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CLINICAL ASSESSMENT OF HIGH-RISK SUICIDE ATTEMPTERS: INTENT, VIOLENCE AND BIOMARKERS

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THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

Background

One of the most important but also difficult tasks that a physician is responsible for is to assess the suicide risk of a patient. Understanding the complex role of distal and proximal risk factors and their impact on the prediction of repetition of suicidal behavior is important to consider when assessing the risk of suicide. The aim of this PhD project was to investigate structured suicide risk assessment scales in the detection of the risk of suicide in high-risk clinical cohorts of suicide attempters with a long-term follow-up. Furthermore, we aimed to investigate the neurobiological underpinnings of well-documented sex differences in suicidal behavior focusing on the main male sex hormone, testosterone.

Methods

A total of 209 patients having their clinical follow-up after a recent suicide attempt at the Psychiatric Department of the Karolinska University Hospital between 1988 and 2005, participated in three clinical studies of biological & psychological risk factors involving suicidal behavior. Patients were assessed using the following scales: the Suicide Intent Scale (SIS), the Beck Hopelessness Scale, the Karolinska Interpersonal Violence Scale (KIVS), the Freeman Scale and the Karolinska Scales of Personality. Patients in this study were followed up for mortality in the Swedish Cause of Death Register. Suicide deaths were ascertained from death certificates. CSF and plasma testosterone as well as cortisol levels were assessed in 28 patients and 19 healthy volunteers.

Results

Studies 1 & 2: Suicide Intent Scale ratings were higher in seven patients who committed suicide during an average follow up time of 13 years. The Positive Predictive Value of SIS was 16.7% and the AUC was 0.74. When combined, SIS + KIVS gave a somewhat higher PPV of 18.8% and an AUC of 0.83.

Study 3: Seventeen patients out of 209 committed suicide over an average follow-up period of 10-22 years. Men had a higher suicide risk compared to women. The mean Freeman total score differentiated between completed suicide and survivors with a PPV of 10.7% and an AUC of 0.73.

Study 4: Male suicide attempters had higher levels of CSF and plasma testosterone compared to age-matched healthy male volunteers. Regarding female suicide attempters, there were, however, no significant differences in CSF and plasma testosterone levels compared to healthy female volunteers. Testosterone levels were not significantly different in suicide victims versus survivors. The CSF testosterone/cortisol ratio was significantly and positively correlated with both impulsivity & aggressiveness and in male suicide attempters.

Conclusions

The findings indicate that an assessment of suicide intent and reversibility of the suicide attempt method, as well as interpersonal violence, may indicate a heightened long term suicide risk among clinically high-risk groups of suicide attempters. Higher CSF testosterone results may be associated with suicide attempts in young males through further association alongside both impulsivity and aggressiveness, in conjunction with stress system regulation. Young men may experience higher CSF testosterone levels in association with attempted suicide, aggression/impulsivity, as well as stress system regulation.

LIST OF SCIENTIFIC PAPERS

I. **Stefansson J**, Nordström P, Jokinen J. Suicide Intent Scale in the prediction of suicide. *Journal of Affective Disorders.* 2012;136:167-171.

II. **Stefansson J**, Nordström P, Runeson B, Åsberg M, Jokinen J. Combining the Suicide Intent Scale and the Karolinska Interpersonal Violence Scale in suicide risk assessments. *BMC Psychiatry*, 2015;15(1):226.

III. **Stefansson J**, Nordström P, Åsberg M, Jokinen J. Severity of Suicide Attempts and the Prediction of Long-Term Risk of Completed Suicide Manuscript.

IV. **Stefansson J,** Chatzittofis A, Nordström P, Arver S, Åsberg M, & Jokinen J. CSF and plasma testosterone in attempted suicide. *Psychoneuroendocrinology*, *74*, 1-6. 2016.

CONTENTS

LIST OF ABBREVIATIONS

5-HIAA	5-hydroxyindoleacetic acid
AUC	Area Under the Curve
BDHI	Buss-Durkee Hostility Inventory
C-SSRS	Columbia-Suicide Severity Rating Scale
CPRS	Comprehensive Psychopathological Rating Scale
CSF	Cerebral Spinal Fluid
CTQ-SF	Childhood Trauma Questionnaire - Short Form
DSH	Deliberate Self Harm
EEQ	Early Experience Questionnaire
HDHQ	Hostility and Direction of Hostility Questionnaire
I.V.	Intravenous
KIVS	Karolinska Interpersonal Violence Scale
KSP	The Karolinska Scales of Personality
NSSI	Non-Suicidal Self-Injury
PD	Personality Disorder
PPV	Positive Predictive Value
ROC	Receiver-Operating Characteristic
SB	Suicidal behavior
SBU	The Swedish Agency for Health Technology Assessment and Assessment of Social Services
SD	Standard deviation
SI	Suicidal ideation
SIS	Suicide Intent Scale
SSP	The Swedish universities Scales of Personality
WHO	World Health Organisation

1 INTRODUCTION

1.1 SUICIDE IN THE GENERAL POPULATION

Annually, about 800,000 people die in the world because of completed suicides (WHO, 2017). The World Health Organization reports that there are tools to reduce the amounts of suicide; however, there is a need for political will and collective action, as well as effective interventions (WHO, 2012).

It is presumed that for every adult who has died by suicide, there are 20 others who attempt suicide (WHO, 2017). This makes it very difficult for the clinician to tell which patient should, for example, be admitted to a hospital because of a high suicide risk and which patient can be treated as an outpatient.

Previously, experts in the USA have noted a trend toward suicide rates decreasing in certain areas, possibly because of such antidepressants such as SSRI's (Gibbons et al., 2005). However, some researchers hypothesize that such factors as decreased access to nonforensic psychiatric inpatient care are increasing the suicide rates in the U.S.A. (Bastiampillai et al., 2016). A fairly recent economic recession could also be one of the reasons why the aforementioned positive SSRI trend seems to be changing toward the negative in major Western countries such as the U.S.A. and Italy (Reeves et al., 2012).

According to the Swedish Cause of Death Register, 1,130 suicides took place in Sweden during the year 2016 (National Board of Health and Welfare, 2017). However, 340 deaths took place with undetermined intent (National Board of Health and Welfare, 2017) and considering that around 70-75% of uncertain suicides have later been believed to be actual suicides (National Center for Suicide Research and Prevention of Mental Ill-Health, 2014), one wonders if the actual suicide total in Sweden during 2016 was not around 1,380. This would equal, on average, around 4 ($\cong$3.8) suicides a day in Sweden during 2016. Overall, the suicide rates in Sweden have gone down over the past 30 years (National Board of Health and Welfare, 2017).

Patients that have committed suicide have previously seen primary care physicians more than twice as often compared to mental health clinicians (Luoma et al., 2002). A review analyzing this clinical situation estimated that 45% of suicide victims saw their general practitioner within one month before their death (Luoma et al., 2002). Only 20% saw a mental health professional during the month before the suicide (Luoma et al., 2002). This shows the importance of suicide risk assessments not just by mental health professionals, but also at the primary care level.

In general, when discussing risk factors for suicide, the involvement of gender and violence is often mentioned (Stack, 2014). It is also widely accepted that certain psychiatric diagnoses, such as schizophrenia, bipolar disorder and depression can increase the overall risk for suicide among suicide attempters treated on psychiatric wards (Tidemalm et al., 2008). The time period close after a suicide attempt greatly increases the risk and, therefore, a focus on relevant

treatment, at least during the first 2 years after a suicide attempt, is warranted (Tidemalm et al., 2008). Substance abuse is also a major risk factor when it comes to the risk of suicide (Nordentoft et al., 2011).

Research has shown that the suicide method itself can be a risk factor for future suicide. With regard to suicide prediction, the method used in a previous suicide attempt is often the same one used in completed suicide attempts (Runeson et al., 2010). It is therefore of importance that patients who have committed violent suicide attempts such as hanging, using firearms or the use of gas, should be looked after with as much psychiatric treatment as possible (Runeson et al., 2010; Stenbacka & Jokinen, 2015). There may even possibly be a biological association between low serotonin levels and violent suicidal methods such as more medically damaging suicide attempts (Mann et al., 1996; Träskman-Bendz et al., 1992).

During a recent consensus meeting with 5 expert groups within the field of suicidology, the general conclusion was that a major obstacle to improvement in Suicidal Ideation/Suicidal Behavior (SI/SB) research continues to be the lack of agreement on specific classifications of suicide-related phenomena (Chappell et al., 2017).

1.1.1 Suicidal Behavior; Definitions and a Continuum of Behavioral Risks

In the Merriam-Websters Dictionary definition of suicide, the focus is on the act of ending one's life voluntarily and intentionally (https://www.merriam-webster.com/dictionary/suicide). The definition of suicide attempts becomes, however, more unclear in that the group of attempters is quite heterogeneous.

There has, however, been difficulties when it comes to accurately defining suicidal intent. In order to correctly identify patients who will commit suicide in the future, the measurement of suicidal intent has to be very accurate (Freedenthal, 2008).

1.1.1.1 Self-Harm

Self-harm is usually referred to in 2 different ways. Europe and Australia often use the term Deliberate Self Harm (DSH) where patients that commit self-harm can either have suicidal intent or not have such intent, but their behavior does not lead to a fatality (Muehlenkamp et al., 2012). Non-Suicidal Self-Injury (NSSI) is the more American and Canadian description of self-harm behavior of self-harm without suicidal intent (Muehlenkamp et al., 2012). DSH excludes self-poisoning (Kelly et al., 2008). A large study examining DSH behavior in the emergency room in Stockholm summarized the following high risk factors:

1)   having both a psychiatric contact as well as a previous episode of DSH,

2)   having suicide intent without a psychiatric contact and

3)   patients with an adult personality disorder without previous DSH but with a current psychiatric contact (Bilén et al., 2011).

1.1.1.2   Suicidal Ideation vs. Suicidal Plans vs. Suicide Attempt

In Sweden, one of the most common approaches to suicide risk assessment is for the doctor to use the Jan Beskow "suicidstegen" scale. Translated into English this would be either the "Suicide Step" or the "Suicide Ladder" Scale. This is a clinically intuitive scale starting with open questions regarding hopelessness and/or depressed mood, and continuing on to more specific areas of questioning such as suicidal ideation, suicidal plans, suicidal intent and attempted suicide.

Although suicidal thoughts can themselves lead towards completed suicide, it is much less common compared to the rate at which suicide plans and attempts ultimately lead to a completed suicide. During the year 2013 in Sweden, around 600 out of 10,000 adults in Sweden thought about suicide (Bremberg et al., 2015). Out of those 10,000 adults, 100 made a suicide attempt and 1.6 on average committed suicide (Bremberg et al., 2015).

It has been shown in many previous studies that attempting to take your own life is one of the most robust predictors of completed suicide (Suominen et al., 2004; Runeson et al., 2010). However, when it comes to suicide prediction after a recent suicide attempt, it has also been shown that the suicidal risk decreases over time. There is a study that shows that, after a self-poisoning attempt, the risk for suicide prevails during the entire adult lifetime (Suominen et al., 2004). In general, life expectancy is clearly reduced in patients who attempt suicide (Jokinen et al., 2018).

1.2   SUICIDE RISK ASSESSMENTS

A recent systematic review showed that suicide risk assessments were not supported by enough studies and that the diagnostic accuracy of the studied assessments was insufficient (Runeson et al., 2017). Partly for this reason, a meta-analysis from 2017 on suicidal thoughts and behaviors proposes that there is a need for a shift in focus over towards machine learning-based risk algorithms (Franklin et al., 2017). Let's therefore look a bit further into suicide risk assessments.

