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Substance Use and Violence

Influence of Alcohol, Illicit Drugs and Anabolic Androgenic Steroids on Violent Crime and Self-directed Violence

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Abstract
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Interpersonal violence and suicide are major health concerns, leading to premature death, extensive human suffering and staggering monetary costs. Although violent behaviour has multiple causes, it is well known that acute substance intake and abuse increase the risks of both interpersonal and self-directed violence. This association is quite well established for alcohol, while a more ambiguous literature exists for other common drugs of abuse. For example, anabolic androgenic steroids (AAS), synthetic analogues to the "male" sex hormone testosterone are suggested to elicit violent and aggressive behaviour. Two studies (I and III) in the present thesis addressed the association between AAS use and being suspected or convicted of a violent crime among remand prisoners and in a general population sample, respectively. Further, using the case-crossover design to control for confounders stable within individuals, I also investigated the triggering (short-term risk) effect of alcohol and drugs such as benzodiazepines and AAS, on violent crime (Study II). Finally, a fourth study (IV) based on a large national forensic sample of suicide completers (n=18,894) examined the risk of using a violent, more lethal, suicide method, when under acute influence of alcohol, central stimulants or cannabis.

The results of this thesis suggested that AAS use in itself is not a proximal risk factor for violent crime; the observed risk is probably due to the co-occurrence of abuse of other substances. Alcohol is a strong triggering risk factor for violent crime, constant across males and females as well as individuals with or without behavioral and psychiatric vulnerability. Intake of high doses of benzodiazepines is associated with an increased risk for violent crime. Cannabis use is associated with an increased risk of using the lethal suicide method of jumping from a height. I conclude that mapping substance abuse patterns may inform violence risk assessment and treatment planning.

Keywords: Substance abuse, violent crime, violent suicide, anabolic androgenic steroids

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Det är ni som e de konstiga
det är jag som e normal

Joakim Thåström 1999

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Lundholm, L., Käll, K., Wallis, S., Thiblin, I. (2010). Use of anabolic androgenic steroids in substance abusers arrested for a crime. *Drug and Alcohol Dependence*, 1;111(3):222-6

II Lundholm, L., Haggård, U., Möller, J., Hallqvist, J., Thiblin, I. (2012). The triggering effect of alcohol and illicit drugs on violent crime in a remand prison population: A case-crossover study. *Drug and Alcohol Dependence,* doi: pii: S0376-8716(12)00383-3. 10.1016/j.drugalcdep.2012.09.019

III Lundholm, L., Frisell, T., Lichtenstein, P., Långström, N. (2012). Anabolic androgenic steroids and violent offending: Confounding by polysubstance abuse in 10,365 men. *Submitted manuscript.*

IV Lundholm, L., Thiblin, I., Runeson, B., Leifman, A., Fugelstad, A. (2012). Acute influence of alcohol, THC or central stimulants on violent suicide: A Swedish population study. *Accepted for publication in Journal of Forensic Sciences.*

Contents

Abbreviations

AAS	Anabolic Androgenic Steroids
ADHD	Attention Deficit Hyperactivity Disorder
ASPD	Anti -Social Personality Disorder
CD	Conduct Disorder
CI	Confidence Interval
CU	Callus and Unemotional
DSM	Diagnostic Statistical Manual of Mental Disorders
GABA	Gamma Amino-Butyric Acid
ICD	World Heath Organizations International Classification of Diseases
ODD	Oppositional Defiant Disorder
OR	Odds Ratio
RR	Relative Risk
SUD	Substance Use Disorder
STD	Sexual Transmitted Diseases
THC	Tetrahydrocannabinol
WHO	World Health Organization

INTRODUCTION

According to the World Health Organization (WHO) violence is defined as "The intentional use of physical force or power, threatened or actual, against oneself, another person, or against a group or community, that either results in or has a high likelihood of resulting in injury, death, psychological harm, maldevelopment or deprivation" [1].

Interpersonal violence is a major public health factor in several aspects. Including sexual and domestic violence, robbery, threats, assault and infringement of a person's integrity, it accounts for a large proportion of physical injury as well as psychological trauma and severe loss of quality of life for the victims. In the worst cases, the violence is lethal. In year 2000, interpersonal violence caused 520,000 deaths worldwide—more than armed conflicts [1]. Interpersonal violence is the third leading cause of death and disability among adolescents and young adults in Europe [2]. The effects of lethal, as well as non-lethal, violence are of paramount concern for society, in terms of monetary costs and human suffering [1, 3].

Annually, approximately 1,300 individuals die due to suicide in Sweden. Suicide is the leading cause of death among men aged 20-44 and the second leading cause of death among women the same age [4]. The world health organization argues that suicidal behavior often is the product of the same underlying social, psychological and environmental factors as other types of violence [5] (e.g., impulsivity, substance abuse and economic factors). Further, several studies have demonstrated a link between antisocial and suicidal behavior [6-8].

In the World report of violence and health [5] a typology describing three types of violence is provided 1) Self-directed violence; including suicidal behavior and self-abuse. 2) Interpersonal violence; family and partner or community violence; acquaintance or stranger. 3) Collective violence; social, political and economic. The nature of violent acts can be physical, sexual, psychological or involving deprivation or neglect. The collective type of violence as well as self-abuse is outside the scope of this thesis.

