirito & Fritz, 1991, Fazaa & Page, 2009, Groholt, Ekeberg & Haldorsen, 2000, Suominen et al., 1997).

3.2.3.3 Mental disorders

Co-occurring mental disorders are important in self-harm and suicide research, and they were taken into account in all the studies. In studies 1, 3 and 4 the presence of mental disorder was

defined as having received any diagnosis of a mental disorder (ICD–8 and ICD–9 codes 290–319; ICD-10 codes F00–99) at the time of inclusion. A history of inpatient psychiatric care was included in Study 2, defined as inpatient care with a mental disorder, using the ICD codes described above.

In Study 3, we evaluated the effects of different mental disorders at the time of the self-harm event on 1/ risk of future suicide and 2/ future mental disorders or need of mental health care. In this study, mental disorders at the time of the self-harm event were categorised into *alcohol and substance use disorders, non-organic psychotic disorders, affective and anxiety disorders, personality disorders,* and *other mental disorders*.

In Study 5, the correlation between an impulsive suicide attempt and different prior and concurrent mental disorders was studied, by use of information on mental disorders derived from medical records and the diagnosis set at the self-harm event. In this study, the disorders were categorised into *substance use disorder* (F10-19), *affective disorder* (F30-39), *personality disorder* (F60-69), *anxiety disorder* (F40-48), *disorders of psychological development* (F80-89) and *ADHD* (F90 and F98.8).

3.3 STATISTICAL ANALYSES

3.3.1 Logistic regressions

Logistic regression models are used to estimate the relationship between one or more independent variables and a dependent variable when the dependent variable is dichotomous. The model generates a ratio between the odds of an outcome given the presence of an exposure and the odds of an outcome given the absence of the exposure. It is possible to include several exposures in the model. Logistic regression was used in Study 4, to estimate the relation between the method of self-harming and psychiatric hospitalisation at self-harm. We also used the model in Study 5 where the relationships between clinical factors, medical severity and a violent method and impulsive suicide attempts were evaluated.

3.3.2 Cox regression models

Survival analyses are useful in studies of the relationship between an exposure and an outcome when time is a relevant factor. When analysing survival data, number of events (outcome) and the time under risk of an event for the included individuals are of interest. Cox regression models (or proportional hazard models) are often used for survival analyses and have been applied in all studies of this thesis. In the Cox model, the hazard function, the rate of an event at each time-point, is of interest. A ratio of the hazard, between those exposed to a variable of interest and those not exposed are presented and therefore the association of the exposure variable on the outcome is analysed. For example, in Study 3 we studied the outcome of suicide during follow-up and calculated the Hazard Ratio (HR) between those exposed to self-harm compared to those not exposed to self-harm. We also performed stratified Cox regressions, since we had matched the exposed subjects with the unexposed on sex and age and hence clusters within the matched sets had to be considered. In all five

studies, confounding factors were included in the analyses. In Study 3 and 4, we also introduced interaction terms of self-harm*mental disorder and self-harm*sex, respectively, to establish whether the results were applicable to those with or without mental disorder and to both men and women.

4 RESULTS

		Study 1	Study 2	Study 3	Study 4	Study 5
Effects of self-harm at a young age compared to general population	**Suicide**	IRR (men[a]) 13.8 (9.7–19.7) IRR (women[a]) 13.2 (9.4-18.4)		Adj[b] HR 16.4 (12.9-20.9)		
	Psychiatric hospitalisation (Adj[b] HR)			6.3 (5.8-6.8)		
	Psychotropic medication (Adj[b] HR)			2.8 (2.7-3.0)		
	Unemployment (Adj[c] HR)		1.58 (1.52-1.64)			
	Sickness absence ≥ 90 days (Adj[c] HR)		2.16 (2.08-2.24)			
	Disability pension (Adj[c] HR)		4.57 (4.34-4.81)			
Signals of elevated suicide-risk after self-harm		• Repetition of self-harm[g] • Mental disorder[g]		• Mental disorders esp. psychotic disorders • Family history of suicide	• Violent method[d] 10-17 year-olds and 18-25 year-old women • Severe cutting [d] 18-25 year-old women	
Impulsive suicide attempts (ISA) in 18-25 year-olds	**Prevalence compared to older patients**					43.7% vs. 30.2% [e]
	High medical severity compared to non-ISA (Adj[f] OR)					1.9 (0.9–3.8)
	Risk of fatal or non-fatal repetition compared to non-ISA (Adj[f] HR)					0.9 (0.5–1.6)

[a] 10-19 year olds

[b] Adjusted for the presence of a mental disorder, family history of suicide, low socioeconomic status in parents and family history of suicide

[c] Adjusted for individual age, sex, country of birth, area of residence, education, previous inpatient care due to somatic disorders, parental education, maternal family situation and the following maternal and paternal risk factors: suicide, death due to other causes, disability pension due to psychiatric and non-psychiatric disorders, psychiatric and somatic inpatient care, suicide attempt.

[d] Among events leading to inpatient care; poisoning was reference category.

[e] p = 0.001

[f] Adjusted for affective disorder, substance use disorder, previous suicide attempt and gender.

[g] During follow-up, 2-9 years after self-harm.

4.1 STUDY 1- AGE-SPECIFIC SUICIDE MORTALITY FOLLOWING NON-FATAL SELF-HARM: NATIONAL COHORT STUDY IN SWEDEN

The cohort consisted of 53 843 individuals exposed to self-harm 1990-1999. During follow-up until end of 2008 the proportion of suicides among men was 8.0% and among women 4.3%. The incidence rate ratio (IRR) compared to unexposed from the population was 23.7 (95% CI 21.8–25.6) among men, and 30.3 (95% CI 27.3–33.6) among women. The IRR varied between age groups, from 13.2 (9.4–18.4) for women of age 10-19 to 45.7 (29.6–70.6) for women aged ≥ 75.

Increasing age as a continuous variable significantly increased the risk of suicide after self-harm for both men and women up to 9 years of follow-up. Suicide proportions were significantly lower in the age group 10-19 years of age, compared to all other age groups: 3.3% among men, and 1.3% among women. With 10-19 year-olds as reference category, the effect of older age was significant; for example, the HR of age group 60-74 on the outcome of suicide within one year after self-harm was 11.1 (5.6–21.8) among men and 41.2 (12.7–134.1) among women.

We studied potentially risk-increasing factors on the risk of suicide within 1 year and 2-9 years after self-harm. Among men aged 10-19 years, a violent self-harm method and the presence of a mental disorder at self-harm increased the one-year risk of suicide. Among the youngest women, none of the studied factors increased the one-year risk. For those aged ≥ 20 years, a violent method, the presence of a mental disorder and repetition of self-harm all increased the one-year suicide risk. All three factors increased suicide risk within 2-9 years after self-harm; repetition of self-harm was evident as a risk increasing factor in the youngest age-group with HR 4.0 (2.0–7.8) for men and 2.6 (2.2–3.1) for women.

4.2 STUDY 2 - FUTURE RISK OF LABOUR MARKET MARGINALIZATION IN YOUNG SUICIDE ATTEMPTERS—A POPULATION-BASED PROSPECTIVE COHORT STUDY

A suicide attempt was registered in inpatient care for 5 649 individuals in the age range 14-30 years between 1992 and 1994. The unexposed group consisted of 1 608 167 individuals who did not have a registered suicide attempt. Those exposed to suicide attempt were younger, more often female and born outside Sweden, and more often had a history of psychiatric inpatient care than the unexposed.

A suicide attempt implied an elevated risk of long-term unemployment, with an adjusted HR of 1.58 (95% CI 1.52-1.64). The HR for the outcome sickness absence ≥ 90 days was 2.16 (2.08-2.24) with people unexposed to suicide attempt as the reference category. The risk of disability pension was also elevated, and the adjusted HR was 4.57 (4.34 - 4.81).

There was an interaction effect between suicide attempt and a history of psychiatric inpatient care on all three outcomes. For unemployment, there was only an effect of suicide attempt among people without a history of psychiatric inpatient care. For long-term sickness absence the effect of suicide attempt was 2.15 (2.05–2.24) among those without a prior psychiatric

inpatient care, and 1.49 (1.38–1.60) among those with previous psychiatric inpatient care. Similarly, for disability pension the HR for suicide attempt among people without previous psychiatric inpatient care was 5.13 (4.78 – 5.50) and 2.87 (2.65 – 3.11) among those with previous psychiatric inpatient care.

A dose-response effect of number of suicide attempts on the risk of each of the three outcomes was sought after, but not found regarding the outcome of unemployment. In the case of sickness absence ≥ 90 days there was a positive dose-response relationship between number of attempts and the risk of the outcome among those without previous psychiatric inpatient care. For the outcome of disability pension, the same dose-response relationship was evident among all individuals, with or without previous psychiatric inpatient care.

4.3 STUDY 3- MENTAL ILLNESS AND SUICIDE AFTER SELF-HARM AMONG YOUNG ADULTS: LONG-TERM FOLLOW-UP OF SELF-HARM PATIENTS, ADMITTED TO HOSPITAL CARE, IN A NATIONAL COHORT

There were 13 731 individuals in the cohort with an event of self-harm between 1990-2003. We followed them until 2009; during this time 3.5% died from suicide. Compared to the 137 310 unexposed sex- and age-matched controls from the general population, the HR for death by suicide was 16.4 (95% CI 12.9 – 20.9) after adjustment for the presence of a mental disorder, birth outside the Nordic countries, family history of suicide, and parental educational level.

Out of those who were exposed to self-harm, 20.5% had a psychiatric hospitalisation 1-5 years after the self-harm event, and 20.3% had a psychiatric hospitalisation more than 5 years after the index event. Psychotropic medication had been prescribed to and purchased by 51.1% >5 years after self-harm. The most often prescribed medications were antidepressants and benzodiazepines and hypnotics. Compared to those unexposed to self-harm the adjusted HR for psychiatric hospitalisation at long-term follow-up was 6.3 (5.8–6.8) and for psychotropic medication 2.8 (2.7–3.0). The effect on the probability of being prescribed ADHD medication was high, with HR of 5.8 (4.9–6.8), and likewise for medication for substance use disorders, with HR of 7.0 (6.1–8.0).

We studied factors that were known at the time of the self-harm event that might affect the risk of adverse outcome during follow-up. The presence of a mental disorder, particularly psychotic disorders with a HR on the outcome of suicide of 7.0 (5.0–9.8), was important. All the studied mental disorders had a significant effect on the outcome of suicide and mental illness later in adult life. Also, a family history of suicide could signal an elevated risk of adverse outcome, especially of suicide.

4.4 STUDY 4 - METHOD OF SELF-HARM IN ADOLESCENTS AND YOUNG ADULTS AND RISK OF A SUBSEQUENT SUICIDE

We studied 38 673 events of self-harm, by 24 072 individuals aged 10-24 years, in 2000-2009. Cutting and poisoning were the most common methods used in events registered in outpatient care, and poisoning was the most common method registered in inpatient care.

Up to follow-up 2009, 1.5% of the events of self-harm performed by men were followed by suicide, and 0.5% of those performed by women ($p < 0.001$). Among events leading to inpatient care among 10-17 year-olds, a violent method elevated the risk of suicide compared to poisoning, with HR 7.8 (95% CI 3.2-19.0), after adjustment for previous self-harm, previous or present mental disorder, sex, low parental education, and family history of suicide. Among events treated in outpatient care there were relatively few suicides, and no differences in suicide risks were seen between the methods used.

Among events leading to inpatient care among 18-24-year-olds, the use of a violent method was associated with a higher risk of suicide compared to poisoning, adjusted HR 2.3 (1.1-4.4), and the use of cutting implied an elevated risk of 1.9 (1.0-3.6). There was an interaction between sex and the use of cutting, and we performed analyses stratified by sex. Among women, both violent method (HR 4.0; 1.5-10.7) and cutting (HR 4.0; 1.9-8.8) were associated with an elevated risk of suicide compared to poisoning. No significant associations were seen in men ($HR_{violent\ method}$ of 1.6;0.6-3.9 and $HR_{cutting}$ of 0.8;0.3-2.6), compared to poisoning. Among events treated in outpatient care, there were no differences in suicide risk between the methods used.

Admission to psychiatric inpatient care after self-harm was more prevalent among 18-24 year-olds than among 10-17 year-olds. In the younger group, a violent method was associated with an odds ratio (OR) of 1.5 (CI 1.0-2.1) for psychiatric inpatient care after self-harm registered in somatic inpatient care, compared to poisoning. After events treated in somatic outpatient care, violent methods were associated with an increased probability of psychiatric inpatient care with OR of 2.5 (1.5-4.4). We noticed no other differences in the probability of post self-harm admission to psychiatric inpatient care.