Aaron T. Beck developed the Suicide Intent Scale as a way to focus more on intent regarding the suicidal patient (Beck, Schuyler & Herman, 1974). He focused on both a subjective and more objective view of the intent to try to commit suicide (Beck, Schuyler & Herman, 1974). The same year Beck et al. also published another scale called the Hopelessness Scale (Beck, Weissman et al., 1974). His findings showed that depressed patients were highly pessimistic and that the accuracy of high suicide intent is more correlated with negative views of the future than it is with depression (Beck, Weissman et al., 1974). According to Dr. Freedenthal, the SIS was considered to be the dominant research instrument in assessing suicide intent in apparent attempts of suicide (Freedenthal, 2008) In this meta-analysis, the predictive validity for future suicide was reported in 5 out of 13 studies, while the predictive validity for future suicide attempts was not significant in most of the included studies (Freedenthal, 2008). The author

concluded that highly accurate measurements of suicidal intent are needed in order to identify potential proxies for suicide victims (Freedenthal, 2008).

One of the main problems with suicide risk prediction is that the more accurate the prediction is, the higher the number of false positive predictions (Fowler, 2012).

Suggesting that everyone with a suicidal thought is admitted to a hospital is unrealistic and therefore it is important that relevant suicide risk assessments are used for each specific patient. An advantage of the Columbia Suicide Severity Rating Scale (C-SSRS), is that, unlike the Suicide Intent Scale, it is not a prerequisite that the patient has committed a suicide attempt within 30 days of the assessment. The scale can therefore also be used on patients with suicidal ideation (Posner et al., 2011).

The Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) reported in 2015 that there was a lack of research regarding whether instruments enhanced the assessment of suicide risk (SBU, 2015).

According to Large et al., around 3% of patients considered to be high risk patients can be expected to kill themselves during the year after discharge (Large et al., 2011). However, around 60% of the patients who take their own lives are likely to be categorized as low risk ones (Large et al., 2011). Therefore, Large et al. conclude that putting patients into risk categories does not lower the amount of completed suicides after discharge (Large et al., 2011). Mulder et al. argue instead for focusing more on the patient and what their individual problems and circumstances are (Mulder et al., 2016).

The positive predictive value (PPV) in this context of predictive validity is defined as the probability that an individual with a positive test result is actually suicidal. Many studies have attempted to predict suicidal behavior by calculating the PPV (Brown et al., 2000; Beck et al., 1999). As mentioned above, Runeson et al. have shown in a recent systematic review article based on 21 studies regarding suicide prediction that none of the risk assessment instruments examined were accurate enough to be used to predict future suicide (Runeson et al., 2017).

1.3 VIOLENCE AND SUICIDE RISK

1.3.1 Childhood Trauma

It has been hypothesized that one important aspect of assessing suicide risk is whether or not the patient has been through any type of previous traumatic event, such as in childhood. Studies show that negative childhood experiences increase the risk for suicide attempts later on in life such as in adulthood. (Johnson et al., 2002; Dube et al., 2001). The negative experiences often lead to depressed affect and substance abuse which then appears to at least partially affect the suicide risk (Dube et al., 2001).

A patient's previous experienced trauma in general is often neglected because clinicians don't always ask the patient about experienced trauma. In a study of 77 women in Southern Sweden, it was concluded that it is important when meeting female patients to remember to ask routine questions about abuse experiences in that it isn't certain that the patients will inform this themselves (Örmon et al., 2016). Relevant guidelines to help abused women should be carried through (Örmon et al., 2016).

In a clinical literature review comprising the years 1988 to 1998, researchers found that adults who had experienced childhood physical and/or sexual abuse also had, in general, a larger amount of suicidal behavior, compared to those without that type of childhood abuse (Mina and Gallop, 1998). Furthermore, Ystgaard and colleagues have shown that there is a significant as well as independent association between sexual and physical behavior in childhood and later repetative suicidal behavior (Ystgaard et al., 2004).

1.3.2 Bullying

The seriousness and detrimental consequences of bullying cannot be overstated enough. It is not just a part of growing up, considering that the victims have a high risk for adult emotional disorders (Copeland et al., 2013). Both bullies and victims have an increased risk when it comes to thinking about or planning suicide (Copeland et al., 2013). One of the possible reasons why change has taken so long is that public assumptions differ considerably from research findings (Berger, 2007).

Findings have shown that there seems to be an elevated risk of suicidal thoughts and/or - attempts related to bullying behavior and cyberbullying (Klomek et al., 2010). There is an indication that bullying and peer victimization can lead to suicidality, depending on gender; there is, however, a need for more research with a focus on severe suicide attempts and completed suicides (Klomek et al., 2010).

An important focus in attempting to decrease childhood and adolescent suicide is looking at childhood bullying. Research has shown important gender differences, such as, with boys: recurrent bullying and victimization is associated with both suicide attempts and completed suicides, but only in relation to conduct and depression symptoms (Klomek et al., 2009). Even when controlling for depression symptoms and conduct, girls who were frequently victims were associated more often with future suicide attempts and completed suicides (Klomek et al., 2009).

1.3.3 Impulsive Aggression

Aggression and violent behavior are significant risk factors for later suicidal behavior. Impulsive and aggressive behaviors seem to have an underlying impact on suicidal risk factors in major depressive disorders (Dumais et al., 2005). In a long-term study of 167 Swedish offenders involved in homicide, followed up for twenty-six years, over 17% of these homicide offenders ended up committing suicide (Jokinen et al., 2009). It has also been shown in a large

Swedish Registry study that self-harm is associated with an heightened risk for conviction for violent crimes in both men and women in a large Swedish registry study (Sahlin et al., 2017).

According to a systematic review of 123 studies, the majority of case-control studies found higher levels of aggression when comparing self-harming populations with controls (O'Donnell et al., 2015). The conclusion was that there was a possible association between aggression and self-harm (O'Donnell et al., 2015), thus indicating a potential connection between external and internal violence.

1.3.4 Violence Risk Assessment in Suicidal Patients

Similarly to suicide risk assessments, violence risk assessments have lacked research evidence in order to help clinicians in their risk predictions. Some researchers focus more on a dynamic risk as apposed to solely focusing on the more static risk (Douglas & Skeem, 2005). The proposed dynamic risk factors in the Douglas & Skeem article are quite similar to suicide risk factors.

Most violence risk assessments involves threats of external violence. However, there have been indications that temperament profiles of both violence offenders and suicide attempters were quite similar, showing high trait anxiety and problems with socialization (Engström et al., 1999). Suicide attempts can in many ways resemble internal violence and therefore violence risk assessments have been used to characterize and assess the common endophenotype: impulsive aggression.

Some of the more well-known scales assessing different aspects of violence and also used in patients with suicidal behaviors are the Buss-Durkee Hostility Inventory (BDHI) as well as the Brown-Goodwin Lifetime History of Aggression interview. (Buss and Durkee, 1957; Brown et al., 1979). In 1979, Brown et al. reported that among 26 males in the military with difficulties fitting into military life as well as certain personality disorders both aggressive and suicidal behaviors negatively correlated with CSF 5-hydroxyindoleacetic acid (5-HIAA) levels (Brown et al., 1979).

Prisoners are often included in research assessing the risk of violence. In 2011, Mandelli et al. used different violence risk assessments such as the Brown-Goodwin Lifetime History of Aggression Interview and the Buss-Durkee Hostility Inventory in order to interview 1553 prisoners (Mandelli et al., 2011). Their research showed that trauma in childhood as well as having aggressive traits were risk factors for suicidal behavior (Mandelli et al., 2011).

Being exposed to community violence seems to be associated in an indirect manner with suicidal-thoughts and -attempts in adolescents (Lambert et al., 2008). It is therefore important to decrease exposure to violence in the community in order to reduce the risk of suicide in adolescence (Lambert et al., 2008).

Having discussed exposure to violence, research has also shown that violent offending along with being victimized is associated with suicide (Stenbacka et al., 2012). Therefore, decreasing violent behavior could have an impact on overall suicide rates, including the actual offender in question (Stenbacka et al., 2012).

1.4 GENDER AS A RISKFACTOR IN SUICIDE

One of the main gender differences when it comes to suicidology is that men more often commit suicide (around 3 times as frequent) whereas women, in a similar ratio, more often make suicide attempts (Diekstra and Gulbinat, 1993). Most experts would agree that gender differences in suicide are not solely a biological dilemma. Qin et al. have shown that such factors such as retirement, unemployment, and being single are important male risk factors whereas females had no significant risk factor except for mental illness, as well as the fact that having a child under 2 years of age reduced the risk of suicide (Qin et al., 2000).

This could point towards socioeconomic factors affecting men more than women when it comes to suicide. Hawton takes this further and wonders whether two different, gender-based, suicidal risk assessments are called for (Hawton, 2000).

Interestingly, Chinese researchers also conclude that a gender specific approach would be more optimal because of, for example, social factors affecting more female attempters (Sun and Zhang, 2017). These geographical differences could possibly explain why China is one of the few countries in the world where more women than men commit suicide compared to men (Sun and Zhang, 2017).

Other differences between the genders that most experts agree on are the suicidal methods chosen, a violent method being "more masculine." This is a complex question, however, in that some researchers say that this theory is only partially supported (Kposowa and McElvain, 2006) and that there are other explanatory factors.

1.4.1 Cultural Explanations for Gender Differences in Suicide?

If gender differences regarding completed suicide could be explained purely by physiological differences between men and women, there would be fairly similar gender differences worldwide, which is not the case.

Hegemony is a theory partially explaining why it is that men commit 4 out of 5 completed suicides in Australia (River, 2014). This could also be the case in many other similar countries around the world. River describes two male case studies where stress in masculine projects were associated with suicidal behavior (River, 2014). Suicide became a symbolic way of "doing masculinity" when the men felt that there was nothing else to do (River, 2014).

Consideration of the fact that gender differences regarding depression are quite similar in many different countries and cultures (starting in early adolescence and decreasing in older patients)

does lead one to believe that neurobiological correlates, such as hormones, could be part of the explanation (Sprock and Yoder, 1997).

1.4.2 Testosterone

Testosterone is a hormone mainly produced by the testes as well as the adrenal cortex (smaller amounts) and in the ovaries (Brittanica.com, 2017).

Research has shown that, among other things, testosterone regulates sex drive, the distribution of fat, and muscle strength, as well as the production of sperm (Wein, 2015). With age, there is also less production of testosterone which also means there is less estradiol (Wein, 2015).

A meta-analysis from 2001 based on 45 studies showed that there was a slightly positive relationship between testosterone and aggression (Book et al., 2001). Other more recent studies regarding testosterone and aggression have shown a correlation, but specifically in males showing high trait dominance or little trait self-control (Carré et al., 2016).

1.4.2.1 Testosterone and Completed Suicide

There is, surprisingly enough, little research regarding testosterone and suicidal behaviour. Considering that it is a well-known fact that the suicide rate is much higher for men than it is for women in almost all Western countries, one would think that biological explanations, such as testosterone, would be rigorously examined. Men have much higher concentrations of testosterone, compared to women and there are multiple researchers who have proposed that this could contribute to the fact that men commit suicide more often (Courtet, 2016).

One of the most active researchers in the area of testosterone/suicide research area is Prof. Leo Sher. His group has shown that there is an association between mood/behavior and testosterone concluding that testosterone levels might have a relationship with both bipolar symptoms and suicidal behavior (Sher et al., 2012). Prof. Sher has also reported that testosterone levels possibly predict female suicidal behavior in bipolar disorder (Sher et al., 2014).

A research group demonstrated in a small group of PTSD patients who had attempted suicide, significantly higher levels of the hormones DHEA and estradiol, while no significant differences were observed in the levels of testosterone (Butterfield et al., 2005). One study indicated variation in both age and circadian rhythm and subsequently showed no support for testosterone as a biological factor in suicidal behavior (Perez-Rodriguez et al., 2010). That being said, this research group also recommended more research on testosterone and that there should be as small a gap as possible between the suicide attempt and blood extraction, as well as acknowledging factors such as BMI, sleep issues and physical activity (Perez-Rodriguez et al., 2010).

1.4.2.2 Testosterone/Cortisol Ratio and Aggression/Impulsivity

There seems to be an inhibitory effect both directly between cortisol and testosterone as well as an indirect bilateral inhibitory effect between the HPA and HPG axes at different levels (Terburg et al., 2009). This could partly explain why large amounts of testosterone and small amounts of cortisol have been associated alongside social aggression (Montoya et al., 2012). This hormonal combination seems to be most violent when combined with social aggression (Terburg et al., 2009).