The burden of violence is neither equally distributed within or between European countries [2] nor is violent behavior or violent crime normal distributed in the population, and the vast majority of violent offenders are male [9]. In Sweden, a few percent of the population are responsible for half of all criminal acts [10, 11]. Indeed, individual predisposition for aggressiveness interacts with external factors to create a situation where violence is likely to occur. Individual risk factors for violence will be further discussed, with the main focus on substance abuse. Substance abuse in general and alcohol abuse in particular have been associated with violent offences [12-14]. Acute influence of alcohol has also proven to have a triggering effect on violent crime [15, 16], while a more ambiguous literature is provided regarding acute influence of other common drugs of abuse [17, 18].

Three studies in the present thesis is focusing on interpersonal violence and one on suicide, all with respect to the association with substance use. Use of Anabolic androgenic steroids have earned attention for the past two decades suggested to induce violent and aggressive behavior, and is for that reason the main focus in two of the studies, one among remand prisoners and one in the general population. Further, one study examines the triggering effect of alcohol, illicit drugs and anabolic androgenic steroids on violent crime. Finally, one study is examining suicide by a violent suicide method when being under the influence of alcohol, THC or central stimulants.

The thesis introduction aim at conceptualize the complex area of substance abuse and violent behavior and describe common risk factors.

Substance use, misuse, abuse and dependence

It seems like humans in all cultures and times have had a desire for altering their state of mind, often with the aid of psychoactive substances. Psychoactive substances refer to substances that affect the neural system and lead to alteration in mood, thoughts and behavior. Most commonly used are caffeine and nicotine, followed by alcohol and cannabis. From a behavioral psychological perspective substance use is maintained by either positive or negative reinforcement, one wants to reach a desirable state or get away from something painful.

In Sweden, all beverages containing an alcohol percent above 3.5 are distributed through the governmental monopoly *Systembolaget*, with limited open hours and an age limit of twenty years for buying, as part of a restricted alcohol policy. Alcohol in moderate doses is used by a majority of Swedish adults for its relaxing and positive mind-altering effects, without causing any behavioral or somatic problems. However, consuming more than 14 standard glasses per week (one standard glass equals 12 grams of alcohol) for men

and 9 standard glasses per week for women is regarded as harmful drinking (misuse or risk drinking), with an enhanced risk for developing somatic and behavioral problems [19]. According to the diagnostic criteria in DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders) [20], alcohol or substance abuse are defined as harmful drinking or using the substance leading to social and/or personal problems for the individual, whereas alcohol or substance dependence refers to a more severe state in which the person needs the substance to function within normal limits and is often related to developing tolerance, withdrawal and risk for relapse. Use of substances classified as narcotics, for example common drugs of abuse and some medications, is illegal without prescriptions. Hence, in Sweden, every kind of use is defined as misuse. DSM-IV-TR criteria for substance abuse and dependence are presented in table 1.

Table 1. *DSM-IV criteria for abuse and dependence*

DSM-IV Substance Abuse Criteria

Substance abuse is defined as a maladaptive pattern of substance use leading to clinically significant impairment or distress as manifested by one (or more) of the following, occurring within a 12-month period:

1. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school or home (such as repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; or neglect of children or household).
2. Recurrent substance use in situations in which it is physically hazardous (such as driving an automobile or operating a machine when impaired by substance use)
3. Recurrent substance-related legal problems (such as arrests for substance related disorderly conduct)
4. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (for example, arguments with spouse about consequences of intoxication and physical fights).

The symptoms for abuse have never met the criteria for dependence for this class of substance. According to the DSM-IV, a person can be abusing a substance or dependent on a substance but not both at the same time.

DSM-IV Substance Dependence Criteria
Substance dependence is defined as a maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring any time in the same 12-month period:

1. Tolerance, as defined by either of the following: (a) A need for markedly increased amounts of the substance to achieve intoxication or the desired effect or (b) Markedly diminished effect with continued use of the same amount of the substance.
2. Withdrawal, as manifested by either of the following: (a) The characteristic withdrawal syndrome for the substance or (b) The same (or closely related) substance is taken to relieve or avoid withdrawal symptoms.
3. The substance is often taken in larger amounts or over a longer period than intended.
4. There is a persistent desire or unsuccessful efforts to cut down or control substance use.
5. A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects.
6. Important social, occupational, or recreational activities are given up or reduced because of substance use.

The substance use is continued despite knowledge of having a persistent physical or psychological problem that is likely to have been caused or exacerbated by the substance (for example, current cocaine use despite recognition of cocaine-induced depression or continued drinking despite recognition that an ulcer was made worse by alcohol consumption).

Prevalence figures of substance abuse in Sweden

Estimating the prevalence of substance abuse is challenging and dependent on information from several sources; surveys, hospital data, police records etc. The prevalence figures below are mostly collected from the government-commissioned report on abuse (Missbruksutredningen) [21].