4.5 STUDY 5 - IMPULSIVE SUICIDE ATTEMPTS AMONG YOUNG PEOPLE- CLINICAL CORRELATES AND PROGNOSTIC VALUE IN YOUNG ADULTS. A PROSPECTIVE MULTICENTRE COHORT STUDY IN SWEDEN

There were 666 individuals with suicide attempts included in the study, and patients aged 18-25 years of age made up 187 of those. Anxiety disorders were common among these individuals, as too were affective disorders. There were more women than men in the cohort, and 83.3% had previously made a suicide attempt. Among young patients, 43.7% had made an impulsive suicide attempt (ISA) compared to 30.2% among other adults ($p = 0.001$). The OR for ISA among young compared to other adults was 1.8 (95% CI 1.3-2.6).

ISA was compared to non-ISA regarding clinical and sociodemographic factors. Concurrent unemployment/sick-leave and the presence of an affective disorder were inversely associated with ISA in both the univariate and the multivariate regression models, with adjusted ORs of 0.4 (0.2-0.8) and 0.3 (0.2-0.7), respectively. A substance use disorder was associated with ISA in the univariate analysis and almost significant in the multivariate analysis, 2.1 (0.99-4.4).

We found no association of a violent method with ISA; adjusted OR 1.3 (0.6-2.7). Among ISAs, 35.2 % were of high medical severity, compared to 21.6% among non-ISAs (p = 0.052). The OR for high medical severity was 1.9 (0.9-3.8) for ISA compared to non-ISA after adjustment for affective disorder, substance use disorder, previous suicide attempt and gender. During follow-up at 6 months, 30.0 % had made a subsequent fatal - or non-fatal attempt after an ISA and 29.1% after a non-ISA.

5 DISCUSSION

5.1 CONCLUSIONS

This thesis provides evidence of the significance of self-harm at a young age, and its association with later mental illness, social marginalisation and death by suicide.

A highly elevated risk of suicide after self-harm in youth was detected, while, at the same time, a difference in the suicide risk after self-harm at a young age compared to older age was observed. Several factors that might help clinicians in assessments of who is at especially high risk of suicide after self-harm were identified. A mental disorder, especially a psychotic disorder, a family history of suicide, and repetition of suicide may be markers of an elevated risk. Among adolescents and young adult women treated in inpatient care after self-harm, clinicians should consider elevated risk following the use of a violent method at self-harm, and also cutting, among the young adult women. An impulsive suicide attempt implies an equally high risk of a subsequent fatal or non-fatal repetition as a more planned attempt.

Among young people who self-harm there is a need to take measures to prevent mental illness and social marginalisation in the future. A large proportion of mental disorders among individuals in long-term follow-up were identified. Both the need of psychiatric hospitalisation and psychotropic medication were highly elevated. Antidepressants were common in long-term follow-up, and there was an especially large effect of self-harm on medication prescribed due to psychotic symptoms or mood stabilisation, ADHD, and substance-use disorders. The risks of unemployment, long-term sickness absence and disability pension were elevated after self-harm. The elevated risk of sickness absence and disability pension was evident both in people with and without prior psychiatric inpatient care. Dose-response effects between the number of self-harm events and the risks of sickness absence and disability pension were evident, and may further exacerbate the association between self-harm and labour-market marginalisation.

The possibility that young individuals might conduct suicide attempts without prior planning should be remembered. The significance of the impulsiveness of suicide attempts among young adults was examined in a clinical setting. Impulsive suicide attempts were more common among younger people than older. Further, affective disorders, as well as unemployment/sickness absence, were associated with more planned suicide attempts, and substance use disorders were associated with more impulsive attempts. The impulsive attempts did not result in less medically severe injuries, and conferred an equally high risk of fatal or non-fatal repetition within six months.

5.2 SELF-HARM WITH OR WITHOUT SUICIDAL INTENT

Several terms are used in this context, and self-injurious behaviour is sometimes defined in terms of the presence or absence of suicidal intent. The term most often used in this thesis is “self-harm”, defined as self-inflicted injury, with or without suicidal intent. This definition denotes acts with a varying degree of suicidal intent, based on the conception that suicidal

intent is present on a continuum rather than being dichotomous (Bennardi et al., 2016, Hawton et al., 2012b). There are claims that suicidal and non-suicidal self-harm differ in aspects such as correlating factors (Nock et al., 2013), and reasons or functions (Brown, Comtois & Linehan, 2002) However, others claim that events, with or without a suicidal intent, often co-occur within the same individuals; those who self-harm without suicidal intent often also attempt suicide, and both carry an elevated risk of a subsequent suicide (Wilkinson et al., 2011, Whitlock et al., 2013, Asarnow et al., 2011). Suicidal intent is a complex phenomenon and, even when operationalized and analysed, such as via the use of Beck´s Suicidal Intent Scale, it offers large variation in predicting repeated self-harm events, and risk of suicide (Freedenthal, 2008).

Self-harm events studied in patient registers have sometimes been referred to as suicide attempts (Lundin, Lundberg, Allebeck & Hemmingsson, 2011, Runeson et al., 2010). In Study 2 the term suicide attempt was used. The main reason behind the choice in studies 1, 3, and 4 to use the term self-harm, defined as self-inflicted injury with or without suicidal intent, is that the information available is based on register data where intent is not addressed. Also, based on the reasoning above, it may be preferable to use the term self-harm in its wider context to acknowledge the complexity of suicidal intentions and motives behind self-harm. In Study 5, the included individuals were asked about their degree of suicidal intent, and only those with a non-zero intent to die were included (O'Carroll et al., 1996). This was mainly a decision based on the aim to focus on impulsivity in the *suicidal* process, its clinical associations, and its effect on medical severity and repetition.

5.3 SUICIDE RISK AFTER SELF- HARM

The risk of suicide after self-harm in youth was highly elevated compared to the general population (studies 1 and 3). Suicide is a tragic outcome in any patient, and particularly in a young person with a long remaining life expectancy. Suicide is the second most common cause of death in 10-24 year-olds globally (Patton et al., 2009), and efforts are made to prevent suicide in young people.

Self-harm is one of the most important risk factors for suicide, and the risk of suicide seem to be higher after self-harm in older age compared to younger age (Haukka et al., 2008, Cooper et al., 2005, Hawton et al., 2015, Carroll, Metcalfe & Gunnell, 2014). Similar findings were seen in Study 1, where the risks of suicide after self-harm in different age groups were investigated. Self-harm among 10-19 year-olds was significantly lower than in all other age groups.

Suicidal intent may be higher among older self-harm patients (Hawton et al., 2008, Freedenthal, 2008), which could partly explain the differences in the suicide/self-harm ratio in younger and older people. It is possible that motives behind an act of self-harm are more multifaceted at a young age compared to an older. Apart from the intent to die, various motives behind youth self-harm have been reported. Relief from a terrible state of mind, self-punishment, the expression of desperation etc. were reported by adolescents in a

questionnaire used on an international community sample (Madge et al., 2008). It may well be of importance to explore the reasons for self-harm for clinicians to be able to prevent further acts. The potential complexity of reasons, where a wish to die might be included together with other reasons, should be kept in mind. Also, the proposed functions of self-harm without suicidal intent e.g. an affect-regulatory mechanism, or a self-punishing function (Klonsky, 2007) might be important to remember in preventive strategies.

There are indications that self-harm events among older people are more often made with a higher degree of planning and premeditation than among the young (Rimkeviciene et al., 2015). Some previous studies have shown that more planned attempts more often result in severe injuries (Baca-Garcia et al., 2005, Baca-Garcia et al., 2001). In Study 5, the proportion of suicide attempts with a low degree of planning, impulsive suicide attempts (ISAs), was higher among the young than other adults. However, the medical severity was at least as high among impulsive suicide attempts than more planned attempts in the young, and also the risk of fatal and non-fatal repetition in the young was equally high after ISA and more planned attempts. These findings do not support potential theories regarding the importance of planning in explaining the differences in the ratio of suicide to self-harm in older and young people.

Even though the risk of suicide after self-harm seems to be lower among young people compared to older it is still highly elevated compared to the general population. In Study 3, the risk of suicide was sixteen-fold after self-harm in young adulthood, after adjustment for, inter alia, the presence of a mental disorder. Suicides have been reported to be 1.7% in 20-year follow-up of 15-24 year-old self-harm patients (Hawton et al., 2007). Also, 0.9% and 2.7%, respectively, died from suicide in single and repeated self-harming 10-24 year-olds over long-term follow-up (Zahl et al., 2004), and a suicide rate of 89.6 per 100 000 person-years was reported among adolescent self-poisoners (Finkelstein et al., 2015). In our cohort, the risk ratio of suicide between those who had self-harmed compared to those who had not was adjusted for a mental disorder. This can be understood as a risk-increasing effect of self-harm, above the suicide risk of a mental disorder. The risk of suicide in common mental disorders is familiar to psychiatrists; in a meta-analysis, risk elevation was almost twenty-fold for patients suffering from depression, seventeen-fold in bipolar patients, 45-fold in people with borderline personality disorder, and thirteen-fold in schizophrenics (Chesney, Goodwin & Fazel, 2014). Hence, the risk of suicide after self-harm among young people, irrespective of the presence or absence of a mental disorder, is well in line with the well-known risk of suicide in people with common mental disorders.

5.4 IDENTIFICATION OF THOSE AT RISK OF SUICIDE AMONG SELF-HARM PATIENTS

The risk of future self-harm events, fatal and non-fatal, is clearly elevated after a self-harm event in youths. The repetition rate has been reported to be 19% within one year among 10-29 year-olds (Bennardi et al., 2016), and 27% among 10-18 year-olds upon presentation to a hospital after self-harm (Hawton et al., 2012a). The high repetition rates, and suicide rates, as

stated in the previous paragraph, highlight the importance of thorough risk assessment of young individuals after self-harm. An important challenge for clinicians is to identify those most at risk for suicide after self-harm.

High suicidal intent, previous self-harm, male gender, and current or previous psychiatric treatment (women) can indicate an elevated risk of suicide after self-harm at a young age (Hawton et al., 2007). Among individuals under age 18, male gender, using cutting as a method, and prior psychiatric treatment were found to be associated with a higher risk (Hawton et al., 2012a). In adolescents with a first episode of self-poisoning, the risk of a later suicide was elevated by repeated self-poisoning, male gender, and a psychiatrist's visit during the past year (Finkelstein et al., 2015). Repetition of self-harm was also an evident risk factor in a British cohort, where the relative risk of suicide among repeaters vs on-repeaters of self-harm was 3.1 (2.0-4.8) in 10-24 years olds (Zahl et al., 2004). The results of that study indicate that repetition might have a larger-risk increasing effect among younger people than older. The risk of repetition among young people has been studied, and previous self-harm elevates the risk of further events (Bennardi et al., 2016). Also, self-cutting compared to poisoning increases the risk among women, and it is even higher among 15-19 year-olds than 20-24 year-olds.

In our study of the risks of suicide and long-term mental illness (Study 3), there was a distinct risk-increasing effect on suicide among people with a diagnosed mental disorder at the time of the self-harm event. Particularly, a psychotic disorder elevated the risk substantially. It has previously been shown that previous psychiatric contact or a visit to a psychiatrist during the past year increases the risk of suicide; that is, there is probably a mental disorder (Hawton et al., 2007, Hawton et al., 2012a, Finkelstein et al., 2015). A suicide attempt in patients with schizophrenia has previously been shown to be associated with a particularly high risk of suicide, in the context of suicide attempts in people with other mental disorders (Tidemalm, Langstrom, Lichtenstein & Runeson, 2008). The association between mental disorders and self-harm and the risk increasing effect of certain mental disorders, are further discussed in section 5.5 in this thesis.

When seeking medical care after an event of self-harm, a psychosocial assessment never occurs in some instances. The probability of a psychosocial assessment is lower among young patients than older patients (Kapur et al., 2008). One of the aims of Study 4 was to explore factors that may be easily assessed even at non-psychiatric facilities, and may indicate a need for a more thorough psychiatric assessment. Our finding that a violent method leading to hospitalisation among adolescents and young adult women elevated the risk of a later suicide is similar to findings in age-mixed populations of self-harm patients (Bergen et al., 2012, Miller et al., 2013, Runeson et al., 2010).