1.4.2.3 Testosterone – an Antidepressant Effect?

In a systematic review and meta-analysis it was shown that therapy with testosterone treatment may have an effect similar to antidepressants in subgroups of patients with depression, particularly those patients with hypogonadism or HIV/AIDS as well as the elderly (Zarrouf et al., 2009). Considering it has been shown that HIV/AIDS patients have a 3.84 adjusted incidence rate ratio to commit suicide compared to non-HIV/AIDS patients (Jia et al., 2012), testosterone could hypothetically also be involved in this etiology.

2 AIMS

Suicide risk assessments present a challenge to both clinicians and scientists since distal and proximal risk factors, psychiatric illness and co-morbidities play a role when assessing suicide risk in the short and long term. Few studies have investigated structured suicide risk assessment scales in the detection of suicide risk in clinical high-risk cohorts of suicide attempters with a long-term follow-up. Furthermore, the neurobiological underpinnings of well-documented sex differences in suicidal behavior are not fully understood. The overall aim of the studies included in this thesis was to fill these knowledge gaps by:

(A)   Studying the predictive power of three validated clinical instruments assessing suicidal intent, interpersonal violence, and reversibility of the suicide attempt method in order to detect patients with a suicide risk and thus to add to evidence of their usefulness in clinical suicide risk assessments after attempted suicide.

(B)   Studying the main male sex hormone testosterone in the CSF and plasma in suicide attempters and healthy volunteers. Similarly, this will also be tested in suicide victims and surviving attempters.

Four studies were designed and performed to answer the following:

(1)   Do suicide attempters with high scores on the Suicide Intent Scale at the index attempt have an elevated risk of committing suicide compared to suicide attempters reporting lower intent during a follow-up? What items and factors in the Suicide Intent Scale are of predictive value in detecting patients at risk?

(2)   Does the combined use of the Suicide Intent Scale and the Karolinska Interpersonal Violence Scale give a better suicide risk prediction than use of only one of the two clinical rating scales?

(3)   Does the assessment of the reversibility of the suicide attempt and the probability of interruption while attempting suicide, measured with the Freeman scales, predict future suicide in a large clinical group of suicide attempters followed up during 6-23 years?

(4)   Are CSF and plasma testosterone levels different when comparing suicide attempters and controls?

Extended background to each study, including specific aims and hypotheses, are presented below.

2.1 STUDY 1

Past clinical follow-up studies assessing suicide intent in relation to suicide risk have reported mixed result with less than half of the studies showing a positive predictive value of suicide intent scores and suicide. Very few studies have compared the underlying factors of the SIS or individual items in suicide prediction. In this study on suicide attempters, we hypothesized that high scores measured with the Suicide Intent Scale may predict future completed suicide after an attempted suicide. The aim of Study 1 was to determine the predictive value of the SIS for future suicide in patients with a high suicide risk, for example, patients admitted to a psychiatric hospital directly after a suicide attempt. The secondary aim was to determine the predictive value of the SIS factors and SIS items to predict future suicide in suicide attempters.

2.2 STUDY 2

Informed by the results in Study 1 showing mean SIS scores distinguishing between committers of suicide and survivors, although with quite a low specificity, we aimed to determine if the combined use of 2 structured clinical instruments, compared with the use of only 1 clinical rating scale (SIS), would offer a better prediction in assessing suicide risk. We hypothesized that a combined screening using largely independent variables that disclose both traits and state-dependent risks would increase the accuracy in predicting suicide risk. The aim was to investigate whether combining 2 structured suicide risk assessment scales (SIS and KIVS) with some evidence of suicide prediction, would provide better prediction rather than using only 1 of the scales.

2.3 STUDY 3

This study involves the Freeman Scale which essentially includes 2 items: the reversibility of a suicide attempt and the probability of interruption of a suicide attempt. The aim of this study on a large number of high risk suicide attempters was to determine whether the Freeman Scale predicts future suicide when followed between 4 and 21 years. Our aim is also to calculate a Receiver Operating Characteristic Curve (ROC Curve) in order to find the threshold that best predicts suicide. We also wanted to use a false discovery rate approach because this can also be clinically useful.

2.4 STUDY 4

In order to further investigate whether biological correlates could at least partially explain the gender differences when it comes to suicide, our primary aim in Study 4 was to investigate testosterone levels in suicide attempters and in healthy volunteers in plasma and CSF. We also examined testosterone levels in the completed suicide group in comparison with those in the surviving suicide attempter group. Impulsion and aggression have previously been shown previously to partly explain an increase in suicide risk. We therefore investigated association between both aggression and impulsivity and the testosterone/cortisol ratio. Data was analyzed separately between the genders.

3 METHODS

3.1 SETTINGS

Two hundred and nine suicide attempters (3 clinical cohorts, see Figure 1) having their clinical follow-up after a recent suicide attempt at the Psychiatric Department of the Karolinska University Hospital between the years 1988 and 2005 were asked to participate in three studies on psychological and biological risk factors for suicidal behavior. The Regional Ethical Review Board in Sweden (Stockholm) approved the study and the participants permitted the written informed consent to take part in the study (Dnrs: 88-216; 91-96; 93-211; 00-194, 2010/3:4).

The inclusion criteria involved: a suicide attempt within one month of the evaluation, being at least 18 years old and ability to communicate verbally and in the Swedish written language. The following patients were excluded: mental retardation, schizophrenia spectrum psychosis, dementia, and i.v. drug abuse. The definition of suicide attempt used in this study was: any nonfatal behavior that was self-injurious with some intent to have a lethal outcome.
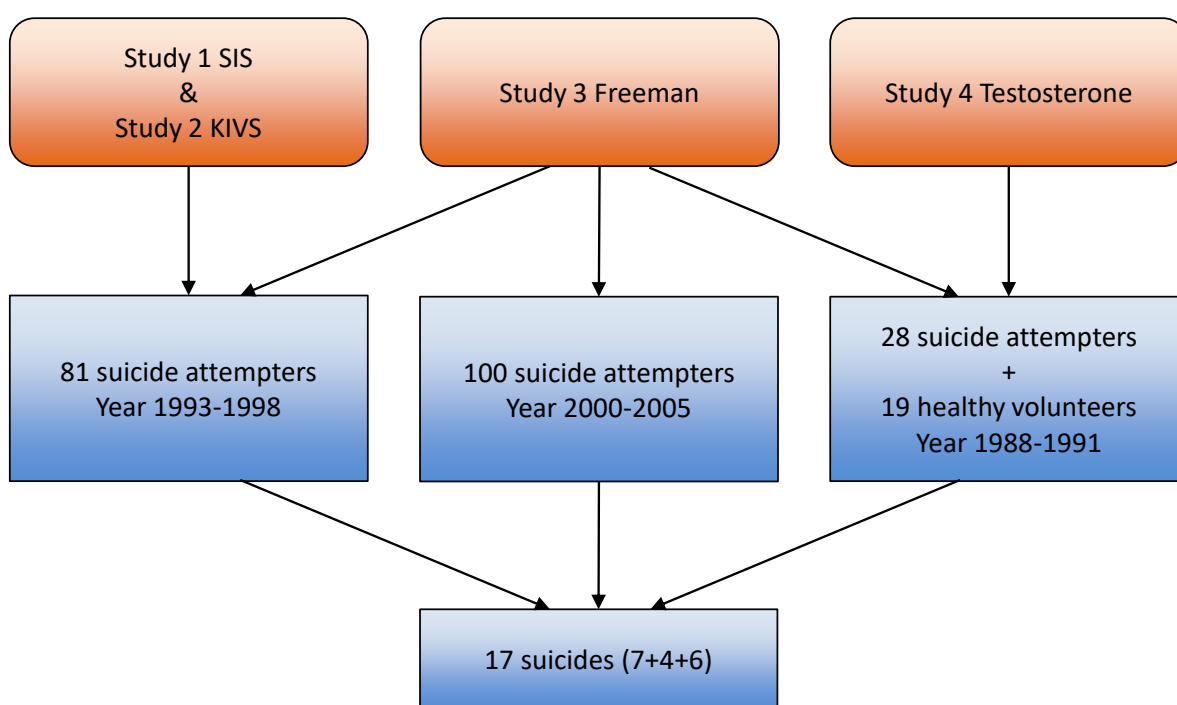

Figure 1. Clinical cohorts included in the thesis.

3.2 PATIENTS

3.2.1 Study 1 and 2

81 suicide attempters, between 1993 and 1998 (35 men & 46 women, mean age = 37 years, SD = 12, range = 18-69 years) were included in the cohort from the psychiatric emergency department and inpatient wards at the Karolinska University Hospital, Stockholm, Sweden. A trained psychiatrist conducted the interviews of the participants using the SCID I Research Version Interview to (if relevant) establish a diagnosis in agreement with the DSM-III. The SCID II Interview was chosen in order to assess whether the patients had Axis II Diagnoses. All clinical interviews and ratings were done within one month of the suicide attempt in accordance with SIS inclusion criteria. Almost all (94%) of the suicide attempters were diagnosed with at least one ongoing Axis I Psychiatric Diagnosis; see Figure 2.
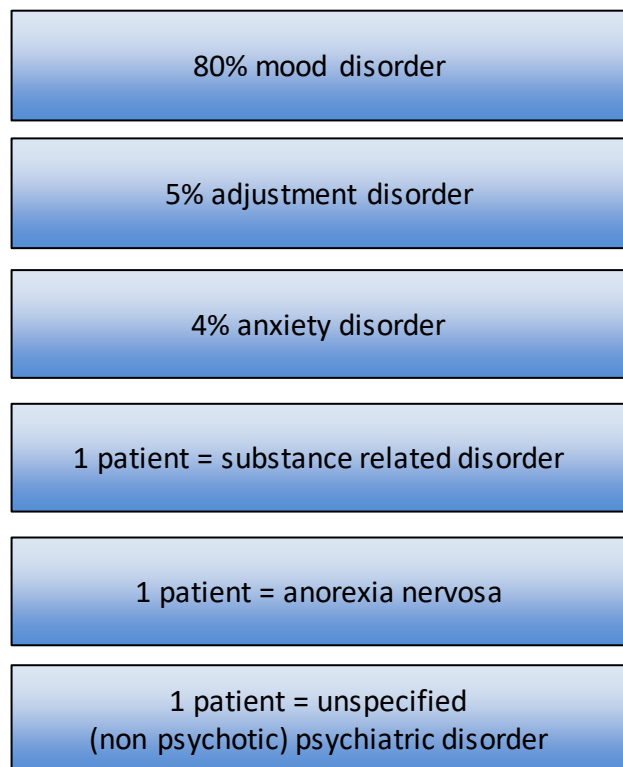
80% mood disorder

5% adjustment disorder

4% anxiety disorder

1 patient = substance related disorder

1 patient = anorexia nervosa

1 patient = unspecified
(non psychotic) psychiatric disorder

Figure 2. Axis I diagnoses.

Figure 3 shows clinical characteristics of suicide attempters with a focus on comorbidity and clinical risk factors.
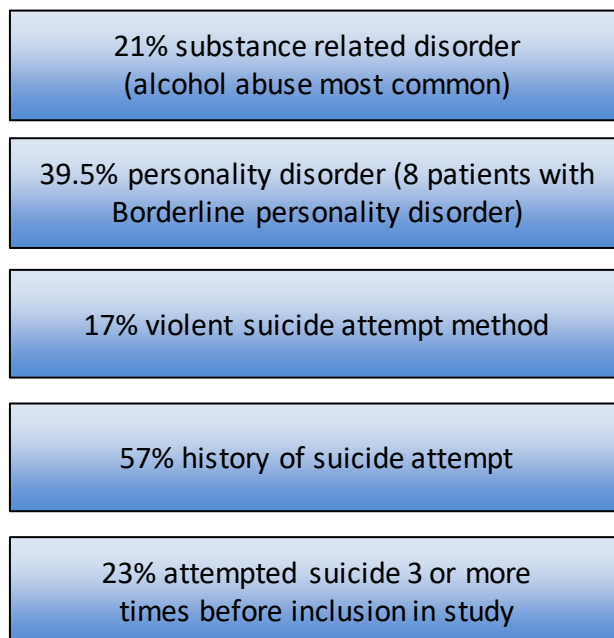

Figure 3. Factors increasing suicidal risk.