It has recently been stated that 450,000 individuals in Sweden have a harmful drinking pattern, 300,000 meet criteria for alcohol abuse, and almost 300,000 meet the criteria for alcohol dependence. Heavy substance abusers, defined as intravenous substance abusers or daily substance abusers is estimated to 26,000 individuals. The abuse of licit drugs (e.g., benzodiazepines and analgesics) is hard to estimate, however, a 2008 population survey with 58,000 randomly chosen participants aged 16-64, suggested that slightly more than 1% illegally used these substances at least four times a week during the past year [21]. However, this survey does probably not capture the frequent use of benzodiazepines and opioid based analgesics as part of a polysubstance abuse pattern.

Cannabis is the most commonly used illicit drug worldwide (legal for personal use in some countries) and 11% of 16-84 year old Swedes claim that they have tried cannabis and 2% (ca 150,000) that they have used the drug during the past year.

In the general population, the life time prevalence of AAS-use is 1-6% with predominantly male users, ten times higher in gym populations [22-24] and frequent users is estimated to 10,000 [21].

Human aggression and interpersonal violence

Human aggression and violence is far from new, by contrary it seems like interpersonal violence has declined through modern history. Steven Pinker demonstrates in his book "The better angels of our nature - Why violence has declined" a ten to fiftyfold decline in homicide rates in Europe from the Middle ages to the 20th century [25]. This decline is argued to be due to a *civilization process* including centralization of the state and a change in cultural norms. However, as homicide rate declined some patterns remained consistent: men were responsible for 90% of the killings and a man killing another man unrelated to him declined more rapidly than did the killing of children, spouses, parents and siblings.

The current global homicide rate is 8.8 per 100,000 inhabitants per year, with a large discrepancy between countries [1]. The current homicide rate in Sweden is 0.9 per 100,000, which corresponds to approximately 90 deaths due to interpersonal violence per year [26].

In the theoretical work of Silvian Tompkins (1911-1991), anger is defined as one of eight core affects that are biological and adaptive, existing universally. The other core affects are; joy, interest, surprise, distress, disgust, shame and fear. The theory is based on evaluation of face expressions, expressing emotions recognized in all cultures [27, 28]. Core affect is a biological product of evolution and therefore is likely to have a function, which is to be found among its consequence. We benefit from altering a negative affect; altering behavior or changing the situation, or, by prolonging a positive affect. Core affects are involved in motivation, reinforcement and can be manipulated by drugs [29]. The human emotion anger is based on a set of neural, endocrine and behavioral mechanisms [30].

From animal models, aggression has been suggested to be categorized in Predatory, Inter-male, Maternal, Territorial and Fear-induced. The typology represents for example aggressive responses to threat and intruders in order to protect offspring, territories and order social hierarchies [31], adaptive behavior in contribution to an individual's survival and reproductive chances. Further, most mammals have submission cues, for example a dog bares its throat, leading to a violence inhibiting effect, in humans a friendly face

expression for example smiling might signal submission (The violence inhibition mechanism model) [32].

Andersson and Buschman define human aggression as "any behavior directed toward another individual that is carried out with the proximate (immediate) intent to cause harm" [33]. Interpersonal violence is often divided into instrumental or reactive violence. Instrumental violence refers to a planned and goal-directed violent act in order to gain something and reactive violence refers to an emotional aggressive reaction on a perceived provocation [34].

Altering in brain functions and cognitive capacities inherent or inflicted due to brain lesion or acute intoxication, in terms of appraisal and evaluation of one's internal state and social cues enhances the risk for aggressive behavior [33]. Several factors conduce to actual acting out ones aggression in terms of violent behavior, hurting or threating to hurt another human being, an interaction between genetics (individual vulnerability e.g., difficulties with inhibition) social norms supportive of violence, lack of alternative skills and role models. The latter is related to social learning theories proposing that people acquire aggressive responses the same way they acquire other complex forms of social behavior—either by direct experience or by observing others and through both direct and vicarious behavioral reinforcement [35].

Developmental pathways of aggression and anti-social behavior

Anti-social behavior is the term defining behavior that violate the right of others and norm breaking behavior, including criminal and aggressive acts. One theoretical model of the development of aggression and other forms of anti-social behavior that has been very influential is the taxonomy of adolescent limited and life course persistent anti-social behavior proposed by Moffitt [36]. Life course persistent offenders would be characterized with early onset and more neuropsychological problems. They would for example be engaged in: "biting and hitting at 4, shoplifting and truancy at 10, stealing cars and selling drugs at 16, robbery and rape at 22, and fraud and child abuse at 30" [31]. Aggression at the age of 3 has shown to predict adolescent aggression [37]. In addition to the temporal continuity, the behavior is displayed across several contexts. In contrast, the adolescent limited offenders represent a contemporary maturity gap, with peer influence, where the teenager mimics criminal behavior [36]. Odgers et al [38] have shown in their longitudinal study of 526 male in the Dunedin study, measuring conduct problems at the age of 7, 9, 11, 13, 15, 21 and 26, that the typology has epidemiological as well as predictive validity.

Violent crime

In line with previous research and the suggested definition from WHO, we are using a broad definition of violent crime [9, 12]. This definition is aimed at capturing offences with the intention of causing physical or psychological harm to, or coercing another individual. The following crimes are included: homicide, assault, robbery, threats and violence against an officer, gross violation of a person's/woman's integrity, unlawful coercion, unlawful threats, kidnapping, illegal confinement, arson, intimidation, and sexual interpersonal violence including rape, sexual coercion, and child molestation.