The significance of the use of a violent method (including hanging, strangulation, suffocation, gassing, drowning, and jumping from a height) is a subject of interest. It may imply higher suicidal intent at the self-harm event, and therefore more often result in a new, fatal, self-harm event. Highly lethal methods, such as a gunshot, hanging and asphyxiation, were related

to higher suicidal intent in a British cohort (Haw, Casey, Holmes & Hawton, 2015). There are findings suggesting that violent suicide attempters are more associated with suicide completers than other suicide attempters. Similarities were, for example, a higher likelihood of a family history of suicide, being of male gender, and showing greater medical lethality in previous attempts (Giner et al., 2014). When biomarkers in CSF among suicide attempters were studied, there were indications that violent suicide attempters differed from non-violent suicide attempters with regard to levels of monoamine metabolites 5-HIAA and HVA, the pro-inflammatory cytokine IL-6, and the HPA-axis associated neuropeptide orexin. The same findings as in violent suicide attempters applied to suicide completers (Lindqvist et al., 2011).

It is possible that some individuals are more inclined to use violent methods than others, independent of differences in intent to die. Associations between higher levels of aggression/impulsivity and the use of a violent method have been seen among suicide completers (Dumais et al., 2005). In relation to the association between impulsivity and use of violent methods, there are findings suggesting that violent methods are more often used at impulsive suicide attempts (Conner et al., 2005). In our clinical cohort (Study 5), however, there were no differences in the use of violent methods between those who made an impulsive suicide attempt and those who made a more planned attempt.

Severe cutting leading to hospitalisation among young adult women increased the risk of suicide compared to poisoning (Study 4). In Study 4 this method was separated from other self-injuries, partly due to the fact that among young people cutting is a common method used at self-harm (Madge et al., 2008) and specific attention should probably be paid to young people whom self-cut. Cutting as a method seemingly includes a variety of injuries with a range of medical consequences, and probably represents both high and low suicidal intent. Cutting in arms and wrist is associated with a lower risk of suicide than cutting in other locations on the body (Carroll et al., 2016). Also, the need for more extensive medical treatment after cutting is an indicator of higher lethality upon repetition of self-harm (Larkin, Corcoran, Perry & Arensman, 2014). There are indications that self-cutting is regarded as less serious by clinicians; those who use self-cutting are less likely to receive a psychosocial assessment at self-harm (Kapur et al., 2008). However, it has previously been shown that cutting as a method among adolescents can imply an increased risk of later suicide (Hawton et al., 2012a). The findings of our study that cutting requiring inpatient care among young adult women implies an elevated suicide risk compared to poisoning, but that cutting treated in outpatient settings did not differ from poisoning in this regard, may add information about heterogeneity with regard to cutting as a method.

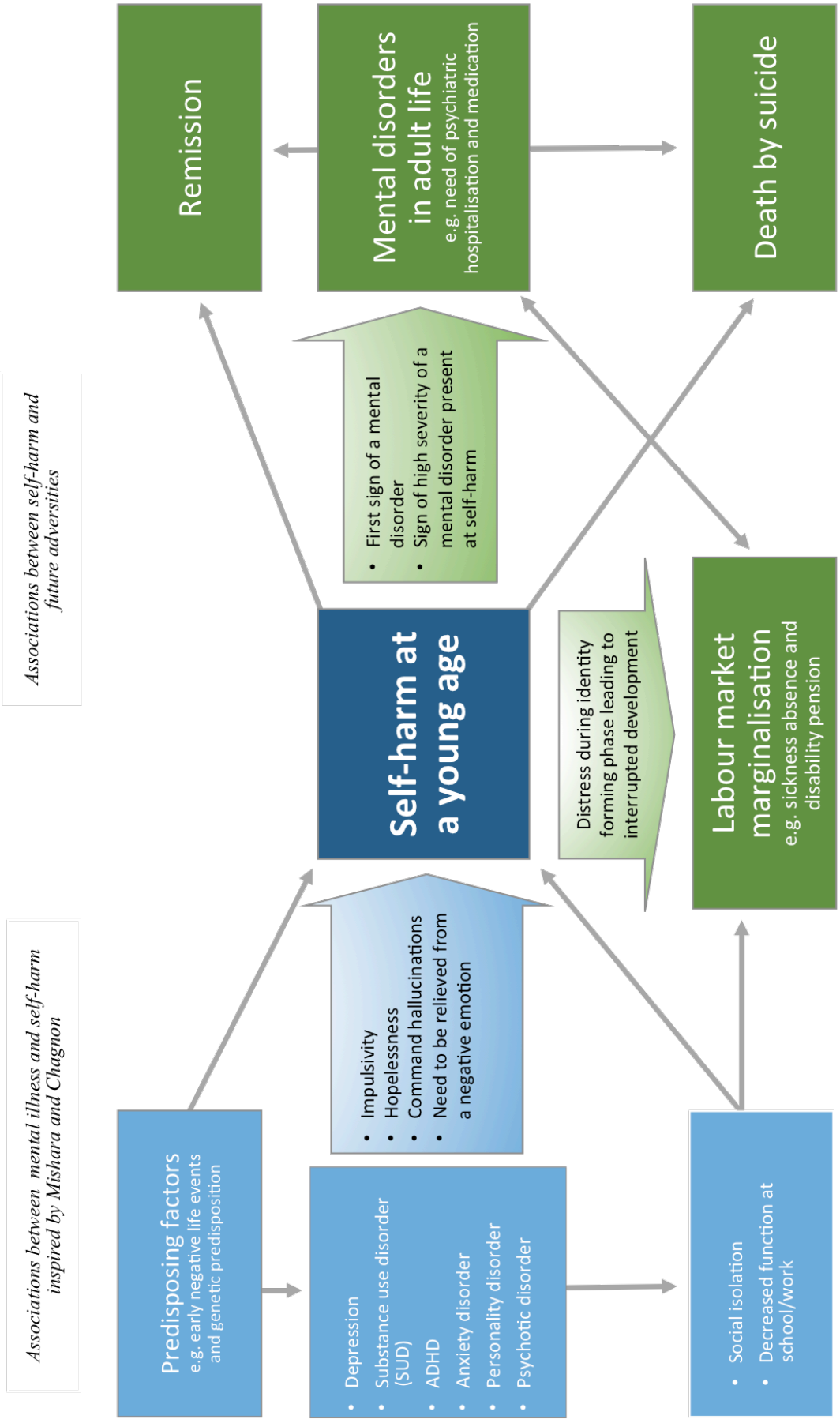

Figure 4, **Associations between mental illness and self-harm and associations between self-harm and possible outcomes.**

5.5 MENTAL ILLNESS AND SELF-HARM

The correlation between self-harm and mental illness is of great importance even though mental illness does not alone explain the occurrence of self-harm. The association between mental illness and suicide has previously been explored. The vast majority of young suicide victims suffer from a mental disorder at the time of suicide (Hawton et al., 2012b). Mishara and Chagnon discuss six models regarding how to understand the associations between mental disorders and suicide (Mishara B L, 2016). Figure 3 is inspired by of some of this reasoning and shows an interpretation of the association between mental disorders and self-harm/ suicidal behaviour. One model described by Mishara and Chagnon concerns the shared etiology between mental disorders and suicide, and point to the overlap between factors that predict suicide and factors that predict mental disorders. A couple of examples are biogenetic vulnerability, e.g. a genetic predisposition for depression and impulsivity, and early negative life events. Another model is that suicide is the direct consequence of mental disorder, e.g. of imperative hallucinations in psychosis that act as a prompt to suicide, or the conception during a depression that you are a burden to others, etc. Another model discussed by Mishara and Chagnon is that the risk of suicide may be elevated due to the effect of the consequences of leading a life with a mental disorder. A mental disorder increases the risk of social isolation, unemployment etc which in turn are known risk factors for suicide. In total, six models are proposed as being explanations for the association between mental disorder and suicide.

Even though the risk of suicidal behaviour in mental disorders is elevated, a large proportion of people with mental disorders never experience suicidal thoughts and behaviour. The causal relationships and the etiology behind suicidal thoughts and behaviour are evidently multifaceted. Risk factors and models for understanding suicidal and non-suicidal self-injuries are discussed in the Introduction. Attempts to explore neurobiological processes potentially involved in suicidal behaviour have also been made, and one focus has been on the serotonergic system (van Heeringen & Mann, 2014). Alterations in the serotonergic system have been identified in post-mortem studies and in PET studies, among individuals with suicidal behaviours compared to those with a mental disorder but no history of suicidal behaviour. Alterations in the function of the hypothalamic-pituitary-adrenal axis have also been suggested to be of relevance. In neuroimaging studies, structural and functional changes in areas suggested to be related to mood regulation, cognitive control and decision-making have been seen among those with suicidal behaviours (van Heeringen et al., 2014). The role of inflammation in suicidal behaviour and in mental disorders has been discussed in recent years. Differences in cytokine levels between depressed patients with or without suicidal behaviours have been noted (Serafini et al., 2013).

Also, the connection to future consequences of self-harm has been incorporated into *Figure 4*, according to the findings of this thesis. The results of Study 3 indicate that there is an association between self-harm in young adulthood and mental illness in adult life, which is above the correlation between a mental disorder at the time of self-harm and future mental illness. The effect of self-harm on future mental illness is not a causal relationship in the

sense that the mental disorder is the consequence of the tissue damage of the self-harm or the like. Self-harm can be interpreted as an indicator of higher severity of the mental disorder present at the time, or as a first sign of a mental disorder not yet diagnosed. The interpretation of self-harm as a signal of future mental illness is also discussed in other long-term follow-up studies (Goldman-Mellor et al., 2014). By addressing the mental disorders relevant to self-harm behaviours present at the time of self-harm or in adult life after self-harm, the relationship might be clearer.

5.5.1 Depression and anxiety disorders

Depression is common among young people who self-harm, and affective and anxiety disorders were diagnosed in 18.1% of the young self-harm patients in our cohort (Study 3). In the long-term follow-up of self-harm patients in Study 3, antidepressants were prescribed to 38.9% of those who had self-harmed in young adulthood. Depression has previously been shown to be important, and perhaps the most important mental disorder, in youth suicidal behaviour (Fergusson et al., 2000, Gould et al., 1998, Shaffer et al., 1996, Fleischmann, Bertolote, Belfer & Beautrais, 2005, Beautrais, 2000), especially in women. In a review of mental disorders among young suicide victims, 42.1% were found to have suffered from a mood disorder, which thereby constitutes the most common mental disorder in suicide victims. However, the authors compare the significance of mood disorders among older suicide victims and state that, since substance use related diagnoses are almost as common as mood disorders in young suicides, mood disorders may be less important among young than older suicide victims (Fleischmann et al., 2005). When risk factors for self-harm with suicidal intent are compared to risk factors for non-suicidal self-harm, both depression and anxiety disorders are more strongly associated with suicidal self-harm than non-suicidal self-harm (Mars et al., 2014a). In studies of non-suicidal self-harm, depression is also seen among people who self-harm without a suicidal intent (Klonsky, Oltmanns & Turkheimer, 2003). The authors conclude, however, that anxiety may play a larger part in non-suicidal self-injury, and that the effect of depression on non-suicidal self-injury is substantially less when anxiety is adjusted for.

Several aspects of depression may affect the risk of self-harm and suicidal behaviour. Among patients with depression, insomnia, weight or appetite loss, feelings of worthlessness or inappropriate guilt, and also reoccurring thoughts of death were found to be associated with suicidal behaviour (McGirr et al., 2007). Hopelessness is a common feature of depression and an important factor in youth self-harm and suicidal behaviour (Thompson et al., 2005, Mazza et al., 1998).

In conclusion, in most studies, depression and anxiety are common in young self-harm patients; also, in our cohort, they apparently played an important role in the initiation of self-harm. Depression and anxiety tend to re-occur during the lifetime and, based on the evidence from Study 3, self-harm in young adulthood indicates an elevated risk of (re-)occurring or continuous depression or anxiety.

5.5.2 Substance use

In Study 3, substance use was found to be common among people who self-harmed; among young men, 19.9% had a substance use related diagnosis at the time of self-harm. High proportions of substance users have also been reported in other studies of self-harm and suicidal behaviour in youth (Fergusson et al., 2000, Mars et al., 2014a, Beautrais, 2000, Hawton et al., 2002, Moran et al., 2015). Moran and colleagues discuss possible mechanisms for the co-occurrence of substance use and self-harm among adolescents, e.g. common risk factors such as impulsivity, family conflicts, and the social transmission of behaviour through peers. Both behaviours can also be used as a response to negative affect. Further, the endogenous opioid system is implicated in addiction, and possibly activated in self-harm (Moran et al., 2015). Substance use can also contribute to self-harm and suicidal behaviour through high comorbidity with mental disorders in youths, especially externalising disorders, e.g. ADHD and conduct disorders, but also internalising disorders, such as depression and anxiety (Couwenbergh et al., 2006). Substance use has been shown to differentiate suicide attempters from suicide ideators (Gould et al., 1998). In O´Connor's model of suicidal behaviour, the transition from the motivational phase of the suicidal process to the volitional phase is mediated by impulsivity, inter alia (*Figure* 3). Substance users may have a higher degree of impulsivity as a personality trait, or substance use itself may increase impulsive behaviour (Dougherty et al., 2008). Impulsivity may contribute to the effect of substance use on suicidal behaviour. Self-harm in adolescence also increases the risk of multiple dependence syndrome in adulthood (Moran et al., 2015). The risk of a need for medication due to substance use disorders was highly elevated in long-term follow-up of self-harm patients in Study 3, even after adjustment for a mental disorder at the time of self-harm.