3.2.2 Study 3

A cohort of 209 suicide attempters, 86 men and 123 women, included in the three studies between the years 1988 and 2005. The mean age of suicide attempters was 36.4 years, (SD = 12.7, range 18-69). Out of 209 patients, 86 were men (mean age 38.3 years, SD = 12.7, range 18-69), and 123 women (mean age: 35.2 years, SD = 12.6, range 18-68).

Ninety percent (n = 189) of the study patients had at least 1 current psychiatric diagnosis (Axis I). Seventy-two percent (n = 150) of the study patients fulfilled the criteria for a mood disorder. Thirty-eight percent (n = 79) of the patients fulfilled the personality disorder (PD) criteria and 21% (n = 44) fulfilled the criteria for a comorbid substance related disorder (mainly alcohol).

3.2.3 Study 4

Twenty-eight suicide attempters without medications: 18 men (mean age: 44 years, SD = 14.6; range 23-65) and 10 women (mean age: 41 years, SD = 12.3, range 26-66) were recruited between 1988-1991.

The psychiatrists who conducted the interviews had had similar training and used instruments similar to those available in the previous studies. Ninety-three percent of patients had at least 1 ongoing Axis I or Axis II Psychiatric Diagnosis. Fifty percent of the patients (n = 14), fulfilled the criteria for mood disorders, 4 patients (14%) had an adjustment or anxiety disorder, 32% of the patients had a substance-related disorder of mainly alcohol, (n = 9), either as a primary Axis I diagnosis or as a comorbid diagnosis. Two thirds of the patients fulfilled the criteria for a PD and one patient had an Organic Personality Syndrome Diagnosis.

Nineteen healthy volunteers (7 women and 12 men) with a mean age of 30 years old (age range, 23-48) were involved in the study during the same time period and assessed by a trained psychiatrist applying the SCID I Interview to exclude any previous or ongoing psychiatric or medical conditions.

3.3 ASSESMENT

A comprehensive research protocol with multiple ratings of behavior and personality dimensions as well as the suicide risk assessment scales SIS, KIVS, and Freeman, were administered. These cohorts are clearly defined with a long follow up time.

3.3.1 Suicide Intent Scale (SIS)

The SIS is a scale developed by Dr. A.T. Beck to assess the intent to die in a patient during a recent suicide attempt (Beck, Schuyler & Herman, 1974).

The Suicide Intent Scale is an instrument using 15 items created to assess the factual aspects of the suicide attempt. These include the patients' feelings and thoughts and in general what was happening during the suicide attempt (Beck, Schuyler & Herman, 1974).

Roughly half of the items in the scale are considered to be objective (for example, whether a suicide note was left behind) whereas the other half is considered more subjective (for example expectations and attitude toward living/dying).

The scale is intended for patients who have committed a suicide attempt within 30 days of the evaluation. The scale contains even supplementary questions not included in the sum score. We used one of these supplementary items (nr 18) in the SIS to determine earlier suicide attempts in Study 2: (1) none, (2) one or two, and (3) three or more prior suicide attempts.

3.3.1.1   Factors in the Suicide Intent Scale

Previous studies on the factorial structure of the Suicide Intent Scale have identified 2-4 factors (Antretter et al., 2008). Mieczkowski et al. performed a factor analysis of the SIS which resulted in a two-factor solution. One factor, which the authors named the Lethal Intent Factor consisted of items with a focus on subjectivity towards Intent, while the Planning Factor consisted of items with a focus on objectivity and planning (Mieczkowski et al., 1993), once again leading back to an almost dichotomous evaluation of the subjective/objective SIS.

Misson et al. created a four-factor model of the Suicide Intent Scale (Conception, Preparation, Precautions and Communication) (Misson et al., 2010). One could also identify the Conception factor as a "subjective" factor since it is the same as Mieczkowski's Lethal intent factor (SIS items 9-14).

3.3.2 Karolinska Interpersonal Violence Scale

A clinical rating scale, the Karolinska Interpersonal Violence Scale (KIVS), measures both the exposure to violence as well as expressed violent behavior as a child (6-14 years of age) and as an older child or adult (15 years of age or older) (Jokinen et al., 2010).

The KIVS has been validated with 4 different Violence Risk Scales:

1) The BDHI as explained earlier (Buss and Durkee, 1957);

2) The "Urge to Act Out Hostility" Subscale from the Hostility and Direction of Hostility Questionnaire (HDHQ) (Arrindell et al., 1984);

3) The "Early Experience Questionnaire" (EEQ) (Fishbein et al., 1989);

4) The Childhood Trauma Questionnaire - Short Form (CTQ-SF) (Bernstein et al., 2003) was used to specifically validate levels of exposure to interpersonal violence in childhood (Chatzittofis et al., 2017).

The scale has been used as a structured interview and as a self-rating scale. The 4 subscales are scored 0-5. The KIVS has in previous articles been shown to have a strong inter-rater reliability, as well as high validity (Jokinen et al., 2010) and has been tested in other suicide research studies (Khemiri et al., 2016; Haglund et al., 2016). The scale is presented in Table 1.

The items of the KIVS are short statements about violent behavior. The clinician has an interview with the subject and then uses the highest score if one or more of the descriptions apply.

Table 1. Karolinska Interpersonal Violence Scale (KIVS).

The steps of this scale are defined by short statements about violent behavior. On the basis of an interview with the subject, use the highest score where one or more of the statements apply.

A. Used violence.

As a child (6–14 years)

0   No violence.
1   Occasional fights, but no cause for alarm among grown-ups in school or in the family.
2   Fighter. Been in fights a lot.
3   Often started fights. Hit a comrade who had been bullied. Continued hitting when the other had surrendered.
4   Initiated bullying. Often hit other children, with fist or object.
5   Caused serious physical injury. Violent toward adult(s). Violent behavior that led to intervention by social welfare authorities.

As an adult (15 years or older)

0   No violence.
1   Slapped or spanked children on occasion. Shoved or shook partner or another adult.
2   Occasionally smacked partner or child. Fought when drunk.
3   Assaulted partner drunk or sober. Repeated corporal punishment of child. Frequent fighting when drunk. Hit someone when sober.
4   Instance of violent sexual abuse. Repeated battering/physical abuse of child or partner. Assaulted/attacked other persons frequently, drunk or sober.
5   Killed or caused severe bodily harm. Repeated instances of violent sexual abuse. Convicted of crime of violence.

B. Victim of violence.

Childhood (6–14 years)

0   No violence.
1   Occasional slaps. Fights in school, of no great significance.
2   Bullied occasionally for short period(s). Occasionally exposed to corporal punishment.
3   Often bullied. Frequently exposed to corporal punishment. Beaten by drunken parent.
4   Bullied throughout childhood. Battered/beaten up by schoolmates. Regularly beaten by parent or another adult. Beaten with objects. Sexually abused.
5   Repeated exposure to violence at home or in school that resulted at least once in serious bodily harm. Repeated sexual abuse, or sexual abuse that resulted in bodily harm.

Adulthood (15 years or older)

0   No violence.
1   Threatened or subjected to a low level of violence on at least one occasion.
2   Beaten by partner on occasion. Victim of purse snatching. Threatened with object.
3   Threatened with a weapon. Robbed. Beaten by someone other than partner. Frequently beaten by partner.
4   Raped. Battered.
5   Repeatedly raped. Repeatedly battered. Severely battered, resulting in serious bodily harm.

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[a]© Copyright 2010, Jussi Jokinen, MD, PhD. The Swedish version of the Karolinska Interpersonal Violence Scale (KIVS) was translated into English by an authorized bilingual translator; the English version of the KIVS was then back-translated into Swedish and the equivalence was checked by the original authors. Copies can be obtained from the author.

3.3.3 The Karolinska Scales of Personality (KSP)

The Karolinska Scale of Personality (KSP) is a self-rating questionnaire designed to assess traits of personality in neurobiological research (Schalling et al., 1987). The scale contains 135 total items grouped into 15 subscales. Each assertion corresponds to using a 4-point Likert-type Scale.

According to Ortet-Fabregat et al., there are four latent traits of the KSP: aggressive nonconformity, negative emotionality, impulsive non-socialized sensation-seeking, along with social withdrawal (Ortet-Fabregat et al., 2002). In Study 4, we used two factors to determine aggression and impulsivity: Aggressiveness (Indirect Aggression, Verbal Aggression, Irritability, Suspicion and Guilt) and Impulsivity (Impulsiveness and Monotony Avoidance) (Gustavsson, 1997).

The KSP has been revised since the studies in this thesis were performed and is now called The Swedish Universities Scales of Personality (SSP) (Gustavsson et al., 2000). The revised version includes 91 items divided into 13 scales, 44 less items compared to the KSP (Gustavsson et al., 2000).

3.3.4 The Freeman Scale

The Freeman scale involves two items, each item rating between 1 and 5 points. The minimum number of points is 2 and the maximum number of points is 10. The first item is Reversibility, signifying how reversible the suicide attempt was. The second item is Interruption Probability, signifying how isolated the suicide attempter was and what the chances of getting help were. Freeman et al. published the scale with a large cohort of suicide attempters (Freeman et al., 1974) showing a high degree of discriminating validity. A previous study by Rajalin et al. showed a trend toward a higher Freeman score in patients with suicide in the family (Rajalin et al., 2013).

3.3.5 Beck's Hopelessness Scale

The Beck Hopelessness Scale is a well-known true/false instrument including 20 items with statements of pessimistic beliefs about the future and oneself (Beck, Weissman et al., 1974).

3.4 CSF AND PLASMA TESTOSTERONE ASSAYS

Shortly after the suicide attempt, lumbar punctures were done using a standard protocol (mean = 8.6 days, range = 2-17 days). Between 08:00 h and 09:00 h after fasting in bed since midnight, 12 milliliters of CSF were drawn. CSF was at once centrifuged and aliquoted in 6 two-ml samples and stored at -80°C. Blood samples (10 ml) were gathered in tubes containing heparin (10 IU ml-l) and centrifuged 15 minutes before lumbar puncture. The plasma was extracted and frozen at -80°C. All biochemical analyses were carried out at the same time using the clinical protocol. The concentrations of cortisol and testosterone sulfate in CSF and plasma were determined by radioimmunoassay (RIA) with antiserum for testosterone obtained from

the WHO Reagent Program (Hedman et al., 1989). There was 100% cross-reactivity of the antiserum for testosterone with the sulpho-conjugated steroid.

3.5 MORTALITY

We have used the unique Swedish personal identification number to connect patients in the study population with the Cause of Death Register, both managed by the Swedish National Board of Health and Welfare (www.socialstyrelsen.se). Suicides were confirmed from the death certificates.

During Study 2, the cause of death investigation continued until April, 2013, and seven suicides were confirmed from the death certificates. Seventeen suicides were confirmed from the death certificates in Study 3 and 6 suicides in Study 4. Please see a summary represented in Figure 1.

3.6 STATISTICAL ANALYSIS

3.6.1 Study 1

A description of the population was given by using the median, the mean, and the range for quantitative variables. To test whether our data came from a population that was normally distributed, we used the Shapiro-Wilk test. T-test: one tailed statistics were applied for between-group comparisons, i.e., between suicide victims and survivors to see, once again, if the data were normally distributed. Using non-parametric statistics, the Kruskal-Wallis test was used in order to see whether the data were skewed in the between-group comparisons. In Paper 2, a nonparametric Wilcoxon test was used in continuous variables for comparability between groups as well as a Fisher's exact test (2-sided) in specific SIS and KIVS comparisons.