The present thesis is based on criminal convictions or suspected violent crimes in remand prisoners. However, far from all violent offences are even reported to the police. Based on national surveys, the Swedish National Council on Crime Prevention (Brottsförebyggande rådet), which is the Swedish government's body of expertise, responsible for crime statistics, estimates that 34% of all assaults and 43% of all robberies get reported to the police and sexual offences has the lowest rate: 13%. Severity of violence and hospitalization increases the likelihood for a crime to be reported, while repeated offences or a young perpetrator decreases the likelihood [39]. Norms and acceptability does also affect victims' propensity to report a crime.

The Swedish legal system

The age of legal responsibility in Sweden is 15 years, consequently, no violent offences committed by a person under that age is documented as a violent crime. The National Criminal Conviction Register (paper III) includes all persons independently of custodial or non-custodial sentences, even when the prosecutor decided to caution or fine without a formal trial and when a defendant was judged to suffer from medico-legal insanity at the time of perpetration. In order to be detained at a remand prison (paper I&II) the law demands that the detainee is at least justifiably suspected (*skäligen misstänkt*) for a crime punishable by imprisonment for at least one year or more. Further, one of three criteria should be met: risk for recidivism, suppression of evidence or escape [40].

Individual risk factors for violence and substance abuse

Childhood conduct problems are associated with a range of negative outcomes, including substance abuse and criminality. Two childhood diagnosis in DSM-IV-TR captures serious disruptive behavior; Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD) [20]. ODD is defined as a "pattern of negativistic, hostile, and defiant behavior that persists over at least six months" The symptoms are causing severe impairment in social or academic

functioning. Conduct disorder is a precursor to the adult personality disorder Anti-social Personality Disorder (ASPD). A diagnosis of CD requires repeated violation of the basic rights of other individuals and meeting three out of the 15 diagnostic criteria, such as aggression to people and animals, destruction of property, deceitfulness or theft, and serious violations of rules, onset before or after the age of 10 is specified.

In the proposed revisions of the DSM-IV-TR to DSM-5 a specifier for "Callous and Unemotional (CU) traits" is suggested. The specifier is diagnosed if the criteria of CD are met, and if the individual shows two or more characteristics of callous and unemotional (CU) behavior (i.e., lack of remorse or guilt, callousness/lack of empathy, lack of concern about performance, and shallow or deficient affect [41]. This addition, as well as early onset, has important implications for the development of delinquent behavior. The adult diagnosis (over 18 years old) of Anti-social Personality Disorder requires a persistent pattern of anti-social behavior and the criteria for CD before the age of 15 must be met [20].

ADHD

Attention deficit hyperactivity disorder (ADHD) is a syndrome of inattention and/or impulsivity and hyperactivity with onset in childhood. The worldwide prevalence of ADHD is estimated to about 5% in the general population [42, 43] while studies of incarcerated men and women have suggested a high prevalence of 25% to 40% [44-46]. ADHD is highly prevalent in populations with substance use disorders (SUD) and associated with a more severe course of the syndrome [47]. A recent systematic review and meta-analysis of 29 studies (excluding those with nicotine as a primary drug of abuse) showed that 23% of all SUD subjects met DSM-criteria for comorbid ADHD [48]. This might be associated with hyperactivity/impulsivity being a predictor of early onset substance abuse [49], wish in turn is a predictor of adult substance abuse and mental health problems [50].

The comorbidity ADHD and CD is high; Larson et al (2011) suggested that 27% of children with ADHD also meet the criteria for CD compared with 2% of children without ADHD [51]. The combination of the two diagnosis inclines a worse prognosis for future criminality and violent behavior than an ADHD diagnosis alone [52]. However, with-in subject analyses of patients with ADHD diagnosis shows a 30% reduction in criminal acts when receiving pharmacologic treatment [53].

General cognitive ability

Wechsler (1944) defined intelligence as "the capacity to act purposefully, to think rationally, and to deal effectively with his or her environment" [54]. Intelligence is a global entity consisting of the sum of specific abilities [55]

and a strong predictor of school and job performance, years of education, income and social status [56]. Low intelligence is suggested as an important risk factor for criminality and the relation seems to be stronger for repeated and violent offenders [57-59]. Frisell et al (2012) showed in a large sample of 18-year old conscripts followed up over 35 years (using sibling comparison models) that cognitive ability was inversely associated with being convicted for a violent crime [60].

Major mental disorders

Major mental disorders, primarily, schizophrenia and bipolar disorder, have been associated with an enhanced risk for violence towards others [61, 62] as well as suicide [63, 64]. Further, the risk of violent crime in patients with major mental disorders seems to be stronger with a present comorbidity of substance use disorder [65-67]. Kim-Cohen et al (2003) have also shown that psychotic disorders often have been preceded by a juvenile history a several psychiatric conditions, including ODD and CD [68].