In summary, substance use seems to be associated with youth self-harm, at the time of self-harm and in future life. It might be speculated that features such as high levels of impulsivity, difficulties with affect regulation, inclination to self-destructive behaviours, high occurrence of depression, anxiety, ADHD and conduct disorder are expressed through elevated levels of both substance use and self-harm.

5.5.3 Psychotic disorders

In a review of risk factors for suicidal behaviour in young people, Beautrais concluded that patients with psychotic disorders represent only a minority among suicide victims and suicide attempters, probably due to the low rates of psychotic disorders in the population. However, the risk of suicide among patients with schizophrenia is high (Beautrais, 2000). In a meta-analysis of studies of suicide mortality in schizophrenia patients, the lifetime suicide prevalence was estimated to be 5.6%, based on first-onset of schizophrenia (Palmer, Pankratz & Bostwick, 2005). In Study 3 we were able to conclude that, even though psychotic disorders were not common among young people who had self-harmed, their presence clearly elevated the risk of suicide, and more so than any of the other mental disorders diagnosed before or at the time of self-harm, with a Hazard Ratio of 7.0 (5.0–9.8). The risk-increasing effect on suicide of a psychotic disorder at the time of self-harm have been seen in previously

studied age-mixed populations with adjusted HR for schizophrenia of 4.1 (3.5–4.8) in men, and 3.5 (2.8-4.4) in women (Tidemalm et al., 2008).

5.5.4 ADHD

We were able to study data on ADHD medication in the long-term follow-up of young people who had self-harmed in Study 3. Among them, 3.9% were prescribed ADHD medication at long-term follow-up, which corresponded to a higher risk of having ADHD medication among self-harmers compared to non-self-harmers; the HR was 5.8 (4.9–6.8). ADHD would be present at the time of young adulthood, and hence at the time of the self-harm events in Study 3. The elevated risks of self-harm and suicidal behaviour among those with ADHD have been explored; in a review, it is stated that the risk of suicidal behaviour is elevated in ADHD, but mainly among people with co-occurring psychiatric conditions, e.g. conduct and emotional problems in males, and depression in females (Nigg, 2013).

5.5.5 Personality disorders

Personality syndromes and certain personality aspects have been explored in studies of self-harm. Perfectionism (O'Connor, 2007), impulsivity (O'Connor et al., 2012), and social problem-solving deficits (Speckens & Hawton, 2005) have been associated with self-harm, as too have personality syndromes, such as anxiety, and anankastic and paranoid as well as emotional unstable personality disorder (Haw, Hawton, Houston & Townsend, 2001), and also borderline, schizotypal, dependent and avoidant personality disorders (Klonsky et al., 2003), etc. Also, personality disorders clearly elevate the risk of suicide; in a recent Swedish register-based study of 25 217 individuals with a personality disorder, the risk of suicide was most evident among women, especially those with co-morbidity with an Axel-1 disorder (Bjorkenstam et al., 2016). The SMR for women with co-morbidity with a mental disorder was 33.6. However relevant, the role of personality disorders in self-harm and suicide has not been within the scope of any of the studies included in this thesis.

5.6 SOCIAL MARGINALISATION IN ADULT LIFE AFTER YOUTH SELF-HARM

In order to map adult life after suicide attempt at a young age, it is important to address not only morbidity and mortality but also social factors. In Study 2 we were able to show that the risk of labour market marginalisation is elevated in long-term follow-up after suicide attempt at a young age, especially marginalisation due to a medical incapacity, i.e. sickness absence and disability pension. The effect of suicide attempt was evident among people with and those without a previous psychiatric inpatient care on the outcomes due to medical incapacity. On the unemployment outcome, there was no effect of a suicide attempt among those with previous psychiatric inpatient care.

Negative social outcomes after self-harm at a young age have previously been explored, and there is a greater likelihood of being in need of social welfare, and also having a disrupted education (Harrington et al., 2006, Goldman-Mellor et al., 2014). The importance of the life phase between late teens and the early twenties (especially 18-25 years of age) for identity

exploration is sometimes stressed, e.g. in Arnett's article on emerging adulthood (Arnett, 2000). Experiences of work and education are important in preparation for adulthood directions in these areas. A possibly distressing time period, represented by a suicide attempt or an event of self-harm at this life phase, may perhaps disturb development towards becoming an independent adult, including involvement in the labour market.

It is also possible that labour market marginalisation, as shown in Study 3, represents further mental illness in adult life. The effect of a suicide attempt was more apparent on the labour market outcomes based on medical incapacity, that is on sickness absence and disability pension, rather than on unemployment. The effect of suicide attempt was present with and without previous psychiatric inpatient care, and there was also a dose-response effect of the number of suicide attempts on the risk of these outcomes. The same associations were not seen regarding the outcome of unemployment. Either way, this can become a vicious circle, where disturbance in introduction to the labour market further impairs the health and vice-versa.

5.7 IMPULSIVE SUICIDE ATTEMPTS

Impulsivity is an important aspect of self-harm and suicidal behaviour (Auerbach et al., 2017, Evans, Platts & Liebenau, 1996, Gvion et al., 2011). As mentioned above, in O´Connor's model of suicidal behaviour, the transition from the motivational phase of the suicidal process to the volitional phase is mediated, inter alia, by impulsivity (O'Connor, 2011). The importance of impulsivity in suicidal behaviour has been seen in a study of adolescents (O'Connor et al., 2012). It is possible that impulsivity is even more important as a feature of youth self-harm and suicidal behaviour; it seems to have more impact on youth self-harm and suicidal behaviour than it does on other adults (McGirr et al., 2008). Impulsivity and risk-taking behaviours occur more often in adolescence, and the capacity for cognitive control and self-regulation increases in adult life (Casey, Jones & Hare, 2008). Accordingly, the significance of impulsive suicide attempts (ISA) in young adults was explored in Study 5. In this clinical cohort we were able to ascertain that ISAs were more common in youth than in older people, and associated with having a substance use disorder. Another of our aims was to discern whether the ISAs resulted in less medically severe events than more planned attempts, which has previously been seen (Baca-Garcia et al., 2005). However, from our data, it was evident that ISAs were at least as medically severe as more planned attempts, and represented equally high risks of further fatal or non-fatal attempts.

In conclusion, the importance of the prevention of impulsive suicide attempts is highlighted by these results. Perhaps, treatment for disorders especially associated with impulsivity (e.g. substance use and ADHD) can be of use. Also, providing young individuals at risk with preventive strategies to handle impulsive suicidal thoughts when they occur, e.g. in an action plan including contact information to health care. Further, impulsive attempts might more often be implemented by easily accessible means (Brown et al., 1991, Conner et al., 2005); hence, restriction on available means of suicide may help to prevent suicidal behaviour where there is only a short time for intervention.

5.8 METHODOLOGICAL CONSIDERATIONS

5.8.1 National Registers

Swedish national registers offer a good opportunity to study rare events, such as suicide, using large cohorts. It is also possible to study associations of exposures with a large time-interval between exposure and outcome. The coverage of the registers is high overall, although some exceptions should be noted. The National Patient Register (NPR) has almost complete coverage of inpatient care since 1987, but outpatient events are only included in the register from 2001, with coverage of around 80%, and with reports on visits from private caregivers and psychiatric facilities largely lacking (Forsberg, 2009). In Study 3, we included data on previous mental disorders from inpatient and specialised outpatient care before their inclusion 1990-2003. Due to the lack of availability of outpatient visits in the NPR, these data consist mainly of diagnoses from inpatient care. It is important to remember that the absence of a mental disorder in the registers does not mean that the individual is healthy. A large proportion of mental disorders are not treated in inpatient care or specialised outpatient care. Also, in Study 4, the self-harm events registered in outpatient care may possibly lack events not included in the register, but we have reasons to believe that inclusion is dependent on the exposure variable, that is the method used at self-harm. Further, the NPR provides data on psychiatric diagnoses according to the ICD system. The positive predictive value of in-patient diagnoses set in the NPR is 85-95% (Ludvigsson et al., 2011), which is high but not 100%. This should be remembered, especially when interpreting the effects of different mental disorders on the suicide risk at self-harm in Study 3. Also, register data lack in-depth information on potentially relevant factors, such as the degree of suicidal intent at self-harm.

The Educational Register lacks data on education completed outside Sweden. Together with a lack of information on parents in the Multi-Generation Register, this results in individuals having missing data on the variable “Educational level of parent”, used in studies 3 and 4. There are reasons to believe that there is an over-representation of individuals born outside Sweden in that category, and due to the risk of excluding these individuals we included them in the regressions, using “missing data” as a separate category. Regarding the Cause of Death register, in the category of suicide in studies 1, 3 and 4, we included deaths with undetermined causes (Y10-34) in order not to underestimate the numbers of suicides. There are arguments that this might instead overestimate the numbers of suicides, since it has proven difficult to find evidence that the majority of deaths with undetermined causes are in fact suicides (Tollefsen et al., 2015). However, the risk of underestimating the numbers of suicides has been repeatedly demonstrated, and has large consequences for the estimation of severity and risks in suicide research (Neeleman et al., 1997, Linsley et al., 2001).

5.8.2 Considerations regarding observational studies

5.8.2.1 Information bias (misclassification)

Misclassification occurs when aspects of the information collection, result in incorrectly categorised exposure or outcome. The consequences of misclassification are varied.

Misclassification of exposure can be non-differential when the misclassification does not depend on the status of the outcome. Similarly, misclassification of outcome is non-differential if it does not depend on the exposure. This tends to bias estimates towards the null. For example, in Study 3 we collected information on exposure to self-harm from the NPR only. This meant that, among both exposed and non-exposed, there are individuals who are exposed to self-harm but have not come to the attention of the health care system. Some individuals in the unexposed category are therefore misclassified, and probably elevate the risk of the outcome (of suicide, for example) in the unexposed category.

There are also misclassifications of exposure that depend on the outcome and misclassification of outcome where that depends on the exposure (differential misclassification). Such misclassification may be present, for example, in Study 3, where the possibility of a future mental illness (outcome) can be affected by the presence of the self-harm event (exposure). The self-harm event might shed light on the need for a thorough investigation of a mental disorder (Goldman-Mellor et al., 2014). There is a possibility that among people not exposed for self-harm, there are individuals with equally severe mental disorders who have not come to the attention of health care, and therefore the disorders are not diagnosed. Such misclassification would bias the estimate of the relative risk of future mental disorder upwards, and should be kept in mind when interpreting the results.

In observational studies, there is a risk of recall bias where people with a disease/outcome report the prevalence of an exposure differently from those unexposed. In Study 5, where patients were asked about their mental state, social problems and suicidal thoughts and behaviour preceding the self-harm event, there was a risk of recall bias. The presence of a suicide attempt would probably affect the recollection of preceding events. However, we do not have any reason to believe that people with impulsive suicide attempts differ from those with non-impulsive attempts in the recollection of preceding events. In register-based studies there is no risk of recall bias.

5.8.2.2 Confounding

An important concern regarding observational studies is, among others, the risk of confounding effects. Confounding in observational studies may be that the association of an exposure variable with an outcome is actually, partly or fully, due to the effect of some other factor, associated with both the exposure and the outcome. In interventional studies, the study population is often randomised to either treatment or placebo groups (exposure/non-exposure), and therefore other factors that might affect the outcome should be equally distributed. In observational studies, known confounders can be dealt with by matching, by stratification, or by being included in a regression model. When adjusted for in a regression model, the effect of the exposure of interest can be evaluated, independently of the confounder. In all of the studies in this thesis, presumed confounders were adjusted for. For example, the confounding effect of previous self-harm was considered when studying the effect of different methods used at self-harm on the risk of suicide (Study 4).