In order to find optimal cut-off measurements for suicide prediction, an ad hoc Receiver-Operating Characteristic (ROC) Curve was created for the scales used in the studies (SIS, the SIS factors, the KIVS, and the Freeman scales). The areas under the curves (AUCs), calculated using the ROC curves, symbolized the diagnostic performance of the scales. The differences in the AUCs were determined in line with the methods of Hanley and McNeil (Hanley and McNeil, 1983). The cut-off level that gave the best sensitivity (ratio of suicides correctly identified) and specificity (ratio of survivors correctly identified) was applied. Pearson Chi-square and Fisher's exact test were chosen for cross-tabulations of categorical variables.

Statistical investigations in study 1, 3 and 4 were calculated using JMP Software, SAS Institute Inc., Cary, NC, USA. The p value was set at <0.05 for Study 1+3. Study 3 used JMP VI and study 4 used JMP 9.

3.6.2 Study 2

Since the same cohort was used in Study 2 as in Study 1, please see additional information in paragraph 3.6.1. We defined a positive result of the combined tests, of SIS and KIVS

(equivalent to high suicide risk) as when both instruments had scores above the thresholds established from ROC curves. Tests of non-parametric or parametric correlations were carried out using Spearman's rho or Pearson's r. A logistic regression analysis was performed using SIS and KIVS scores as predictors of suicide. Confidence intervals for the AUCs in Study 2 were determined using the SPSS statistical software package (IBM, SPSS TM, version 22).

3.6.3 Study 3

The patient population was described using such characteristics as the median, the mean, and range for quantitative variables. For data involving a normal distribution, parametric statistics (t-test) were applied for between-group comparisons (survivors vs. suicide victims). For skewed data, nonparametric statistics (Kruskal Wallis test) in continuous variables were used for comparisons between groups. To see whether Freeman total scores and gender were predictors of suicide, a standard logistic regression analysis was done.

As partly described under item 3.6.1 (Study 1), ROC curves were created for both the total Freeman scale score and the 2 subscales: Reversibility and Probability of Interruption probability. The ROC Area Under the Curves (AUCs) were measured. The methods of Hanley & McNeil (Hanley and McNeil, 1983) were once again used to calculate the differences in the AUCs. Optimal cut-off points were measured as under item 3.6.1. The positive predictive value (PPV) and the False Discovery Rate (FDR) were determined. Fisher's exact test and Pearson Chi-square were used as in item 3.6.1.

3.6.4 Study 4

In order to determine the skewness and shape of the distribution, the Shapiro-Wilk test was used. Regarding group differences, the Wilcoxon test or Anova was used in continuous variables. Men and women were assessed separately.

Male patients and healthy male volunteers were age-matched since the patients were older than the volunteers and testosterone measurements declined steadily in male patients because of their age.

In order to find out whether CSF and/or plasma testosterone measurements were predictors of suicide in this study, standard logistic regression analyses were applied, adjusted for age and gender. A multiple linear regression model was chosen to test a dual hormone hypothesis involving aggression of the impulsive type by examining interaction effects (Solberger and Ehlert, 2016).

Similarly to the studies mentioned above, tests of correlations (non-parametric or parametric) were executed using Spearman's rho or Pearson's r. A post-hoc power analysis was calculated using the F-tests linear multiple regression with medium effect sizes (0.15) and large effect sizes (0.35). This gave a power of 0.8, an alpha at 0.05 and 3 predictors with a complete sample size of 77 and 36, respectively (Faul et al., 2009). These calculations showed that, considering

our smaller study numbers, we would only be able to identify large effect sizes. The alpha was set at 0.05. Cohen's D (Cohen, 1992) was used to calculate effect sizes.

3.7   ETHICAL REFLECTIONS

The following study protocols (Dnr 88-216, Dnr 91-96, Dnr 93-211, Dnr 00- 194, and Dnr 2010/3:4) were all approved by the Regional Ethical Review Board located in Stockholm, Sweden. Patients with a high risk of committing suicide are, unfortunately, quite often excluded from research studies. We find it of ethical importance to try to understand suicidal patients from different aspects (both psychometrically and at a biomarker level) in order to increase suicide prevention. All patients also gave their written informed consent.

Although certain patients in Study 4 experienced a lumbar puncture which can be painful in certain situations, we find that the overall advantages of gaining knowledge about biomarkers in the cerebral spinal fluid exceed the disadvantages for the patients. The risk for post-spinal headache for these patients was estimated to be around 10%.

It is possible that certain patients will feel that they have contributed to the field of suicide research and get a certain form of satisfaction in that respect, not to mention helping other future patients in similar situations. The results from multiple psychological examinations were made available to the clinicians who were responsible for the patients.

4 RESULTS

4.1 STUDIES 1 & 2

4.1.1 Suicide Intent Scale

Fourteen patients enrolled between 1993 and 1998 died during the follow-up period up to April 2013. 7 suicides (8.6%) occurred during the follow- up period: three women (6.5%) and four men (11.4%). The percentage of patients with suicide as the cause of death in the cohort was therefore 50% (7/14).

Normal distribution of the SIS scores, but not regarding SIS factors. The mean SIS scores were higher among patients who later committed suicide (mean + SD) (20.1 $\pm$ 3.2) compared to survivors (15.7 $\pm$ 5.8) (n = 80, t ratio = 1.98, p = 0.026, t test, one-tailed); Figure 4.
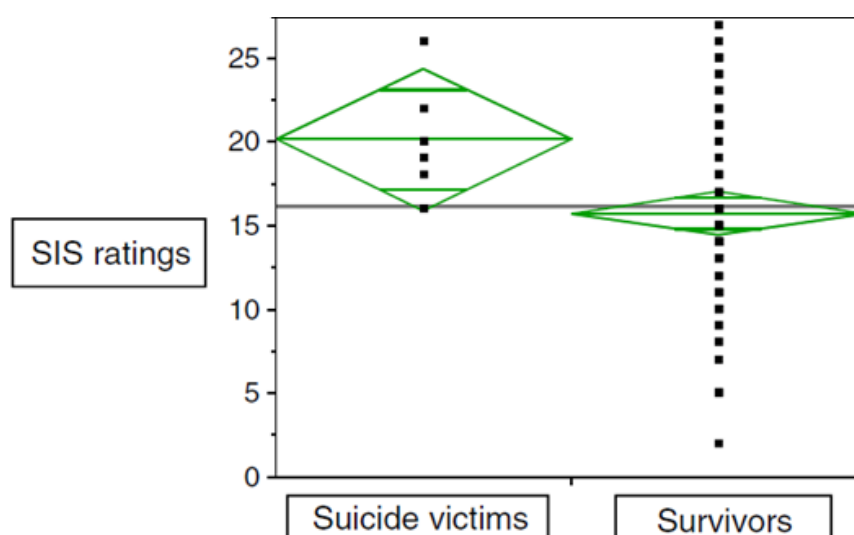

Figure 4. Suicide Intent Scores in suicide victims and in survivors.

We also analyzed the ratings of SIS factors in suicide victims and survivors however it was the planning subscale (the more objective subscale) that exclusively reached statistical significance.

The four items (4, 7, 12 and 13) of the SIS scale were different in survivors compared with suicide victims, being under the level of significance, p < 0.1, and were combined and used to test a brief version of the SIS in suicide predictions. An optimal cut-off of 6 gave a specificity of 59% and a sensitivity of 100%. The PPV was 19% and the Area Under the Curve was 0.82.

Table 2. The ratings of suicide intent and interpersonal violence in suicide victims and survivors.

Rating	Suicide victims				Survivors				
	Mean	Median	SD	Range	Mean	Median	SD	Range	Statistic
SIS	20.1	20	3.2	16-26	15.7	15	5.8	0-27	t ratio=2.0 p=0.026
SIS planning	10.1	10	2.5	7-15	7.3	7	3.8	0-15	Z=2.0 p<0.045
KIVS total	9.5	9	3.1	6-14	6.5	6	3.4	0-15	t ratio=2.1 p=0.018
Expressed violent behavior during childhood (6-14 years)	1	1	0.9	0-2	0.8	1	0.8	0-5	Z=0.8 p<0.44
Expressed violent behavior as adult (>15 years)	2.5	2.5	1.0	0-4	1.4	2	1.1	0-5	Z=2.3 p<0.023
Exposure to violence during childhood (6-14 years)	3.2	3.5	1.0	2-4	2.2	2	1.3	0-5	Z=1.8 p<0.073
Exposure to violence as adult (>15 years)	2.8	3	1.0	1-4	2.1	2	1.4	0-5	Z=1.3 p<0.19

4.1.2 Combining SIS with Assessment of Interpersonal Violence

KIVS and SIS total scores were notably higher in suicide victims as opposed to survivors, as can be seen in Table 2. There was missing KIVS data that involved 1 suicide victim.

There were no significant correlations between the SIS and the KIVS and the SIS planning subscale. Figure 5 shows KIVS and SIS total scores for suicide victims and suicide attempters that survived.
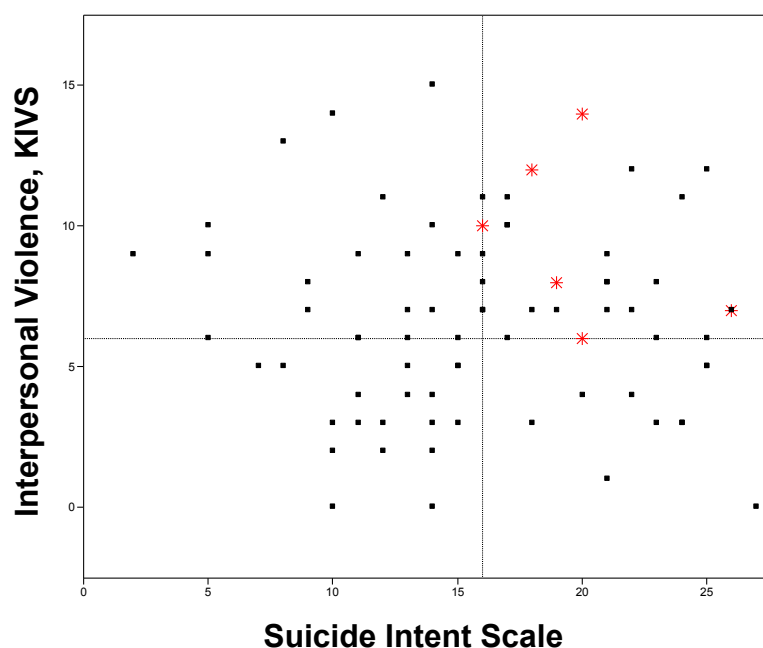

Figure 5. Correlation between SIS and KIVS total scores. *=completed suicides, dotted lines=cut-offs from ROC; SIS cut-off=16. KIVS cut-off=6.

4.1.3 Repeated Suicide Attempts

Having reported prior suicide attempts resulted in higher KIVS total scores in suicide attempters vs. those suicide attempters without previous suicide attempts at the beginning of the study (significant difference) (Z = -2.8, p = 0.0044).

4.1.4 Receiver-Operating Characteristic Analysis

See section 3.6.1 and 3.6.2. The ROC analysis was performed in order to establish the best cut-off values for the SIS and KIVS. The SIS was calculated to have an optimal cutoff at 16 points which resulted in a specificity of 52% and a sensitivity of 100%. The PPV or positive predictive value for SIS alone was 16.7% with an Area Under the Curve (AUC) of 0.74. By maintaining a sensitivity of 100%, the optimal KIVS cut-off of 6 was calculated with a specificity of 40% (n= 81 suicide attempters). The KIVS PPV was 12.2% and the AUC for KIVS was 0.75.