Childhood maltreatment

Adverse childhood experiences have been pointed out as a risk factor for substance abuse as well as anti-social behavior [69]. However, the association with future violent behavior does not appear to be simple. A meta-analytic review based on 18 studies with overall 18,245 participants found a small effect in prospective studies and a large effect in cross sectional studies, suggesting that many factors influence this relationship [70]. It has been shown that characteristics of the child and parent modify this relation [71] and that the observed risk rather is due to genetic and/or family environmental liability for abusive and violent behavior than a causal effect of maltreatment [72]. Thus, it seems like childhood maltreatment co-occurs with a load of risk factors in vulnerable families.

Substance abuse and violent crime

As mentioned above, substance and alcohol abuse are associated with an increased risk of interpersonal violent behavior. The relation is complex, addressing issues of proximal and distal risk factors, pharmacological effects, social context, and personal expectancy, as well as biological and psychological vulnerability [17, 18, 73]. Further, the propensity for aggressive behavior enhances the risk of being aggressive when under the influence of alcohol or illicit drugs [74].

Substance abuse and the effect of alcohol on aggression and violent behavior has been studied from the perspective of several disciplines, [13, 73]

and in relation to a variety of violent offenses, e.g., assault, homicide, domestic violence, and sexual assault [75, 76]. Substance abuse can enhance the risk for violence in several ways; the altering in behavior and perception due to the acute influence, withdrawal, drug induced psychosis, drug seeking behavior and circumstances related to drug dealing, for review see [17, 18].

A register based Swedish study found that 16% of all violent crimes during 1988-2000 were committed by people being discharged from hospital, treated with an inpatient diagnosis of alcohol misuse and slightly more than 10% of all violent crimes were committed by patients diagnosed as having misused drugs [12]. Inpatient diagnosis does of course only capture heavy alcohol and substance abusers, and it seems likely to argue that many more use or misuse alcohol and drugs occasionally, and might be involved in violent behavior. The Swedish National Council on Prevention (Brottsförebyggande rådet), report that 60% of assault offenders are under the influence of alcohol or narcotics as well as 50% of the victims [77].

A Swedish study on homicide in the 1970s and early 1980s revealed that 70% of homicide victims and perpetrators had been drinking alcohol in relation to the crime [78]. Forensic pathologist have since then noticed a change in misuse patterns, with more victims positive for illicit drugs, suggesting that the perpetrators might follow the same pattern [79].

The strong link between substance abuse and violent offences may also be due to a common underlying risk factor for both substance abuse and delinquency, in terms of impulsive and externalizing personality traits [80].

Neural effects

The increased risk of violent behavior when under the influence of alcohol and some psychoactive drugs can be explained by the neurophysiological effect of the substance. Hoaken and Stewart (2003) [17] suggests four pathways through which the pharmacological effects of psycho active substances (intoxication) act on violent behavior or aggression: effects on psychomotor activities (reward system) including approaching, sensation seeking, and attack behaviors; alteration of anxiety and/or threat systems, which dampens internal inhibitory mechanisms; alteration of the pain perception system, suggesting that either diminishing or increasing pain sensitivity would increase aggressiveness; and alteration of higher order cognitive capacities (e.g., planning, goal directedness, perception, and evaluation of information). According to the authors, [17] these pathways provide a framework that is neither mutually exclusive nor collectively exhaustive.

Different drugs have different effects and interact with several neurotransmitter systems, including dopamine, serotonin, and GABA (gamma-aminobutyric acid), that affect the risk of aggression [81, 82].

A psychoactive substance can either be *agonists;* contribute to enhance the occurrence of a certain neurotransmitter, or *antagonists*; having an inhib-

iting effect on the occurrence of a certain transmitter. For example, the degradation is prevented so the neurotransmitter remains in the synaptic cleft or the reuptake of the neurotransmitter is inhibited. The substance either mimics the neurotransmitter and binds on the receptor or inhibits the production of new neurotransmitters [83]. Often, intake of a substance affects several neurotransmitters and the central nervous system is very complex. I will briefly mention some neurotransmitters important for the regulation of behavior. Glutamate is considered to be the major mediator of excitatory signals in the mammalian central nervous system and is probably involved in most aspects of normal brain function including cognition, memory and learning [84]. Glutamate is popular referred to "the gas pedal" of the nervous system. GABA has the opposite function and is the major inhibitory neurotransmitter. Dopamine is above all involved in the reward system, but does also help to regulate movement and emotional responses. Serotonin is involved in mood regulation and aggressiveness. Noradrenaline is a hormone and neurotransmitter, for example involved in fight-flight responses. Endorphin, an endogenous opioid peptide binding on the opioid receptor, alleviates pain and gives a feeling of pleasure [83].

Alcohol

A large body of literature is provided regarding the association between alcohol and aggressive and violent behavior [15, 73, 74, 85, 86]. Alcohol intake has been associated with all types of violent offences; assault, homicide, sexual offences, domestic violence and child abuse [17]. Alcohol intoxication interferes with the higher order cognitive construct executive functioning, including for example inhibition, planning and decision-making. Further, the capacity of detecting internal and external cues is diminished [17]. Consequently, an alcohol-intoxicated person may experience less fear, interpret a social situation wrongly and act on impulses without evaluating any consequences. Hence, alcohol intake increases impulsive and risk-taking behavior. Alcohol is affecting several neurotransmitters in the central nervous system. At first, dopamine and the reward system generates a feeling of wellbeing. The inhibiting and anxiety reduced effect is due to alcohol binding to the GABA-receptor which in turn leads to a reduced activity in the serotonin-system, affecting impulse control and planning. Further, glutamate is inhibited and endorphins are released. [87].