However, in most studies, there may be residual confounders that are not adjusted for. Residual confounders can depend on lack of information on possible confounders in the data. In register-based studies, we lack important information on the individuals that might be associated with both the exposure and the outcome. For example, a possible residual confounder may be a traumatic life event that affects the probability of both self-harm and later suicide in Study 3. This is not captured in the registers, and is therefore not in our study design. Residual confounding can also be caused by lack of knowledge of possible associations or causalities. It is possible that there are, for example, unknown genetic factors that would explain parts of the variability in self-harm and suicide. The difficulty in trying to assess causality with this study design should be kept in mind. When conclusions are drawn regarding the associations between self-harm and outcomes such as suicide, causality is difficult to address, partly due to the obvious possibility that other factors, known or unknown, are the cause of both behaviours. In the included studies, self-harm should be considered as an indicator, not a cause, of the risk of an adverse outcome and a reminder of the need for assessment and support.

The concept of causality is difficult to grasp in the included studies. For example, in Study 3, regarding the outcomes of future mental illness, we cannot assume that mental disorder in adult life is the effect of an actual self-harm event, i.e. the result of actual tissue damage. Rather, the self-harm event could be a signal of the early stage of a mental disorder, a mental disorder not yet diagnosed, or the higher severity of a mental disorder present at the time (Goldman-Mellor et al., 2014). Also, in a cohort study, when the association between the exposure and the outcome is addressed, it is necessary for the cohort to be free of the outcome at the time of exposure. In Study 3, however, we included people with a mental disorder at the time of self-harm, even though one of the outcomes was future mental illness. This was done to avoid the risk of excluding people with possibly a worse prognosis. Instead, adjustment for a mental disorder at the time of self-harm was made. Also, we included an interaction term to explore the link between mental disorder and self-harm. The interaction was significant, and survival curves were presented of the effects of self-harm on the outcomes, with and without a present mental disorder.

5.8.3 Considerations regarding study populations and generalizability (external validity)

Even though suicide is a devastating outcome and therefore important to study, it is still a rare event; it is therefore difficult to study, and to establish results with certainty. The large cohorts in this thesis make for more confident interpretations, but the results are still unreliable, especially for certain groups. For example, the results that concern adolescents and the methods of self-harm as risk factors for suicide are based on small numbers of suicides and therefore show wide confidence intervals (Study 4).

More importantly, the study populations in the cohorts derive from health care settings. The events of self-harm that were included in studies 1-4 were only those that are recorded in health care registers. They may represent self-harm events that are severe enough to warrant

specialised medical care, or have a co-occurring mental disorder severe enough to warrant inpatient care. Most young people who self-harm never seek medical attention (Madge et al., 2008), and the results from the included studies cannot be generalised to young people who do not come to the attention of health care, or to those treated outside specialised health care. This selection bias should be kept in mind when interpreting the results. It is reasonable to assume that the events that lead to specialized medical attention/hospitalization carry a higher risk of adverse outcomes, such as suicide, than events of less medical severity that are therefore not treated in specialized medical facilities. However, for health care personnel, the results in the included studies could be of use.

In Study 5 we included patients presented for psychiatric evaluation after self-harm, either at a medical care facility, in a psychiatric emergency unit, or for psychiatric in-patient care. The cohort probably consists of individuals with a medically severe event of self-harm, or with a mental disorder that is in need of specialised psychiatric care, or where there are reasons to suspect an elevated risk of suicide. Also there is selection regarding which patients are subject to psychiatric evaluation (Kapur et al., 2008). Further, to be included in Study 5, the patient had to be able to participate in an hour and a half interview in Swedish; hence, those who suffered from pronounced anxiety, delusions, or were in a manic state, or not Swedish speaking were excluded. Therefore, certain patient categories and some cultural groups might not be represented in the study population.

5.9 ETHICAL CONSIDERATIONS

In research based on patient data, whether it comprises collected data or data derived from national registers, the researcher must treat the data with the utmost respect. In register-based studies, the data are collected from the register holder and are de-identified before being made available to the researcher. The personal identification number is replaced with a code, and information on date of birth is replaced by month and year of birth. There is no possibility for the researcher to identify the individuals in a study, which maintains the integrity of the individuals but also makes it impossible to request consent from them. Under current Swedish law, this is not necessary, and the potential harm to the included individuals would be low. Even so, one must keep in mind that the data are based on individuals, and, here, their potentially traumatic experiences of self-harm and suicidal behaviours. Therefore, for example, in communications of the results of the research within and outside the research community, the possibility of addressing individuals included in the study should be kept in mind.

The data in Study 5 derive from a clinical cohort of participants who had recently had a self-harm event. Information about the study was presented to them, in written as well as in oral form, and written consent was collected. They were informed that they could withdraw their acceptance of participation at any time, without any questions being asked. The interviewers were all specialised nurses, psychologists and psychiatrists with long experience of helping patients at difficult times. The perceptions of the interviewers were that many participants felt relieved to talk about their experiences. These perceptions, however, have not been evaluated

and can obviously not be said to apply to every participant. It must be remembered that the people taking part were asked about their participation in a vulnerable situation, which must be treated with delicacy. All in all, their contribution to the knowledge in the field should not be underestimated.

Also, self-harm and suicide are subjects of a sensitive nature, perhaps especially when they concern young and vulnerable individuals, and we can all feel strongly about them. For those us who work within mental health care, discussions are important in order to deepen our knowledge of self-harm and suicide. However, the sensitive character of the subjects should be kept in mind when communicating the research to people outside the health care system.

5.10 FUTURE DIRECTIONS

The elevated risk of suicide after self-harm was confirmed in this thesis and several factors that might indicate a particularly elevated risk were identified. The risk of future mental illness and labour market marginalisation was also addressed. This can add information in the challenges of assessing young individuals after self-harm. However, self-harm and suicidal behaviour are heterogeneous phenomena that occur in heterogeneous groups. In future studies, it would be of interest to study these phenomena in more homogenous groups, based on similarities in mental illness or personality characteristics. Self-harm in young people with specific mental disorders would be of interest to characterise. For example, in young individuals with ADHD it would be interesting to explore dynamic factors important in elevating the risk of self-harm and suicide. If e.g. high levels of impulsivity or difficulties in affect regulation were identified, as most important, targeted interventions that would influence these factors would be of further interest to study.

Some studies of biomarkers for suicidal behaviour and for subtypes of self-harm and suicidal patients have been performed. The neurobiology of self-harm and suicidal behaviour would be of interest to explore further, e.g. genetic associations perhaps with the support of the large national registers and quality register that are available for research in Sweden. Studies on more homogenous groups, complemented by more studies on neurobiological factors or pathways and genetic predispositions, would add important knowledge to the studies discussed in this thesis that highlight the associations of mental disorders, personality factors, life adversity etcetera in self-harm and suicide research.

6 SVENSK SAMMANFATTNING

Syfte

Självskador är relativt vanligt förekommande hos unga och ett angeläget ämne för forskning och klinisk verksamhet. Syftet med avhandlingen var att studera betydelsen av självskada hos unga människor och belysa dess effekter på lång och kort sikt. Huvudsaklig fokus var risk för självmord efter självskada men också prognos vad gäller framtida psykiatrisk sjuklighet liksom möjlighet att etablera sig på arbetsmarknaden. Vidare avsågs att försöka finna faktorer som kan signalera en negativ prognos efter självskada, för att lättare identifiera individer med exempelvis särskilt ökad risk för självmord vid självskada.

Metod

I fyra av de inkluderade studierna användes svenska nationella register. Självskador i ung ålder identifierades genom det nationella patientregistret och information om bland annat metod vid självskadan, psykiatriska diagnoser, självmord i familjen och föräldrars socioekonomiska status insamlades via länkning till andra nationella register. All data avidentifierades innan det kunde användas i forskningssyfte. Information om senare arbetslöshet, sjukskrivning, psykiatrisk vård och medicinering, liksom självmord inkluderades.

Den femte studien baserades på data från en multicenterstudie som har genomförts på tre psykiatriska kliniker i Sverige. Personer som hade genomfört en självskada och därefter erhållit en psykiatrisk bedömning tillfrågades om att medverka i studien. En längre intervju tillsammans med diverse skattningsskalor låg till grund för information om psykiatriska diagnoser, avsikt med självskadan liksom övriga samtidiga svårigheter. En uppföljning via medicinska journaler genomfördes sedan.

För att kunna mäta risk för negativa konsekvenser av självskada användes statistiska metoder såsom logistiska regressioner och överlevnadsanalyser. Skillnader i förekomst av samtidiga och framtida faktorer av intresse beräknades också.

Resultat

En tydligt förhöjd risk för senare självmord efter självskada kunde ses (studie 1 och 3). Risken för självmord föreföll vara lägre efter en självskada under tonåren jämfört med en självskada i vuxen ålder men klart förhöjd jämfört med risken i den allmänna befolkningen (studie 1). Faktorer som kan indikera en särskilt förhöjd risk var bland annat en samtidig psykiatrisk sjukdom, framför allt en psykossjukdom, förekomst av självmord i familjen och tidigare självskada (studie 1 och 3). Efter en självskada i tonåren samt i ung vuxen ålder (som kvinna) var användandet av en våldsam metod (ex hängningsförsök eller hopp från hög höjd) en signal för förhöjd risk för självmord (studie 4). Hos unga vuxna kvinnor kunde skärskador som krävt slutenvård också innebära en förhöjd risk, jämfört med förgiftning som metod. Självmordsförsök i ung vuxen ålder var oftare impulsiva än de försök som genomfördes av övriga vuxna. De impulsiva handlingarna resulterade minst lika ofta i medicinskt allvarliga

skador som de mer planerade försöken och innebar en lika hög risk för ett nytt försök eller ett självmord inom sex månader.

Hälften av de unga vuxna som hade slutenvårdats efter en självskada behandlades mer än fem år efter händelsen med någon form av medicinering mot psykiatriska tillstånd (studie 3). De vanligaste medicinerna var antidepressiva, lugnande och sömnmediciner. En femtedel behövde psykiatrisk slutenvård vid något tillfälle, mer än fem år efter skadan. Risken för arbetslöshet, långtidssjukskrivning och sjukpension var klart förhöjd efter en självskada i ung ålder (studie 2). Tydligast var risken för sjukskrivning och förtidspension.

Slutsatser

Självskada i ung ålder är förknippat med en tydligt förhöjd risk för senare självmord. Vid riskbedömning i samband med en självskada kan förekomst av samtidiga psykiatriska sjukdomar, framför allt en psykossjukdom, och vissa självskademetoder, såsom våldsamma metoder, betraktas som en signal för särskilt förhöjd risk. Eventuell förekomst av tidigare självskador liksom självmord i familjen bör också uppmärksammas. Självmordsförsök kan utföras impulsivt, utan föregående planering, oftare hos unga och ska då inte betraktas som mindre allvarliga än planerade. Vid bedömning av stöd och insatser för unga som har självskadat ska den förhöjda risken för senare psykiatrisk sjuklighet liksom utanförskap i arbetslivet hållas i minnet och insatser bör också innefatta förebyggande åtgärder mot dessa svårigheter i vuxenlivet.

7 ACKNOWLEDGEMENTS

I would like to express my gratitude to everyone who has contributed to this thesis and all the work behind it. I would especially like to thank the following:

First, I would like to thank my main supervisor **Marie Dahlin** for your commitment to the research and to my growth as a researcher. You have showed a genuine dedication from the very beginning, when you introduced me to research, up until the bitter end, and always kept an open door for me. I am truly grateful that you gave me this opportunity to learn more about research and I have very much enjoyed these years of co-working.

I would also like to thank my co-supervisor **Bo Runeson** for generously sharing your knowledge on suicide and suicide research with me. Together with Marie, you have created an enjoyable and fruitful atmosphere for us doctoral students.

I am very grateful to my co-supervisor **Ellenor Mittendorfer-Rutz** who has been most helpful in my attempts to perform epidemiological studies. Your knowledge in this area has been important to me and you have always been available for questions and discussions. The weight of being a novice on methodological issues and trying to address complex epidemiological questions has been made much easier by our meetings.

To my dear friends and co-workers **Axel Haglund** and **Henrik Lysell**. I am so very grateful for the years spent with the two of you, both at and outside work. Genuine help and important discussions, and also immense and silly fun. You have been so missed at plan 1!

A big thanks to my fellow student/ coffebuddy **Åsa Lindh** for all the time spent sketching models, discussing results and even more so drinking coffee and talking about larger issues in life and work. So enjoyable!

Another big thanks to my former co-worker **Dag Tidemalm** for your help, among other things, in my first small steps in learning SPSS. Thank you for pretending that my questions were not annoying and stupid.

Also, I am very happy for the rather recent add to the research group, **Jie Song** and **Christine Takami**. Thank you for our discussions regarding both research and others.