By combining the scales, the sensitivity of 100% was maintained along with a specificity of 63%. The PPV for SIS and KIVS combined was 18.8% and an AUC of 0.83; see Figure 6.
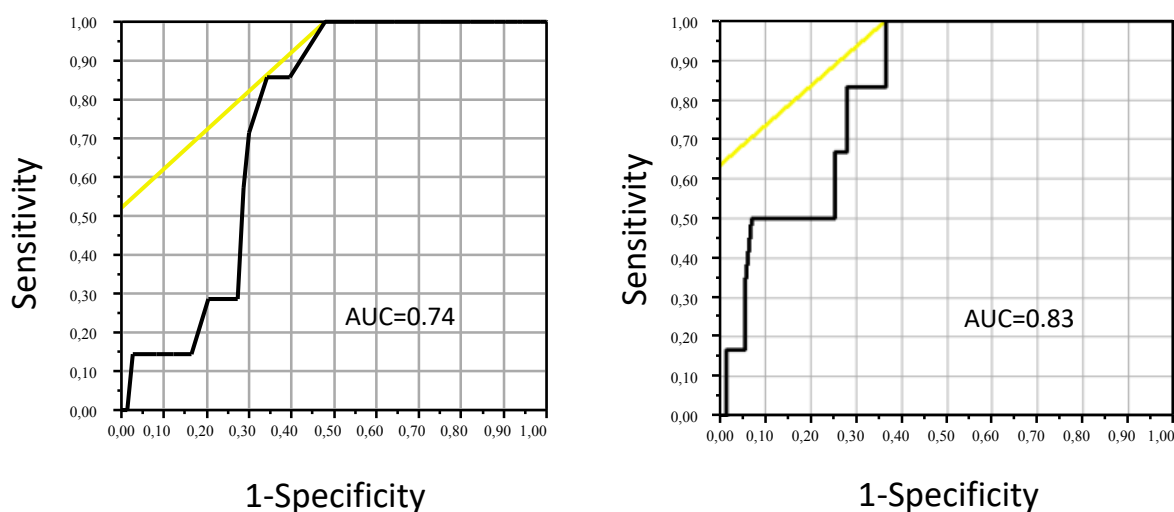
Figure 6. Combining KIVS with SIS gave a higher specificity in suicide prediction.

4.2   STUDY 3

4.2.1   Clinical Characteristics and Freeman Intentionality Scale Rating

Study 3 involved 209 suicide attempters. See Figure 7 for a summary of important diagnoses as well as the percentage of violent suicide attempts.
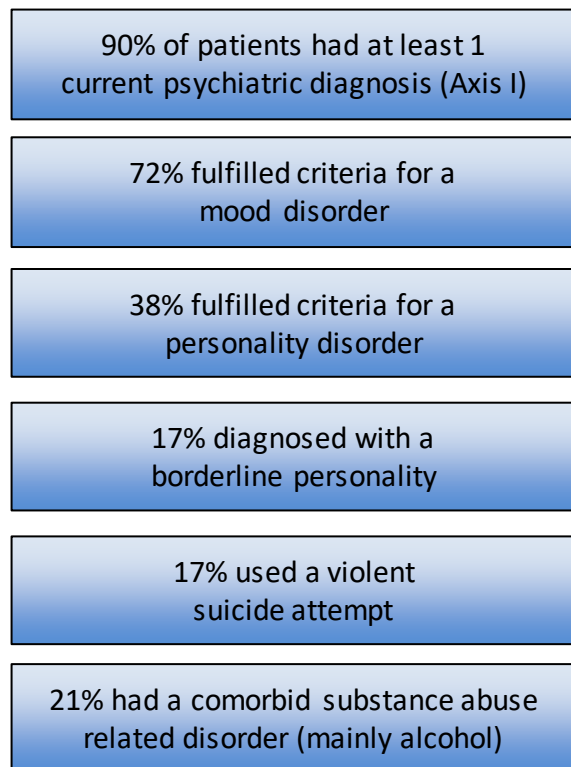
90% of patients had at least 1 current psychiatric diagnosis (Axis I)

72% fulfilled criteria for a mood disorder

38% fulfilled criteria for a personality disorder

17% diagnosed with a borderline personality

17% used a violent suicide attempt

21% had a comorbid substance abuse related disorder (mainly alcohol)

Figure 7. Demographic description of patients in Study 3.

The mean total Freeman score in all participants (n = 205) was (Mean + SD) (5.6 ± 1.5), Interruption probability (Mean + SD) (2.8 ± 1.0) and reversibility (Mean + SD) (2.8 ± 1.2). Please note Table 3. Men had significantly higher ratings of interruption probability and the Freeman total score (Mean + SD) (3.1 ± 1.1) (Mean + SD) (6.0 ± 1.6) compared to women (Mean + SD) (2.6 ± 0.9) (Mean + SD) (5.4 ± 1.3) (Z = 2.56, p = 0.01) (Z = 2.14, p = 0.03) but not in the Reversibility ratings.

There were significant positive correlations between age and the Freeman total score (rho = 0.24, p = 0.0004) as well as between age and interruption probability (rho = 0.19, p = 0.007) and reversibility (rho = 0.17, p = 0.02). The correlation between interruption probability and reversibility was significant in all study participants (n = 205, rho = 0.25, p = 0.0003).

Table 3. Description of data comparing Freeman total score with the two separate Freeman item.

Rating	Suicide victims n=15				Survivors n=190				
	Mean	Median	SD	Range	Mean	Median	SD	Range	Statistic
Interruption probability	3.4	3	0.7	2-5	2.8	3	1.0	1-5	Z=2.3 p=0.02
Reversibility	3.1	3	0.7	2-5	2.8	3	0.8	1-5	Z=1.5 p=0.12
Freeman total	6.5	6	1.3	5-9	5.6	6	1.5	2-10	Z=2.4 p=0.02

4.2.2 Freeman Scale - Suicides

There was a total of 17 suicides occurred during the follow-up period: 6 women and 11 men. The suicide risk was significantly higher in male suicide attempters compared to women ($\chi^2 = 4.2$, p = 0.04). One of the main significant results was that the Freeman total score differentiated between survivors and completed suicides, See Figure 8.
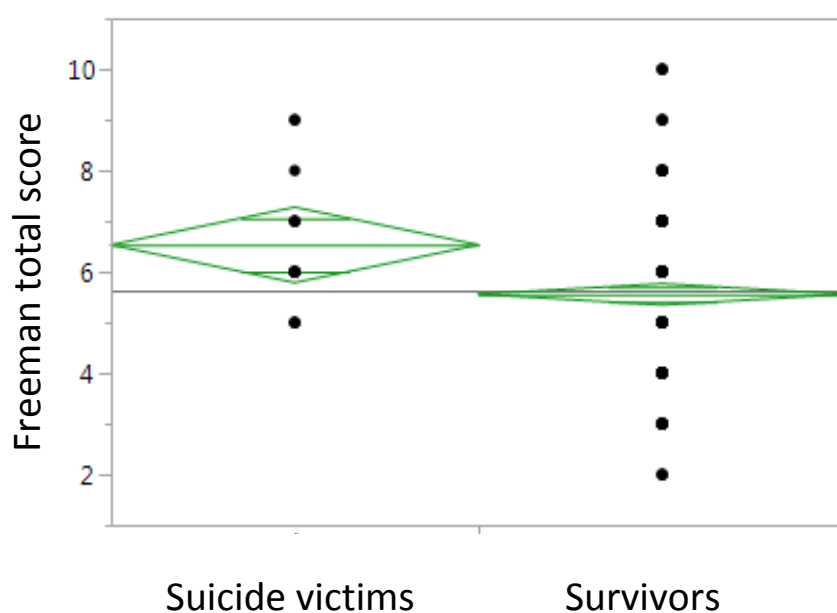
Figure 8. Freeman total score significantly differentiates between suicide victims and survivors.

4.2.3 Freeman - ROC Analysis

The ROC analysis for the Freeman scale gave an optimal cut-off of 6 with a sensitivity of 80% as well as a specificity of 47%. Positive predictive value (PPV) for Freeman total was 10.7%, false discovery rate (FDR) was 89.3% and the area under the curve (AUC) of 0.68. AUC adjusted for gender was 0.73, Figure 9.
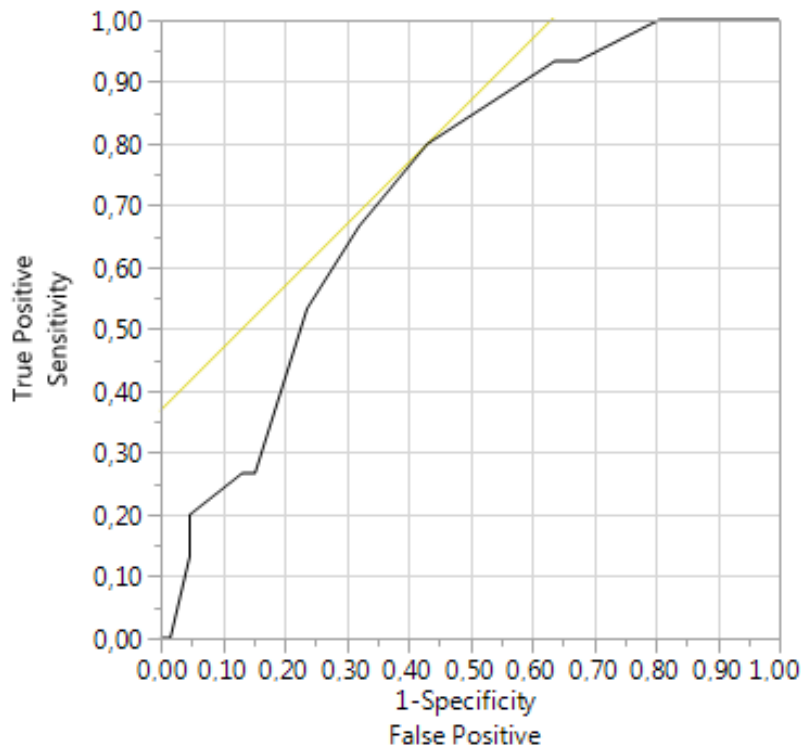
Figure 9. ROC curve for Freeman total score to predict suicide adjusted for gender.

4.2.3.1 Logistic Regression

One logistic regression analysis was performed with gender and Freeman total scores as predictors of completed suicide. The model used in the regression analysis was significant ($\chi^2 = 7.0$, DF = 2, p = 0.030). Freeman total score ($\chi^2 = 4.4$, p = 0.036), but not gender ($\chi^2 = 1.2$, p = 0.28) was a statistically significant predictor of suicide.

4.3 STUDY 4

4.3.1 CSF & Plasma Testosterone; Patients + Volunteers

There were higher levels of CSF and plasma testosterone in the male suicide attempters in comparison to age-matched male healthy volunteers, as can be seen in Figure 10.

Age was a confounding factor in the male subjects, but not among women, with regards to testosterone. The female groups were therefore compared without adjusting for age.
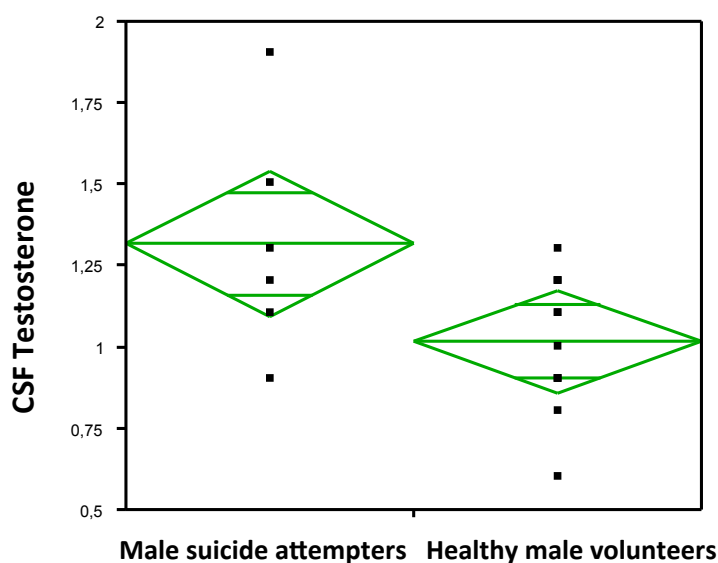
CSF testosterone sulfate levels (nmol/l) in age-matched male
suicide attempters and healthy male volunteers (p =0.03)

Figure 10. CSF testosterone levels in male suicide attempters and healthy male volunteers.