Nevertheless, there are individual differences in alcohol aggressive eliciting responses and results from meta-analyses support this individual variation by showing that alcohol has a "medium" (d =0.49–0.61) effect on aggression [88].

Benzodiazepines

Benzodiazepines are prescribed for anxiety, insomnia and alcohol withdrawal. They are rare as primary drug of abuse but common as part of a polysubstance abuse pattern. It has been suggested that certain benzodiazepines with a short induction time (i.e., flunitrazepam) may induce aggressive behavior and anterograde amnesia [89-91]. Further, so called, paradoxical reactions, including aggressive behavior have been reported [91]. Benzodiazepines are, like alcohol, binding on the GABA receptor, but on a different site of the receptor, so were alcohol mimics the effect of GABA benzodiazepines does enhance the action [83].

Amphetamine

Amphetamine is a synthetic compound, first presented by a German chemist 1886. Introduced in healthcare in 1930s for treating depression, narcolepsies and to calm children with hyperactivity problems (later recognized as ADHD), an inhaler under the brand Benzedrine could be purchased over the counter for nasal congestion. Frequently used during the World War II for its effects on sleep, endurance and appetite. After the war, in 1945, pharmaceutical companies had large stocks of amphetamines and it was marketed as diet pills.

Amphetamine intensifies the release of dopamine and norepinephrine, while blocking the re-uptake and degradation of them. This is related to an enormous sense of wellbeing but it can also induce fear and paranoia that might trigger aggressive behavior [92]. Short term effects are for example: enhanced mood and body movement, euphoria, insomnia, reduced appetite and increased wakefulness and physical activity, while long term effects are for example, confusion, paranoia, hallucinations and weight loss [93]. Heavy abuse for a long period may trigger a drug-induced psychosis [94]. In Sweden amphetamine is the most commonly used illicit drug after cannabis and intake can be oral or intravenous.

Cocaine

The Latin American coca plant *(Erythroxylaceae*) has a long history of being used as a stimulant, and cocaine is derived from chemically processed cocaleaves. It was popularized as an anti-depressant by Sigmund Freud, who wrote the paper “In praise of Coca” in 1884 and the soft drink Coca Cola once contained cocaine.

The effect is similar to the effect of amphetamine, albeit shorter (15-30 minutes) due to the absence of inhibiting dopamine degradation. Intake is usually nasal, intravenous or through inhaling the smoke. The latter concern

crack cocaine, cocaine chemically altered so that it vaporizes at low temperatures. Crack cocaine is less common in Sweden.

Cannabis

Cannabis is derived from the Indian plant Hemp *(Cannabis sativa)*, also with a long tradition of use for its relaxing effects. The active compound in herbal cannabis is tetrahydrocannabinol (THC). Hashish (the resin) or marihuana (the leaves) is normally inhaled through smoking but can also be ingested. As mentioned above cannabis is the most commonly used illicit drug worldwide, even legally in some parts of the world.

Cannabis is not primary related to violence or aggression but it has side effects that might enhance the risk for violence; drug induced psychosis [95] and cognitive deficits [96] and a recent longitudinal study could prove that persistent cannabis users have a decline neuropsychological functional from childhood to midlife [97]. It has also been shown in laboratory studies that small doses or withdrawal enhances the risk for aggressive behavior [17]. The neural effect of cannabis is complex, but it includes copying the neurotransmitter anandamid and binding to the cannabinoid receptor, implicit, enhancing the release of dopamine [83]. A curious thing with cannabis is, opposed to other drugs, that it might give race to a reverse tolerance, where one need smaller intake for a desired effect [98].

Opiates

Opiates is the term referring to substances derived from the Opium poppy *(Lachrymal papaveris)*, while there synthetic analogues are named opioids. The German pharmaceutical company Bayer introduced heroin in the late 1890s as an alternative to the highly addictive morphine. Morphine is derived from opium and heroin in turn from morphine. Unfortunately, heroin had the same highly addictive potential as morphine, with severe withdrawal symptoms.

Opiates are above all very lethal, and in general not related to violent behavior but rather associated with drug and property crimes [14]. The effect is sedative, pleasant and analgesic. However, withdrawal and drug seeking behavior may increase the risk for violence [17, 18].

Anabolic androgenic steroids (AAS)

It might have been the desire of strength and youth, or just curiosity, that made the French physiologist Brown-Séquard, in 1886, inject himself with extracts from the testis of animals, claiming a both physically and mentally rejuvenating effect [99]. The male hormone testosterone was simultaneously

identified by two research groups and lead up to Adolf Butenandt and Leopold Ruszia achieving the Nobel Prize in chemistry 1939.

Anabolic androgenic steroids, the male hormone testosterone and its synthetic analogues, promote growth and effect the development and maintenance of secondary male sexual characteristics. AAS is used for therapeutic purposes, treating for example hypogonadism and amnesia. Illicit administration of anabolic androgenic steroids (AAS) has primarily aimed at enhancing athletic performance and body appearance. AAS use spread in the general population during the 1980s and is seen today as a major health problem [100]. Clinical observations, case reports and anecdotes have repeatedly reported a relation between use of anabolic androgenic steroids and violence and a quite large body of literature, with divergent results, have aimed to confirm the association. For that reason, AAS has earned more focus in the present thesis than other common drugs of abuse.