And a warm thank you to **Ingela Kärkkäinen Malmsjö** for your help in the areas where I am definitely weak. We both know that my thesis would not have looked the same, if trusted only with my hands.

My gratitude to all my co-authors, e.g. **Henrik Larsson, Tomas Niederkrotenthaler, Catharina Almqvist Malmros, Paul Lichtenstein, Margda Waern and Ellinor Salander Renberg**. You have been very helpful and patient with me in all the work and the turns of the manuscripts. Thank you!

A special thank you to the participants in the **Multicenter Study on Self-Harm**. This research could not have been conducted without your generosity at an often difficult time. I hope that your contribution will add to knowledge that will help others in similar situations. Also, thank you to all the co-workers in the project.

I am very grateful to all my co-workers at **ADHD mottagningen at Norra Stockholms Psykiatri** for giving me time off from our important clinical work to conduct this research. I know that it has sometimes led to a higher workload for you, and even so you have always made me feel very welcome when returning to you and to clinical work. Thank you!

I am grateful for the **Research School** for clinicians in psychiatry at Karolinska Institutet/ SLL. This school has been a very good way to be introduced to research.

I am very grateful for my beloved **family and friends**, my **mother** and **father** for your love and support (incl. software support), my dear siblings **Anna, Kerstin and Olle. Nenne and Maria**. My whole family has, in different ways, with warmth and generosity, contributed to this work. To my dear friends, darling **CF**, your support has been more important to me than you probably know. To all of my friends here in Stockholm and all of my long-time friends from Uppsala and Skåne; you make the world spin.

Slutligen, mitt viktigaste tack vill jag ge till **Alva** och **Clara** - med oändlig kärlek.

8 REFERENCES

Arnett, J. J. (2000). Emerging adulthood. A theory of development from the late teens through the twenties. *American Psychologist,* 55**,** 469-480.

Asarnow, J. R., Porta, G., Spirito, A., Emslie, G., Clarke, G., Wagner, K. D., Vitiello, B., Keller, M., Birmaher, B., McCracken, J., Mayes, T., Berk, M. & Brent, D. A. (2011). Suicide attempts and nonsuicidal self-injury in the treatment of resistant depression in adolescents: findings from the TORDIA study. *Journal of the American Academy of Child and Adolescent Psychiatry,* 50**,** 772-781.

Auerbach, R. P., Stewart, J. G. & Johnson, S. L. (2017). Impulsivity and Suicidality in Adolescent Inpatients. *Journal of Abnormal Child Psychology,* 45**,** 91-103.

Baca-Garcia, E., Diaz-Sastre, C., Basurte, E., Prieto, R., Ceverino, A., Saiz-Ruiz, J. & de Leon, J. (2001). A prospective study of the paradoxical relationship between impulsivity and lethality of suicide attempts. *Journal of Clinical Psychiatry,* 62**,** 560-564.

Baca-Garcia, E., Diaz-Sastre, C., Garcia Resa, E., Blasco, H., Braquehais Conesa, D., Oquendo, M. A., Saiz-Ruiz, J. & de Leon, J. (2005). Suicide attempts and impulsivity. *European Archives of Psychiatry and Clinical Neuroscience,* 255**,** 152-156.

Beautrais, A. L. (2000). Risk factors for suicide and attempted suicide among young people. *Australian and New Zealand Journal of Psychiatry,* 34**,** 420-436.

Beck, R. W., Morris, J. B. & Beck, A. T. (1974). Cross-validation of the Suicidal Intent Scale. *Psychological Reports,* 34**,** 445-446.

Beckman, K., Dahlin, M., Tidemalm, D. & Runeson, B. (2010). [Drastic increase of hospitalized young people following self-inflicted injury. Drugs the most frequently used method]. *Lakartidningen,* 107**,** 428-431.

Bennardi, M., McMahon, E., Corcoran, P., Griffin, E. & Arensman, E. (2016). Risk of repeated self-harm and associated factors in children, adolescents and young adults. *BMC Psychiatry,* 16**,** 421.

Bergen, H., Hawton, K., Waters, K., Ness, J., Cooper, J., Steeg, S. & Kapur, N. (2012). How do methods of non-fatal self-harm relate to eventual suicide? *Journal of Affective Disorders,* 136**,** 526-533.

Bjarehed, J. & Lundh, L. G. (2008). Deliberate self-harm in 14-year-old adolescents: how frequent is it, and how is it associated with psychopathology, relationship variables, and styles of emotional regulation? *Cognitive Behaviour Therapy,* 37**,** 26-37.

Bjorkenstam, C., Ekselius, L., Berlin, M., Gerdin, B. & Bjorkenstam, E. (2016). Suicide risk and suicide method in patients with personality disorders. *Journal of Psychiatric Research,* 83**,** 29-36.

Blakemore, S. J. (2008). The social brain in adolescence. *Nature Reviews: Neuroscience,* 9**,** 267-277.

Boergers, J., Spirito, A. & Donaldson, D. (1998). Reasons for adolescent suicide attempts: associations with psychological functioning. *Journal of the American Academy of Child and Adolescent Psychiatry,* 37**,** 1287-1293.

Brener, N. D., Krug, E. G. & Simon, T. R. (2000). Trends in suicide ideation and suicidal behavior among high school students in the United States, 1991-1997. *Suicide and Life-Threatening Behavior,* 30**,** 304-312.

Brent, D. A., Baugher, M., Bridge, J., Chen, T. & Chiappetta, L. (1999). Age- and sex-related risk factors for adolescent suicide. *Journal of the American Academy of Child and Adolescent Psychiatry,* 38**,** 1497-1505.

Briere, F. N., Rohde, P., Seeley, J. R., Klein, D. & Lewinsohn, P. M. (2015). Adolescent Suicide Attempts and Adult Adjustment. *Depression and Anxiety,* 32**,** 270-276.

Brooke, H. L., Talback, M., Hornblad, J., Johansson, L. A., Ludvigsson, J. F., Druid, H., Feychting, M. & Ljung, R. (2017). The Swedish cause of death register. *European Journal of Epidemiology,* 32**,** 765-773.

Brown, L. K., Overholser, J., Spirito, A. & Fritz, G. K. (1991). The correlates of planning in adolescent suicide attempts. *Journal of the American Academy of Child and Adolescent Psychiatry,* 30**,** 95-99.

Brown, M. Z., Comtois, K. A. & Linehan, M. M. (2002). Reasons for suicide attempts and nonsuicidal self-injury in women with borderline personality disorder. *Journal of Abnormal Psychology,* 111**,** 198-202.

Carroll, R., Metcalfe, C. & Gunnell, D. (2014). Hospital presenting self-harm and risk of fatal and non-fatal repetition: systematic review and meta-analysis. *PloS One,* 9**,** e89944.

Carroll, R., Thomas, K. H., Bramley, K., Williams, S., Griffin, L., Potokar, J. & Gunnell, D. (2016). Self-cutting and risk of subsequent suicide. *Journal of Affective Disorders,* 192**,** 8-10.

Casey, B. J., Jones, R. M. & Hare, T. A. (2008). The adolescent brain. *Annals of the New York Academy of Sciences,* 1124**,** 111-126.

Chapman, A. L., Gratz, K. L. & Brown, M. Z. (2006). Solving the puzzle of deliberate self-harm: the experiential avoidance model. *Behaviour Research and Therapy,* 44**,** 371-394.

Chesney, E., Goodwin, G. M. & Fazel, S. (2014). Risks of all-cause and suicide mortality in mental disorders: a meta-review. *World Psychiatry,* 13**,** 153-160.

Conner, K. R., Hesselbrock, V. M., Meldrum, S. C., Schuckit, M. A., Bucholz, K. K., Gamble, S. A., Wines, J. D., Jr. & Kramer, J. (2007). Transitions to, and correlates of, suicidal ideation, plans, and unplanned and planned suicide attempts among 3,729 men and women with alcohol dependence. *J Stud Alcohol Drugs,* 68**,** 654-662.

Conner, K. R., Phillips, M. R., Meldrum, S., Knox, K. L., Zhang, Y. & Yang, G. (2005). Low-planned suicides in China. *Psychological Medicine,* 35**,** 1197-1204.

Conwell, Y., Duberstein, P. R., Cox, C., Herrmann, J., Forbes, N. & Caine, E. D. (1998). Age differences in behaviors leading to completed suicide. *American Journal of Geriatric Psychiatry,* 6**,** 122-126.

Cooper, J., Kapur, N., Webb, R., Lawlor, M., Guthrie, E., Mackway-Jones, K. & Appleby, L. (2005). Suicide after deliberate self-harm: a 4-year cohort study. *American Journal of Psychiatry,* 162**,** 297-303.

Costello, E. J., Pine, D. S., Hammen, C., March, J. S., Plotsky, P. M., Weissman, M. M., Biederman, J., Goldsmith, H. H., Kaufman, J., Lewinsohn, P. M., Hellander, M.,

Hoagwood, K., Koretz, D. S., Nelson, C. A. & Leckman, J. F. (2002). Development and natural history of mood disorders. *Biological Psychiatry,* 52**,** 529-542.

Couwenbergh, C., van den Brink, W., Zwart, K., Vreugdenhil, C., van Wijngaarden-Cremers, P. & van der Gaag, R. J. (2006). Comorbid psychopathology in adolescents and young adults treated for substance use disorders: a review. *European Child and Adolescent Psychiatry,* 15**,** 319-328.

Crosby, A. E., Han, B., Ortega, L. A., Parks, S. E., Gfroerer, J., Centers for Disease, C. & Prevention (2011). Suicidal thoughts and behaviors among adults aged >/=18 years--United States, 2008-2009. *MMWR: Surveillance Summaries,* 60**,** 1-22.

Deisenhammer, E. A., Ing, C. M., Strauss, R., Kemmler, G., Hinterhuber, H. & Weiss, E. M. (2009). The duration of the suicidal process: how much time is left for intervention between consideration and accomplishment of a suicide attempt? *Journal of Clinical Psychiatry,* 70**,** 19-24.

Diggins, E., Kelley, R., Cottrell, D., House, A. & Owens, D. (2017). Age-related differences in self-harm presentations and subsequent management of adolescents and young adults at the emergency department. *Journal of Affective Disorders,* 208**,** 399-405.

Dougherty, D. M., Marsh-Richard, D. M., Hatzis, E. S., Nouvion, S. O. & Mathias, C. W. (2008). A test of alcohol dose effects on multiple behavioral measures of impulsivity. *Drug and Alcohol Dependence,* 96**,** 111-120.

Dumais, A., Lesage, A. D., Lalovic, A., Seguin, M., Tousignant, M., Chawky, N. & Turecki, G. (2005). Is violent method of suicide a behavioral marker of lifetime aggression? *American Journal of Psychiatry,* 162**,** 1375-1378.

Ekbom, A. (2011). The Swedish Multi-generation Register. *Methods in Molecular Biology,* 675**,** 215-220.

Evans, E., Hawton, K. & Rodham, K. (2004). Factors associated with suicidal phenomena in adolescents: a systematic review of population-based studies. *Clinical Psychology Review,* 24**,** 957-979.

Evans, J., Platts, H. & Liebenau, A. (1996). Impulsiveness and deliberate self-harm: a comparison of "first-timers' and "repeaters'. *Acta Psychiatrica Scandinavica,* 93**,** 378-380.

Fazaa, N. & Page, S. (2009). Personality style and impulsivity as determinants of suicidal subgroups. *Arch Suicide Res,* 13**,** 31-45.

Fergusson, D. M., Horwood, L. J., Ridder, E. M. & Beautrais, A. L. (2005). Suicidal behaviour in adolescence and subsequent mental health outcomes in young adulthood. *Psychological Medicine,* 35**,** 983-993.

Fergusson, D. M., Woodward, L. J. & Horwood, L. J. (2000). Risk factors and life processes associated with the onset of suicidal behaviour during adolescence and early adulthood. *Psychological Medicine,* 30**,** 23-39.

Finkelstein, Y., Macdonald, E. M., Hollands, S., Hutson, J. R., Sivilotti, M. L., Mamdani, M. M., Koren, G., Juurlink, D. N., Canadian Drug, S. & Effectiveness Research, N. (2015). Long-term outcomes following self-poisoning in adolescents: a population-based cohort study. *Lancet Psychiatry,* 2**,** 532-539.

Fleischmann, A., Bertolote, J. M., Belfer, M. & Beautrais, A. (2005). Completed suicide and psychiatric diagnoses in young people: a critical examination of the evidence. *American Journal of Orthopsychiatry,* 75**,** 676-683.