There was no significant difference in CSF and plasma testosterone between female suicide attempters and the healthy female volunteers.

Table 4 shows CSF & plasma testosterone levels in the study patients as well as study volunteers.

Table 4. CSF & plasma testosterone in age-matched suicide attempters vs. healthy volunteers in males and females.

Endocrine measure (nmol/l)	Male suicide attempters (n=9)				Healthy male volunteers (n=12)			
	Mean	Median	SD	Range	Mean	Median	SD	Range
CSF testosterone	1.32	1.25	0.35	0.9-1.9	1.02	1.05	0.20	0.6-1.3
Plasma testosterone	114.71	115	21.50	97-156	98.25	95	10.34	84-113

Endocrine measure (nmol/l)	Female suicide attempters (n=10)				Healthy female volunteers (n=7)			
	Mean	Median	SD	Range	Mean	Median	SD	Range
CSF testosterone	0.39	0.4	0.19	0.2-0.8	0.50	0.5	0.2	0.3-0.8
Plasma testosterone	52.75	52	18.99	28-85	57.71	55	8.46	48-72

Diagnoses such as major depression, substance abuse or personality disorder did not show significant differences regarding CSF and plasma testosterone (p-values of 0.21-0.97).

Supporting the theory that plasma testosterone levels were reliable measurements in this study, there were positive correlations that were significant between plasma testosterone and CSF in patients of both genders, as well as the healthy volunteers and participants of both genders. (r = 0.62-0.77).

4.3.2 Testosterone/Cortisol Ratio vs Impulsivity and Aggression

Cortisol levels (both CSF and plasma) were more elevated in suicide attempters than in healthy controls and have been reported previously (Chatzittofis et al., 2013).

There was a significant positive correlation between both impulsivity and aggressiveness and CSF testosterone/cortisol ratio in male suicide attempters. Figure 11 demonstrates the above mentioned correlations between the CSF testosterone/cortisol ratio, aggressiveness and impulsivity.
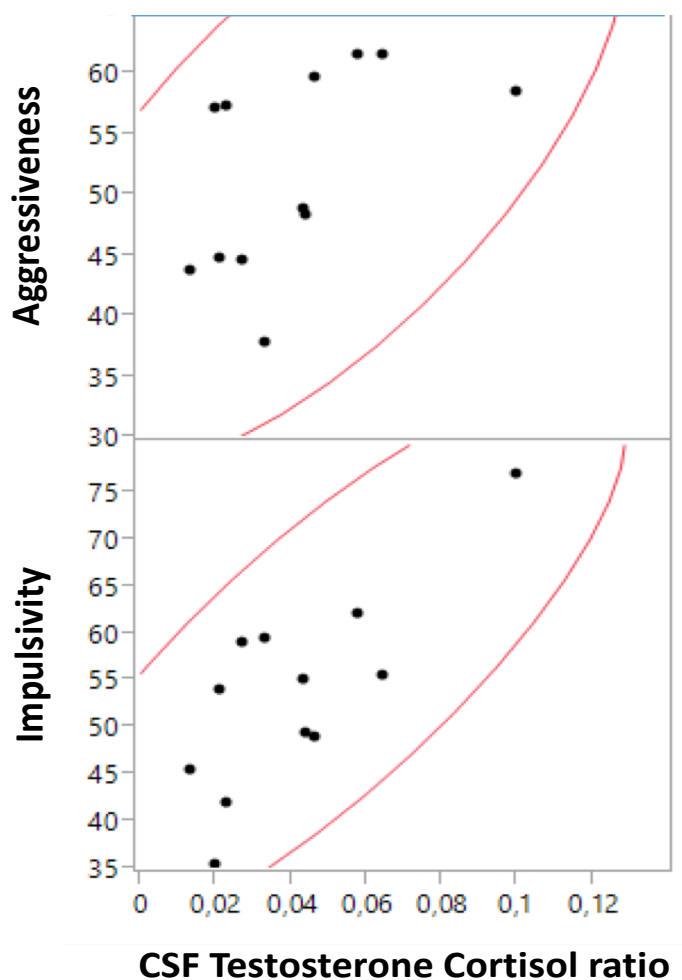

CSF Testosterone Cortisol ratio

Figure 11. Correlation in male suicide attempters between Testosterone-Cortisol ratio and Impulsivity (n=12, rho=0.67, p=0.0168) + Aggressiveness (n=12, rho=0.67, p=0.0174).

A multiple linear regression analysis was created, although statistically underpowered. Interestingly, the impulsivity model in the male group of suicide attempters was significant (F = 10.7, p = 0.0036) as R^2 = 0.80 and adjusted R^2 = 0.72. Once again, in male suicide attempters, the two statistically significant predictors of impulsivity were CSF cortisol (t ratio = -5.39, p = 0.0007) and CSF testosterone (t ratio = 2.62, p = 0.03). There was a non-significant interaction variable (t ratio = -.78, p = 0.46).

4.3.3 Completed Suicide

There were six suicides that took place during the follow-up period. The suicides comprised of two women and four men. Mean plasma and CSF testosterone measurements did not differ in a significant way between survivors and suicide victims (t ratio = 0.05, p = 0.96; t ratio = 0.13, p = 0.90), adjusted to age and gender.

Jón Stefánsson

5 DISCUSSION

5.1 SUICIDE INTENT, INTERPERSONAL VIOLENCE AND REVERSIBILITY OF THE SUICIDE ATTEMPT METHOD

We have reported and gathered information on four psychometrically validated scales in this PhD project the Suicide Intent Scale, the Beck Hopelessness Scale, the Karolinska Interpersonal Violence Scale, and the Freeman scale. We found that 3 of the 4 scales may have a purpose in suicide risk management in that they measure different aspects of suicide risk and showed some predictive validity in a high-risk group of suicide attempters. Suicide intent measured with both the SIS and the Freeman Scale detected the suicidal patients (attempters) with an elevated long-term risk for suicide.

The Suicide Intent Scale is in some ways similar to the Freeman Scale in that the first 4 items in the SIS also focus on the likelihood for interruption of the suicide attempt (Beck, Schuyler & Herman, 1974). These 4 items involve the isolation of the attempter, the chance of intervention, if anything was done to avoid intervention and whether there anything was done to get assistance either during or after the suicide attempt (Beck, Schuyler & Herman, 1974). When analyzing the Freeman subscales, the interruption probability ratings (as opposed to the reversibility ratings) were significantly higher in suicide victims.

Neither the SIS nor the KIVS, however, focuses on how reversible or violent the suicide attempt was which is an important aspect to take into account in suicidal risk assessments and is something that the reversibility item in the Freeman Scale covers in detail. The method of suicide as described under item number 4 under subscale Freeman Reversibility (such as gassing or drowning) or the next and last option item number 5 under Reversibility (attempts such as using firearms or jumping from a dangerous height) ultimately leads to a higher suicide risk and requires a more intense follow-up regarding treatment (Stenbacka & Jokinen, 2015, Runeson et al., 2010).

We found that the victims of suicide generally tended to use more irreversible suicide attempt methods. As mentioned above, the reversibility item in the Freeman Scale involves questions about the use of weapons. A similar theme around violence involves questions in the KIVS although the Freeman Scale focuses more on whether there was any reversibility of the suicide attempt and the KIVS focuses on the violence affecting victims as well as bullies. It has been shown that expressed violence as an adult in KIVS was higher in suicide attempters who used a violent method (Jokinen et al., 2010). The KIVS detects the more vulnerable patients with both exposure to violence in childhood and then ultimately end up using violence themselves as adults. These two KIVS subscales showed some predictive validity for suicide and were able to identify patients at a higher risk even when the subscales were combined with SIS.

Intuitively speaking, the more dangerous a behavior is, the higher the risk of dying. In fact, Runeson et al. have shown that the more violent the suicidal method is, the higher the risk for

suicide (Runeson et al., 2010). In a new systematic review of serious suicide attempts (the attempt very close to being lethal), it was discussed how serious suicide attempters are distinctly different from other suicide attempters and epidemiologically more similar to suicide completers (Gvion and Levi-Belz, 2018). Using the Freeman Scale while assessing serious suicide attempters would help the clinician assess the degree of violence and lethality of the method that was used in the suicide attempt. In fact, the total score in our Freeman Scale Study, including both the reversibility ratings and the probability of interruption ratings, was significantly higher in the group of suicide victims versus the survivors.

The question is, are these 3 scales measuring the same risk? The answer is no. We have reported that the correlation between the KIVS and the SIS was not significant (Stefansson et al., 2015). Although there are some correlations between the Freeman Scale and the SIS (mainly SIS planning subscale) (Jokinen et al., 2012), the reversibility item captures other risks not solely conveyed by the SIS.

Another way of comparing these 3 scales is the temporal aspect. KIVS assesses early life risk factors, thereby giving more of a long term perspective, whereas the SIS and primarily the Freeman Scale focus more on the short-term aspect concerning the actual suicide attempt.

It is of course important to look at the positive predictive value (PPV) of these scales when talking about suicide risk prediction. The Suicide Intent Scale had a PPV of 16.7%. The KIVS had a PPV of 12.2% and the Freeman Scale had a PPV of 10.7%. Although the study population involved high-risk suicide attempters, the PPV was still rather low in our results. Outcomes with low prevalence/rare events such as completed suicide, are not likely to be predicted by a risk assessment instrument, even in high-risk clinical populations, because of the statistical impact that prevalence has on PPV (Carter et al., 2017).

5.2 TESTOSTERONE

5.2.1 Testosterone and the Testosterone/Cortisol Ratio – Our results vs. the Literature

In a 2012 letter, Dr. Sher explains that there could be a dichotomy between young and old men regarding different levels of testosterone and its effect on suicidal behavior (Sher, 2012). He therefore proposed that testosterone should be evaluated separately depending upon whether the individual is young or old (Sher, 2012). In our study, testosterone levels declined with age among male participants and due to the fact that the healthy male volunteers were younger, we analyzed testosterone measurements in young suicide attempters that were men compared with age-matched healthy males.

In a Chinese study on 490 suicide attempters and controls, it was shown, in their study, that testosterone measurements are relatively higher for high-risk suicide attempters, and particularly for male suicide attempters (Zhang et al., 2015). The same study showed that there

was even a trend toward higher testosterone levels among female suicide attempters (Zhang et al., 2015).

Some research findings such as those of Markianos and Tripodianakis, respectively, showing that lower testosterone results in a more dangerous suicidal behavior go against other results that have shown that higher testosterone seems to be the more dangerous predictor (Markianos et al., 2009; Tripodianakis et al., 2007). This shows the importance of controlling for certain known biases such as age (as we did in our study) since male testosterone levels are known to decrease with age (Wein, 2015).

An older study by Roland et al. has investigated testosterone in cadavers after both suicides and other causes of death. There was a higher level of testosterone in suicide victims compared to the sudden death group when observing the 23-45 year-old age group. These results partly support the theory that Dr. Sher and other researchers have put forward regarding younger suicide attempters in that higher testosterone levels could partly explain the increased suicide risk (Roland et al., 1986).

Our results show that there are higher CSF and plasma testosterone measurements in young age-matched male suicide attempters vs. healthy male volunteers. Although it is difficult to generalize these results, mainly due to the rather small number of patients, they are in line with theories presented by other research groups, such as Zhang et al. (Zhang et al., 2015).

The CSF testosterone/cortisol ratio was significantly and positively correlated with both aggression and impulsivity in male suicide attempters. This is quite similar to the dual hormone theory regarding aggression in humans (Montoya et al., 2012). In 2014, Horn et al. showed that a high testosterone/cortisol ratio could be seen in patients with a high prevalence of both suicidal behavior and Borderline personality disorder, as well as criminal behavior (Horn et al., 2014). The interaction between testosterone and cortisol may, however, be more complex than a high-to-low testosterone/cortisol model and may be impacted by gender, aggression, health and/or psychopathic traits (Rosell and Siever, 2015). A lowered cortisol measurement in response to stress and, in general, a weak HPA axis seems as well to be involved in suicidal behavior (O'Connor et al., 2017).