Beyond the desired anabolic muscle building effects, AAS use has been associated with a range of somatic (e.g., cardiovascular and reproductive) complications, and psychiatric side effects (e.g., depression, irritability, mania) [100-102]. AAS are indeed psychoactive substances and affect several neurotransmitters across different brain regions, including the reward system and aggression-related pathways [103], often thought to be expressed as improved self-esteem but impaired impulse control, extreme mood swings, and aggression [104, 105].

As mentioned above, a substantial but divergent literature has tested the association of AAS with aggression and violent behavior in humans. In a randomized controlled trial, Pope et al (2000) [106] studied possible psychiatric effects of supraphysiologic doses of testosterone, the group of 56 normal men showed testosterone-induced mania and verbal hostility responses. However, effects varied considerably across individuals; most (84%) reported minimal effects, a few (4%) large effects and the rest (12%) reported mild effects. Thus, few subjects contributed substantially to the overall significant effect on manic scores and verbal hostility, while none of the 56 participants was involved in a violent act during the study period.

Klötz et al (2006) [107] examined registered criminality in a selected clinical cohort of individuals tested for AAS use in Sweden. Among 1440 tested individuals over 6 years, the 241 (16.7%) who were AAS-positive had significantly more often been convicted of fraud and weapons offences, but not for violent or property crime. Further, our own study on remand prisoners with known substance abuse reported AAS use more often (odds ratio [OR]=1.65), when suspected of a violent crime as compared to other offence categories [108]. However, no temporal relation to the suspected offence was identified, which argues against a direct pharmacological AAS effect on violent behavior.

The lifetime prevalence of AAS use is much higher among criminal offenders than general population controls [108, 109], and there are common

risk factors for AAS use, criminality and substance abuse in general. Childhood conduct disorder is a major risk factor for AAS use among weight lifters [110]. This childhood condition substantially increases the risk for adult antisocial personality disorder, criminality and substance abuse [68, 111]. Use of AAS has been related to risk factors including dissatisfaction with school, truancy and living alone at early age [112]. Further, use of AAS has been associated with other forms of risk-taking behavior; physical fights, carrying a gun and sexual risk taking [113].

A growing body of literature has confirmed use of AAS as part of a substance abuse pattern in general [110, 112, 114, 115] and it seems like use is overrepresented among abusers of other forms of drugs, even without being engaged in physical exercises [116]. Further, heavy AAS users engage in poly pharmacy including licit drugs as well as common drugs of abuse, due to, for example, enhance endurance, burn fat, calm down and reveal pain [117].

Substance abuse and suicide

The term ‘suicide’ comes from the Latin word sui (of oneself) and caedere (to kill) and is, as mentioned previously in the introduction, regarded as an act of violence.

Knowledge about the role of acute alcohol and substance abuse in suicidal behaviour is sparse [118] even though several studies report alcohol and substance abuse as a risk factor for suicide. A review of articles examining studies on acute alcohol intake preceding suicide found a range 10%-69% [119] and in the United States, at least one quarter of all suicides are reported to involve alcohol abuse [120], but very little is known about suicide under acute intoxication of illicit drugs.

In a meta-analysis on suicide as an outcome for mental disorder that assessed 32 papers with a total of 45,000 participants from 11 countries, Harris and Barraclough (1997) [64] showed that the risk for suicide in alcohol abusers or alcohol dependents was six times greater than expected, and in cannabis dependents four times greater.

However, it is more challenging to determine if the increased suicide risk is due to the direct influence of substance use or if it is related to psychiatric comorbidity or social factors. The general population risk factors for suicide include gender, psychopathology, family dysfunction, social isolation, childhood trauma, and earlier suicide attempts; these also apply for substance abusers [121-123] and as, with other forms of violence there are often a combination of several risk factor that contribute to an enhanced risk.

Suicide methods

The choice of suicide method is related to gender, intention, availability and cultural norm [124-129]. It is common to classify the methods according to how violent they are, with poisoning and sometimes single wrist cuts as non-violent methods and others (e.g., hanging, drowning, jumping, repeated deep cutting) as violent [130, 131]. Violent suicide methods are in general more lethal [132] and a suicide attempt with such a violent method inclines a worse prognosis in terms of a future completed suicide [133]. A prior history of aggression and violent behaviour is associated with both suicidal ideation and completed suicide [134-136]. Further, suicide risk and violence risk has shown to be positively correlated [137] and substance abuse, lifetime aggression, impulsivity, and young age have been associated with using a violent suicide method [138].

As mentioned above, little is known about acute intoxication and suicide and even less about acute intoxication and suicide methods. Kaplan et al (2012) revealed in a large (n= 57, 813) study of suicide descendants in USA that suicide methods related to acute alcohol intoxication was in urban areas: self-inflicted firearm injury, hanging/suffocation and falling. In rural areas: self-poisoning [118].