Forsberg, L. R., H. Jacobsson, A. Nyqvist, K. Heurgren, M. (2009). Kvalitet och innehåll i patientregistret. Utskrivningar från slutenvården 1964-2007 och besök i specialiserad öppenvård (exklusive primärvårdsbesök) 1997-2007. (Quality and content of the Patient Register)(2009-125-15) *National Board of Health and Welfare*.

Fortune, S., Stewart, A., Yadav, V. & Hawton, K. (2007). Suicide in adolescents: using life charts to understand the suicidal process. *Journal of Affective Disorders,* 100**,** 199-210.

Freedenthal, S. (2008). Assessing the wish to die: a 30-year review of the suicide intent scale. *Arch Suicide Res,* 12**,** 277-298.

Giner, L., Jaussent, I., Olie, E., Beziat, S., Guillaume, S., Baca-Garcia, E., Lopez-Castroman, J. & Courtet, P. (2014). Violent and serious suicide attempters: one step closer to suicide? *Journal of Clinical Psychiatry,* 75**,** e191-197.

Goldman-Mellor, S. J., Caspi, A., Harrington, H., Hogan, S., Nada-Raja, S., Poulton, R. & Moffitt, T. E. (2013). Suicide Attempt in Young People: A Signal for Long-term Health Care and Social Needs. *JAMA Psychiatry*.

Goldman-Mellor, S. J., Caspi, A., Harrington, H., Hogan, S., Nada-Raja, S., Poulton, R. & Moffitt, T. E. (2014). Suicide Attempt in Young People: A Signal for Long-term Health Care and Social Needs. *JAMA Psychiatry,* 71**,** 119-127.

Goldston, D. B., Daniel, S., Reboussin, D. M., Kelley, A., Ievers, C. & Brunstetter, R. (1996). First-time suicide attempters, repeat attempters, and previous attempters on an adolescent inpatient psychiatry unit. *Journal of the American Academy of Child and Adolescent Psychiatry,* 35**,** 631-639.

Gould, M. S., King, R., Greenwald, S., Fisher, P., Schwab-Stone, M., Kramer, R., Flisher, A. J., Goodman, S., Canino, G. & Shaffer, D. (1998). Psychopathology associated with suicidal ideation and attempts among children and adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry,* 37**,** 915-923.

Groholt, B. & Ekeberg, O. (2009). Prognosis after adolescent suicide attempt: mental health, psychiatric treatment, and suicide attempts in a nine-year follow-up study. *Suicide and Life-Threatening Behavior,* 39**,** 125-136.

Groholt, B., Ekeberg, O. & Haldorsen, T. (2000). Adolescents hospitalised with deliberate self-harm: the significance of an intention to die. *European Child and Adolescent Psychiatry,* 9**,** 244-254.

Guyer, A. E., Silk, J. S. & Nelson, E. E. (2016). The neurobiology of the emotional adolescent: From the inside out. *Neuroscience and Biobehavioral Reviews,* 70**,** 74-85.

Gvion, Y. & Apter, A. (2011). Aggression, impulsivity, and suicide behavior: a review of the literature. *Arch Suicide Res,* 15**,** 93-112.

Harrington, R., Pickles, A., Aglan, A., Harrington, V., Burroughs, H. & Kerfoot, M. (2006). Early adult outcomes of adolescents who deliberately poisoned themselves. *Journal of the American Academy of Child and Adolescent Psychiatry,* 45**,** 337-345.

Haukka, J., Suominen, K., Partonen, T. & Lonnqvist, J. (2008). Determinants and outcomes of serious attempted suicide: A nationwide study in Finland, 1996-2003. *American Journal of Epidemiology,* 167**,** 1155-1163.

Haw, C., Bergen, H., Casey, D. & Hawton, K. (2007). Repetition of deliberate self-harm: A study of the characteristics and subsequent deaths in patients presenting to a general hospital according to extent of repetition. *Suicide and Life-Threatening Behavior,* 37**,** 379-396.

Haw, C., Casey, D., Holmes, J. & Hawton, K. (2015). Suicidal Intent and Method of Self-Harm: A Large-scale Study of Self-Harm Patients Presenting to a General Hospital. *Suicide and Life-Threatening Behavior,* 45**,** 732-746.

Haw, C., Hawton, K., Houston, K. & Townsend, E. (2001). Psychiatric and personality disorders in deliberate self-harm patients. *British Journal of Psychiatry,* 178**,** 48-54.

Hawton, K., Bergen, H., Cooper, J., Turnbull, P., Waters, K., Ness, J. & Kapur, N. (2015). Suicide following self-harm: findings from the Multicentre Study of self-harm in England, 2000-2012. *Journal of Affective Disorders,* 175**,** 147-151.

Hawton, K., Bergen, H., Kapur, N., Cooper, J., Steeg, S., Ness, J. & Waters, K. (2012a). Repetition of self-harm and suicide following self-harm in children and adolescents: findings from the Multicentre Study of Self-harm in England. *Journal of Child Psychology and Psychiatry and Allied Disciplines,* 53**,** 1212-1219.

Hawton, K., Fagg, J., Platt, S. & Hawkins, M. (1993). Factors associated with suicide after parasuicide in young people. *BMJ,* 306**,** 1641-1644.

Hawton, K., Hall, S., Simkin, S., Bale, L., Bond, A., Codd, S. & Stewart, A. (2003a). Deliberate self-harm in adolescents: a study of characteristics and trends in Oxford, 1990-2000. *Journal of Child Psychology and Psychiatry and Allied Disciplines,* 44**,** 1191-1198.

Hawton, K. & Harriss, L. (2007). Deliberate self-harm in young people: characteristics and subsequent mortality in a 20-year cohort of patients presenting to hospital. *Journal of Clinical Psychiatry,* 68**,** 1574-1583.

Hawton, K. & Harriss, L. (2008). How often does deliberate self-harm occur relative to each suicide? A study of variations by gender and age. *Suicide and Life-Threatening Behavior,* 38**,** 650-660.

Hawton, K., Harriss, L., Hall, S., Simkin, S., Bale, E. & Bond, A. (2003b). Deliberate self-harm in Oxford, 1990-2000: a time of change in patient characteristics. *Psychological Medicine,* 33**,** 987-995.

Hawton, K., Rodham, K., Evans, E. & Weatherall, R. (2002). Deliberate self harm in adolescents: self report survey in schools in England. *BMJ,* 325**,** 1207-1211.

Hawton, K., Saunders, K., Topiwala, A. & Haw, C. (2013). Psychiatric disorders in patients presenting to hospital following self-harm: A systematic review. *Journal of Affective Disorders,* 151**,** 821-830.

Hawton, K., Saunders, K. E. A. & O'Connor, R. C. (2012b). Self-harm and suicide in adolescents. *The Lancet,* 379**,** 2373-2382.

Hawton, K., Simkin, S., Gunnell, D., Sutton, L., Bennewith, O., Turnbull, P. & Kapur, N. (2005). A multicentre study of coproxamol poisoning suicides based on coroners' records in England. *British Journal of Clinical Pharmacology,* 59**,** 207-212.

Hyde, J. S., Mezulis, A. H. & Abramson, L. Y. (2008). The ABCs of depression: integrating affective, biological, and cognitive models to explain the emergence of the gender difference in depression. *Psychological Review,* 115**,** 291-313.

Impey, M. & Heun, R. (2012). Completed suicide, ideation and attempt in attention deficit hyperactivity disorder. *Acta Psychiatrica Scandinavica,* 125**,** 93-102.

Jokinen, J., Forslund, K., Ahnemark, E., Gustavsson, J. P., Nordstrom, P. & Asberg, M. (2010). Karolinska Interpersonal Violence Scale predicts suicide in suicide attempters. *Journal of Clinical Psychiatry,* 71**,** 1025-1032.

Kapur, N., Murphy, E., Cooper, J., Bergen, H., Hawton, K., Simkin, S., Casey, D., Horrocks, J., Lilley, R., Noble, R. & Owens, D. (2008). Psychosocial assessment following self-harm: results from the multi-centre monitoring of self-harm project. *Journal of Affective Disorders,* 106**,** 285-293.

Kerr, D. C. & Capaldi, D. M. (2011). Young men's intimate partner violence and relationship functioning: long-term outcomes associated with suicide attempt and aggression in adolescence. *Psychological Medicine,* 41**,** 759-769.

Kessler, R. C., Borges, G. & Walters, E. E. (1999). Prevalence of and risk factors for lifetime suicide attempts in the National Comorbidity Survey. *Archives of General Psychiatry,* 56**,** 617-626.

Klonsky, E. D. (2007). The functions of deliberate self-injury: a review of the evidence. *Clinical Psychology Review,* 27**,** 226-239.

Klonsky, E. D., Oltmanns, T. F. & Turkheimer, E. (2003). Deliberate self-harm in a nonclinical population: prevalence and psychological correlates. *American Journal of Psychiatry,* 160**,** 1501-1508.

Kokkevi, A., Rotsika, V., Arapaki, A. & Richardson, C. (2011). Increasing self-reported suicide attempts by adolescents in Greece between 1984 and 2007. *Social Psychiatry and Psychiatric Epidemiology,* 46**,** 231-237.

Lahti, A., Harju, A., Hakko, H., Riala, K. & Rasanen, P. (2014). Suicide in children and young adolescents: a 25-year database on suicides from Northern Finland. *Journal of Psychiatric Research,* 58**,** 123-128.

Larkin, C., Corcoran, P., Perry, I. & Arensman, E. (2014). Severity of hospital-treated self-cutting and risk of future self-harm: a national registry study. *J Ment Health,* 23**,** 115-119.

Lewinsohn, P. M., Rohde, P. & Seeley, J. R. (1994). Psychosocial risk factors for future adolescent suicide attempts. *Journal of Consulting and Clinical Psychology,* 62**,** 297-305.

Lindqvist, D., Janelidze, S., Erhardt, S., Traskman-Bendz, L., Engstrom, G. & Brundin, L. (2011). CSF biomarkers in suicide attempters--a principal component analysis. *Acta Psychiatrica Scandinavica,* 124**,** 52-61.

Linsley, K. R., Schapira, K. & Kelly, T. P. (2001). Open verdict v. suicide - importance to research. *British Journal of Psychiatry,* 178**,** 465-468.

Lockwood, J., Daley, D., Townsend, E. & Sayal, K. (2016). Impulsivity and self-harm in adolescence: a systematic review. *European Child and Adolescent Psychiatry*.

Ludvigsson, J. F., Almqvist, C., Bonamy, A. K., Ljung, R., Michaelsson, K., Neovius, M., Stephansson, O. & Ye, W. (2016). Registers of the Swedish total population and their use in medical research. *European Journal of Epidemiology,* 31**,** 125-136.

Ludvigsson, J. F., Andersson, E., Ekbom, A., Feychting, M., Kim, J. L., Reuterwall, C., Heurgren, M. & Olausson, P. O. (2011). External review and validation of the Swedish national inpatient register. *BMC Public Health,* 11**,** 450.

Ludvigsson, J. F., Otterblad-Olausson, P., Pettersson, B. U. & Ekbom, A. (2009). The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *European Journal of Epidemiology,* 24**,** 659-667.

Lundin, A., Lundberg, I., Allebeck, P. & Hemmingsson, T. (2011). Psychiatric diagnosis in late adolescence and long-term risk of suicide and suicide attempt. *Acta Psychiatrica Scandinavica,* 124**,** 454-461.

Madge, N., Hewitt, A., Hawton, K., de Wilde, E. J., Corcoran, P., Fekete, S., van Heeringen, K., De Leo, D. & Ystgaard, M. (2008). Deliberate self-harm within an international community sample of young people: comparative findings from the Child & Adolescent Self-harm in Europe (CASE) Study. *Journal of Child Psychology and Psychiatry and Allied Disciplines,* 49**,** 667-677.

Mann, J. J. (2003). Neurobiology of suicidal behaviour. *Nature Reviews: Neuroscience,* 4**,** 819-828.

Mars, B., Heron, J., Crane, C., Hawton, K., Kidger, J., Lewis, G., Macleod, J., Tilling, K. & Gunnell, D. (2014a). Differences in risk factors for self-harm with and without suicidal intent: findings from the ALSPAC cohort. *Journal of Affective Disorders,* 168**,** 407-414.

Mars, B., Heron, J., Crane, C., Hawton, K., Lewis, G., Macleod, J., Tilling, K. & Gunnell, D. (2014b). Clinical and social outcomes of adolescent self harm: population based birth cohort study. *BMJ,* 349**,** g5954.

Mazza, J. J. & Reynolds, W. M. (1998). A longitudinal investigation of depression, hopelessness, social support, and major and minor life events and their relation to suicidal ideation in adolescents. *Suicide and Life-Threatening Behavior,* 28**,** 358-374.