5.2.2 Analysis of Testosterone

When studying testosterone, it is important to remember when studying testosterone that a correct analysis of testosterone requires knowledge of it's variation depending on the season, the patient's gender, the time of day, and the situation the patient happens to be in as well as the age of the patient (Seidman and Roose, 2006). This could greatly affect the outcomes if not carefully considered when studying for example suicidal behavior and testosterone. In our study, a standard protocol was used and both blood tests and lumbar punctures were carried out relatively quickly, on average, 8.6 days after the suicide attempt.

5.3   ARE SUICIDE RISK PREDICTIONS RELIABLE?

In my opinion the term suicide risk prediction is not an entirely relevant one in this regard in that no one, neither layman nor specialist, can predict the future 100%. And that includes predicting whether someone will commit suicide. That being said, similar risk assessments are made within other fields of medicine such as the risk for a serious cardiac event and whether one should prescribe antihypertensives or not, without the assumption that the cardiologist should be obliged to 100% correctly predict any future cardiac event and preferably the timing of the event. The difference in suicide risk assessments is that there is a clinical assessment of risk factors without validated biomarkers, making the suicide risk assessment even more complicated than the somatic risk assessment.

Runeson et al. have recently shown that most of the common suicide risk assessment instruments used in the clinic today are not supported by enough research studies and among the few instruments that could be assessed, none of them met the requirements for adequate diagnostic accuracy (Runeson et al., 2017). A recent international systematic review and meta-analysis by Chan et al. came to a similar conclusion regarding self-harm patients and that scales such as the Suicide Intent Scale were not supported by sufficient evidence to warrant their use (Chan et al., 2016). At the same time, the same review showed that suicide intent was a risk factor that emerged with robust effect sizes. I would argue that suicidal intent is quite complicated and considering the fact that there is a specific scale of 20 items (SIS) attempting to define suicidal intent per se, these results in my opinion support the use of the SIS. As Grøholt et al. conclude, it is important to ask about suicide intent in that a large amount of suicide victims in their study had mentioned intent before their suicide (Grøholt et al., 1999). Not to mention the fact that information about a previous suicide attempt (another risk factor with a robust effect size)(Chan et al., 2016) is also an item in the complete SIS.

Freedenthal published a review of the Suicide Intent Scale looking at around 30 years of different research studies (Freedenthal, 2008). The conclusion was that the results were mixed. Five studies showed that, in different populations, the SIS could significantly predict suicide. However, there were even more (7) negative studies that showed no significant association between suicide and SIS scores (Freedenthal, 2008).

One of Freedenthal's main conclusions was that the Suicide Intent Scale needed to either be updated or a new way of measuring suicide intent needed to be created (Freedenthal, 2008). Not only was a new scale for suicide intent created a few years later (Posner et al., 2011), it was also validated for adolescents which was another critique that Freedenthal mentioned regarding the SIS (Freedenthal, 2008). The Columbia Suicide Severity Rating Scale (C-SSRS) is a prominent suicide risk assessment scale comprising items that analyze a possible previous suicide attempt and examining how violent it was (Posner et al., 2011). In comparison with the scales studied in this thesis, the C-SSRS (Posner et al., 2011) does not analyze interruption probability as much as the Freeman Scale does, which could be a reason for the Freeman Scale to be used in addition to other risk assessment scales.

To be clear, when I recommend such scales as the SIS, the KIVS or the Freeman Scale, I do not, in any way, mean that the clinician should not take into account the specific needs of the individual patient, as well as the psychosocial assessment of the patient as Chan et al. discuss (Chan et al., 2016). What I mean is that it should be possible to use relevant psychometric scales along with other proper clinical judgment. One clinical behavior does not rule out the other. Runeson et al. also conclude that it is still unclear whether using risk assessment scales as a complement to a good clinical assessment gives better suicide risk prediction (Runeson et al., 2017).

5.4 CAN THESE RESULTS BE USED BY FUTURE RESEARCHERS AND CLINICIANS?

I believe the answer is yes. Of course the results must first be controlled in a larger sample of patients, but the assumptions in this PhD thesis regarding SIS, KIVS, the Freeman Scale and testosterone are intuitive when it comes to clinical relevance. I believe the future of suicidal risk assessments involves a "package" of both laboratory tests and relevant risk assessment tests. The fact of the matter is that in the field of Psychiatry as well as the field of Internal Medicine, some things are difficult to assess, some things are difficult to remember and some are both. It is quite difficult, if not impossible, to remember all potential pharmaceutical interactions, and we therefore rely to a great deal on interaction screening in our everyday clinical life (Abarca et al., 2006). A similar example involves everyday clinical predictions used in determining whether patients should take antihypertensives depending on a 10-year risk of stroke/heart attack (Kikuya et al., 2005).

I believe the very difficult task of suicide risk prediction could as well possibly be assisted by a computer-generated risk analysis. If there is, for example, a traffic light system for determining which patients have a higher risk of committing suicide with a red light, this could be a ground-breaking new way of decreasing suicide rates. In order for this to have clinical relevance, it would have to pick up on possibly relevant biomarkers, as well as possibly relevant scale results, such as the SIS or the KIVS or the Freeman Scale.

Last but not least, it should be prioritized that a clinician be informed when their patient has had a recent suicide attempt and react accordingly since research data has shown that the follow-up of suicide attempts has strong support (Zalsman et al., 2016). A 12-year prospective study in a municipality in Norway has as well concluded that using follow- up systems with regards to suicide attempters may have reduced the rate of suicide attempts during that same period of time (Dieserud et al., 2000).

5.5 STRENGTHS

As has been shown throughout this thesis, the psychometric scales, as well as the hormones that were chosen during the creation of the hypotheses, are supported by previous evidence in the literature and were well thought out during the planning process of this project. The many specialists and general experts involved in this project guaranteed a high level of diagnostic, as well as analytical, quality.

Suicide intent is very difficult to investigate in the research setting (Silverman et al., 2007). Regarding suicide intent in this project, the follow-up, directly in relation to the suicide attempt, as well as over many years regarding a later cause of death, demonstrated a proxy of the actual intent of the patients (both short-term and long-term). It is also quite unique to have simultaneous data about both suicide intent and interpersonal violence in high-risk suicide attempters.

There have been very few studies demonstrating the effect that testosterone, as well as the testosterone/cortisol ratio, have on suicidal patients. It is very rare to gather biological markers such as CSF and plasma markers in suicidal patients, thus making this project unique in many ways.

5.6 LIMITATIONS

There are several limitations in these studies. First, we do not have information on how many patients were asked to participate or how many were denied to participate in the first 2 clinical cohorts, which negatively impacts the generalizability of the findings. The patients included had mood disorders and the findings cannot be applied to patients with psychosis spectrum disorders.

Since it is well known that it is generally difficult to include highly suicidal patients in a research setting, a possible limitation in this thesis, and particularly in Studies 1, 2 and 4, is the relatively small number of patients. This raises the question of whether there is sufficient statistical power to detect any differences in groups. Furthermore, we did not have information on treatment received during the follow-up among the study participants and could not take this into account when assessing the future suicide risk.

Also, a cross-sectional design was used in the sampling of biological markers in this research project, making it difficult to determine causality.

Patients in Study 2 were asked about their childhood experiences and childhood adversity regarding KIVS. A recall bias might have affected the quality of the KIVS results in that it can be difficult for some adults who have recently attempted suicide to remember specific events in their childhood. In the same study, there was missing KIVS data on one of the suicide attempters who later committed suicide. This might have had an impact on the change in predictive value.
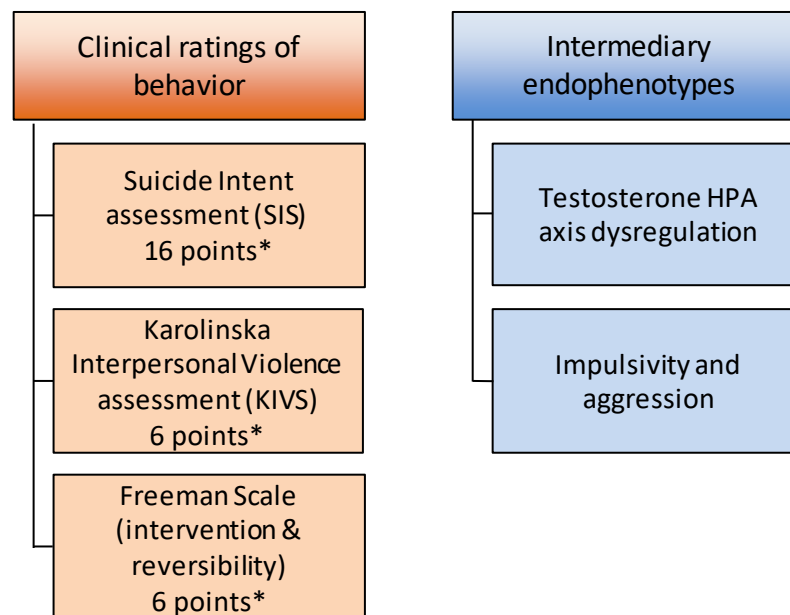
6 CONCLUSION

Figure 12. Behaviors and endophenotypes studied in relation to suicide risk in the thesis (*=cutoff).

The main finding from Study 1 was that the Suicide Intent Scale (SIS) can be used as part of a suicide risk assessment along with good clinical judgement after a recent suicide attempt. A shorter SIS version with questions about telling others about the attempt, writing a suicide note, expressing a clear suicide intent and ambivalence to life and/or death may capture the suicide risk.

Combining the Karolinska Interpersonal Violence Scale (KIVS) with the SIS can be considered since they measure different aspects of risk. KIVS is a useful clinical instrument in long-term suicide prevention. Our results suggest that the 2 subscales of exposure to violence as a child as well as violent behavior towards others as an adult increase suicide risk in the long term perspective.

The Freeman scale measuring 2 domains (reversibility of method and probability of intervention) is a suicide risk assessment tool that can screen for long term risk in high risk populations in combination with good clinical judgement.

Testosterone is likely to be related to suicidal behavior among young male attempters through association with impulsivity and aggression. Figure 12 is a summary of the conclusions in this thesis.

7   FUTURE PERSPECTIVES

Two things to consider in order for suicide prediction, and therefore suicide prevention, to become more optimal:

1)   A recent review has shown that current common suicide risk assessment scales do not have scientific support for predicting suicidal acts, although they might help less experienced staff and they might improve suicde risk prediction when used as a complement to a good clinical global assessment (Runeson et al., 2017). When is staff assessing suicide risk considered experienced? How is research done on the quality of a good clinical global assessment?

2)   Why do men commit suicide, on average, more than twice as often as women? In many countries over four times as often? Could there be a biological explanation? Or is the difference merely based on differences in cultures? Or, more likely, a combination of the two?

Future studies should focus on suicide risk assessments while simultaneously attempting to control for a good clinical global assessment. One option for maintaining good quality control is for clinicians working with patients that have psychiatric illnesses being required to go on a course on a regular basis in order to keep themselves updated on the newest guidelines in suicide risk assessment and suicide prevention.

Future studies on the effect of testosterone, and similar hormones, on suicidal behavior are needed. During these studies, it is of vital importance, as mentioned before, to try to shorten the time gap between suicide attempt and hormone measurement. One could also assume that it is important to control for cultural differences when measuring biomarkers.

Future studies on computer evaluation of previous journal records, giving a quick summary of what could be perceived as suicidal risk factors, are needed. This is highly important precisely in psychiatry where it is almost impossible to be 100% up to date on all of the patients' previous clinical information. Considering suicide risk prediction with biomarkers and psychometric scales is still not optimal and considering that most suicides involve patients with psychiatric diagnoses, it would be interesting to see whether computer programs can assist in the suicide risk prediction process, both in the short- and long-term.

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