McGirr, A., Renaud, J., Bureau, A., Seguin, M., Lesage, A. & Turecki, G. (2008). Impulsive-aggressive behaviours and completed suicide across the life cycle: a predisposition for younger age of suicide. *Psychological Medicine,* 38**,** 407-417.

McGirr, A., Renaud, J., Seguin, M., Alda, M., Benkelfat, C., Lesage, A. & Turecki, G. (2007). An examination of DSM-IV depressive symptoms and risk for suicide completion in major depressive disorder: a psychological autopsy study. *Journal of Affective Disorders,* 97**,** 203-209.

Miller, M., Hempstead, K., Nguyen, T., Barber, C., Rosenberg-Wohl, S. & Azrael, D. (2013). Method choice in nonfatal self-harm as a predictor of subsequent episodes of self-harm and suicide: implications for clinical practice. *American Journal of Public Health,* 103**,** e61-68.

Miranda, R., De Jaegere, E., Restifo, K. & Shaffer, D. (2014). Longitudinal follow-up study of adolescents who report a suicide attempt: aspects of suicidal behavior that increase risk of a future attempt. *Depression and Anxiety,* 31**,** 19-26.

Miranda, R., Scott, M., Hicks, R., Wilcox, H. C., Harris Munfakh, J. L. & Shaffer, D. (2008). Suicide attempt characteristics, diagnoses, and future attempts: comparing multiple

attempters to single attempters and ideators. *Journal of the American Academy of Child and Adolescent Psychiatry,* 47**,** 32-40.

Mishara B L, C. F. (2016). Why Mental Illness is a Risk Factor for Suicide. In P. J. O`CONNOR R (Ed. *The International Handbook of Suicide Prevention.* Wiley Blackwell.

Moran, P., Coffey, C., Romaniuk, H., Degenhardt, L., Borschmann, R. & Patton, G. C. (2015). Substance use in adulthood following adolescent self-harm: a population-based cohort study. *Acta Psychiatrica Scandinavica,* 131**,** 61-68.

Moran, P., Coffey, C., Romaniuk, H., Olsson, C., Borschmann, R., Carlin, J. B. & Patton, G. C. (2012). The natural history of self-harm from adolescence to young adulthood: a population-based cohort study. *Lancet,* 379**,** 236-243.

Morgan, C., Webb, R. T., Carr, M. J., Kontopantelis, E., Green, J., Chew-Graham, C. A., Kapur, N. & Ashcroft, D. M. (2017). Incidence, clinical management, and mortality risk following self harm among children and adolescents: cohort study in primary care. *BMJ,* 359**,** j4351.

Muehlenkamp, J. J., Claes, L., Havertape, L. & Plener, P. L. (2012). International prevalence of adolescent non-suicidal self-injury and deliberate self-harm. *Child Adolesc Psychiatry Ment Health,* 6**,** 10.

Neeleman, J. & Wessely, S. (1997). Changes in classification of suicide in England and Wales: time trends and associations with coroners' professional backgrounds. *Psychological Medicine,* 27**,** 467-472.

Nelson, E. E., Leibenluft, E., McClure, E. B. & Pine, D. S. (2005). The social re-orientation of adolescence: a neuroscience perspective on the process and its relation to psychopathology. *Psychological Medicine,* 35**,** 163-174.

Nigg, J. T. (2013). Attention-deficit/hyperactivity disorder and adverse health outcomes. *Clinical Psychology Review,* 33**,** 215-228.

Nock, M. K. (2012). Future directions for the study of suicide and self-injury. *Journal of Clinical Child and Adolescent Psychology,* 41**,** 255-259.

Nock, M. K., Green, J. G., Hwang, I., McLaughlin, K. A., Sampson, N. A., Zaslavsky, A. M. & Kessler, R. C. (2013). Prevalence, correlates, and treatment of lifetime suicidal behavior among adolescents: results from the National Comorbidity Survey Replication Adolescent Supplement. *JAMA Psychiatry,* 70**,** 300-310.

Nock, M. K. & Prinstein, M. J. (2004). A functional approach to the assessment of self-mutilative behavior. *Journal of Consulting and Clinical Psychology,* 72**,** 885-890.

O'Carroll, P. W., Berman, A. L., Maris, R. W., Moscicki, E. K., Tanney, B. L. & Silverman, M. M. (1996). Beyond the Tower of Babel: a nomenclature for suicidology. *Suicide and Life-Threatening Behavior,* 26**,** 237-252.

O'Connell, H., Chin, A. V., Cunningham, C. & Lawlor, B. A. (2004). Recent developments: suicide in older people. *BMJ,* 329**,** 895-899.

O'Connor, R. C. (2007). The relations between perfectionism and suicidality: a systematic review. *Suicide and Life-Threatening Behavior,* 37**,** 698-714.

O'Connor, R. C. (2011). The integrated motivational-volitional model of suicidal behavior. *Crisis,* 32**,** 295-298.

O'Connor, R. C., Rasmussen, S. & Hawton, K. (2012). Distinguishing adolescents who think about self-harm from those who engage in self-harm. *British Journal of Psychiatry,* 200**,** 330-335.

O`Connor R, C. S., Eschle S, Wetherall K, Kirtley O (2016). The Integrated Motivational-Volitional Model of Suicidal Behaviour. Un Update. *The International Handbook of Suicide Prevention.*: Wiley Blackwell.

Olfson, M., Gameroff, M. J., Marcus, S. C., Greenberg, T. & Shaffer, D. (2005). Emergency treatment of young people following deliberate self-harm. *Archives of General Psychiatry,* 62**,** 1122-1128.

Palmer, B. A., Pankratz, V. S. & Bostwick, J. M. (2005). The lifetime risk of suicide in schizophrenia: a reexamination. *Archives of General Psychiatry,* 62**,** 247-253.

Patton, G. C., Coffey, C., Sawyer, S. M., Viner, R. M., Haller, D. M., Bose, K., Vos, T., Ferguson, J. & Mathers, C. D. (2009). Global patterns of mortality in young people: a systematic analysis of population health data. *Lancet,* 374**,** 881-892.

Patton, G. C., Hemphill, S. A., Beyers, J. M., Bond, L., Toumbourou, J. W., McMorris, B. J. & Catalano, R. F. (2007). Pubertal stage and deliberate self-harm in adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry,* 46**,** 508-514.

Paykel, E. S., Myers, J. K., Lindenthal, J. J. & Tanner, J. (1974). Suicidal feelings in the general population: a prevalence study. *British Journal of Psychiatry,* 124**,** 460-469.

Posner, K., Brown, G. K., Stanley, B., Brent, D. A., Yershova, K. V., Oquendo, M. A., Currier, G. W., Melvin, G. A., Greenhill, L., Shen, S. & Mann, J. J. (2011). The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *American Journal of Psychiatry,* 168**,** 1266-1277.

Rimkeviciene, J., O'Gorman, J. & De Leo, D. (2015). Impulsive suicide attempts: a systematic literature review of definitions, characteristics and risk factors. *Journal of Affective Disorders,* 171**,** 93-104.

Runeson, B., Tidemalm, D., Dahlin, M., Lichtenstein, P. & Langstrom, N. (2010). Method of attempted suicide as predictor of subsequent successful suicide: national long term cohort study. *British Medical Journal,* 341.

Runeson, B. S. (1998). History of suicidal behaviour in the families of young suicides. *Acta Psychiatrica Scandinavica,* 98**,** 497-501.

Runeson, B. S., Beskow, J. & Waern, M. (1996). The suicidal process in suicides among young people. *Acta Psychiatrica Scandinavica,* 93**,** 35-42.

Rutz, E. M. & Wasserman, D. (2004). Trends in adolescent suicide mortality in the WHO European Region. *European Child and Adolescent Psychiatry,* 13**,** 321-331.

scb.se/lisa-en.

Schaffer, A., Sinyor, M., Kurdyak, P., Vigod, S., Sareen, J., Reis, C., Green, D., Bolton, J., Rhodes, A., Grigoriadis, S., Cairney, J. & Cheung, A. (2016). Population-based analysis of health care contacts among suicide decedents: identifying opportunities for more targeted suicide prevention strategies. *World Psychiatry,* 15**,** 135-145.

Schmidtke, A., Bille-Brahe, U., DeLeo, D., Kerkhof, A., Bjerke, T., Crepet, P., Haring, C., Hawton, K., Lonnqvist, J., Michel, K., Pommereau, X., Querejeta, I., Phillipe, I., Salander-Renberg, E., Temesvary, B., Wasserman, D., Fricke, S., Weinacker, B. &

Sampaio-Faria, J. G. (1996). Attempted suicide in Europe: rates, trends and sociodemographic characteristics of suicide attempters during the period 1989-1992. Results of the WHO/EURO Multicentre Study on Parasuicide. *Acta Psychiatrica Scandinavica,* 93**,** 327-338.

Schrijvers, D. L., Bollen, J. & Sabbe, B. G. (2012). The gender paradox in suicidal behavior and its impact on the suicidal process. *Journal of Affective Disorders,* 138**,** 19-26.

Serafini, G., Pompili, M., Elena Seretti, M., Stefani, H., Palermo, M., Coryell, W. & Girardi, P. (2013). The role of inflammatory cytokines in suicidal behavior: a systematic review. *European Neuropsychopharmacology,* 23**,** 1672-1686.

Shaffer, D., Gould, M. S., Fisher, P., Trautman, P., Moreau, D., Kleinman, M. & Flory, M. (1996). Psychiatric diagnosis in child and adolescent suicide. *Archives of General Psychiatry,* 53**,** 339-348.

socialstyrelsen.se/statistik/statistikdatabas.

Speckens, A. E. & Hawton, K. (2005). Social problem solving in adolescents with suicidal behavior: a systematic review. *Suicide and Life-Threatening Behavior,* 35**,** 365-387.

Spirito, A. & Esposito-Smythers, C. (2006). Attempted and completed suicide in adolescence. *Annual Review of Clinical Psychology,* 2**,** 237-266.

Suominen, K., Isometsa, E., Henriksson, M., Ostamo, A. & Lonnqvist, J. (1997). Hopelessness, impulsiveness and intent among suicide attempters with major depression, alcohol dependence, or both. *Acta Psychiatrica Scandinavica,* 96**,** 142-149.

Thompson, E. A., Mazza, J. J., Herting, J. R., Randell, B. P. & Eggert, L. L. (2005). The mediating roles of anxiety depression, and hopelessness on adolescent suicidal behaviors. *Suicide and Life-Threatening Behavior,* 35**,** 14-34.

Tidemalm, D., Langstrom, N., Lichtenstein, P. & Runeson, B. (2008). Risk of suicide after suicide attempt according to coexisting psychiatric disorder: Swedish cohort study with long term follow-up. *BMJ,* 337**,** a2205.

Tollefsen, I. M., Helweg-Larsen, K., Thiblin, I., Hem, E., Kastrup, M. C., Nyberg, U., Rogde, S., Zahl, P. H., Ostevold, G. & Ekeberg, O. (2015). Are suicide deaths under-reported? Nationwide re-evaluations of 1800 deaths in Scandinavia. *BMJ Open,* 5**,** e009120.

van Heeringen, K. & Mann, J. J. (2014). The neurobiology of suicide. *Lancet Psychiatry,* 1**,** 63-72.

Van Orden, K. A., Witte, T. K., Cukrowicz, K. C., Braithwaite, S. R., Selby, E. A. & Joiner, T. E., Jr. (2010). The interpersonal theory of suicide. *Psychological Review,* 117**,** 575-600.

Wettermark, B., Hammar, N., Fored, C. M., Leimanis, A., Otterblad Olausson, P., Bergman, U., Persson, I., Sundstrom, A., Westerholm, B. & Rosen, M. (2007). The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiology and Drug Safety,* 16**,** 726-735.

Whitlock, J., Muehlenkamp, J., Eckenrode, J., Purington, A., Baral Abrams, G., Barreira, P. & Kress, V. (2013). Nonsuicidal self-injury as a gateway to suicide in young adults. *Journal of Adolescent Health,* 52**,** 486-492.

Wilkinson, P., Kelvin, R., Roberts, C., Dubicka, B. & Goodyer, I. (2011). Clinical and psychosocial predictors of suicide attempts and nonsuicidal self-injury in the Adolescent Depression Antidepressants and Psychotherapy Trial (ADAPT). *American Journal of Psychiatry,* 168**,** 495-501.

Zahl, D. L. & Hawton, K. (2004). Repetition of deliberate self-harm and subsequent suicide risk: long-term follow-up study of 11,583 patients. *British Journal of Psychiatry,* 185**,** 70-75.