Gender differences

There are prominent gender differences in both the rate of violent offending, completed suicide, using a violent suicide method and substance abuse. The men: women ratio in alcohol abuse/dependence is 1:3 and 1:4 in substance abuse/dependence [139, 140]. The lifetime risk for being convicted for a violent crime is ten times higher among men, however criminal convictions with a female perpetrator increased from 5% in 1973 to 10% in 2009 [141].

Men account for more than twice as many completed suicides in comparison with women, and are more likely to use a violent suicide method. Women on the other hand account for a higher proportion of suicide attempts [142, 143].

Gender above is synonym with the biological sex, but observed differences may be due to gender as in the social sex. Expectancies on male and females may contribute to behavior but also to perception and interpretation of behavior.

The externalizing spectrum

As already touched upon, substance abuse, impulsive, aggressive and antisocial behavior often co-occurs and prospective studies have reported conduct

problems to precede substance abuse [50, 68, 144]. Further, individuals with the propensity for aggressive behavior react more aggressive under the influence of alcohol [145]. Krueger et al (2007) suggests an underlying factor, *the externalizing spectrum*, linking substance abuse, anti-social behavior and impulsive-aggressive personality traits [80]. Examine this underlying factor with genetically informative models reveal that the variance of the externalizing factor is mostly genetic, but both genetic and environmental factors account for distinctions among phenotypes within the spectrum [146].

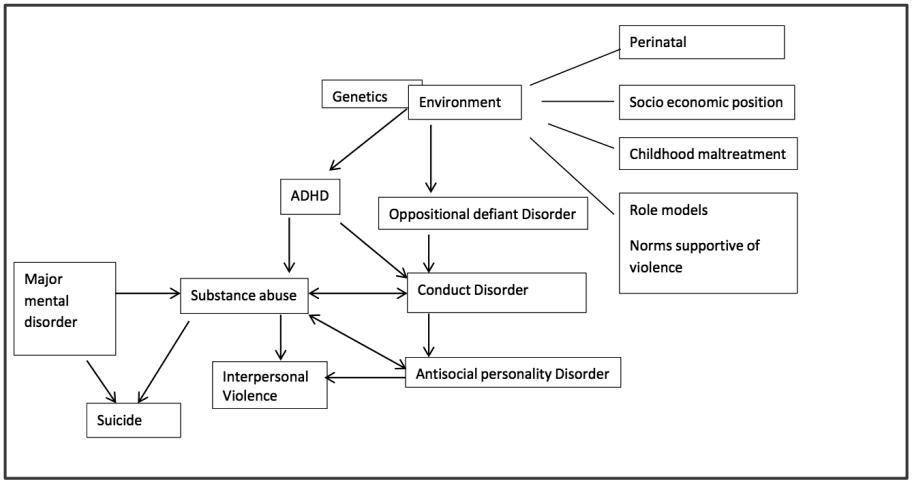
Risk factors and violence prevention

A general definition of a risk factor is something that occurs prior to an undesired event. Risk factors can be categorized as static or stable versus acute or dynamic. They can also be individual or contextual. Static risk factors indicate stability over time and include stable individual characteristics (e.g., gender, ethnicity) and historical factors (e.g., age at first conviction, adverse childhood experiences). Acute or dynamic risk factors can be individual (e.g., substance abuse, impulsivity) or contextual (e.g., lack of social support, violent neighborhood). Static risk factors are informative for prognosis but dynamic risk factors more meaningful as targets for intervention. Violence prevention can be addressed on several levels, global, societal, group and individual levels. Primary prevention is aimed at preventing the risk overall, on a global or societal level by diminishing racial or gender discrimination or economic inequalities. Secondary prevention targets early signs, for example children with conduct problems. Tertiary prevention would aim at reducing relapse in violence among those who already exhibited this behavior.

To summarize

The propensity or risk for violent behavior is multifactorial and many of the factors that increase the risk of violence are shared across different types of violence. Figure 1 illustrates tentative pathways and risk factors. Substance misuse is one risk factor that interacts with several others. The clinical significance for paying attention to substance misuse is that it is potentially modifiable and might occur closer to the onset of violence.

Figure 1. Tentative pathways of individual risk factors for substance abuse and violence



AIM

The overall aim of this thesis is to investigate substance use in relation to violent offences and violent suicide.

Specific aims

In paper I, our aim was to examine the occurrence of AAS-use among other forms of substance abusers suspected of a variety of crimes, in order to test the relation between self-reported AAS-use and being suspected of a violent offence.

In paper II, we examined the triggering effect of alcohol, illicit drugs, benzodiazepines and anabolic androgenic steroids on violent crime.

In paper III, we examined the link between AAS use and violent crime in a population-based sample while controlling for polysubstance abuse and additional suggested risk factors for violence.

In paper IV, we investigated suicide method in relation to acute intoxication of alcohol, THC and central stimulants.

MATERIAL AND METHODS

Participants

The studies are based on four data collections: paper I (n=3,594) and II (n=194) are based on interviews with remand prisoners. Paper III is based on the "Screening Twin Adults: Genes and Environment: STAGE" (n=10,365) under The Swedish Twin Register. Finally paper IV is register based, including nearly all suicides in Sweden 1994-2009 (n=18,894).

Paper I

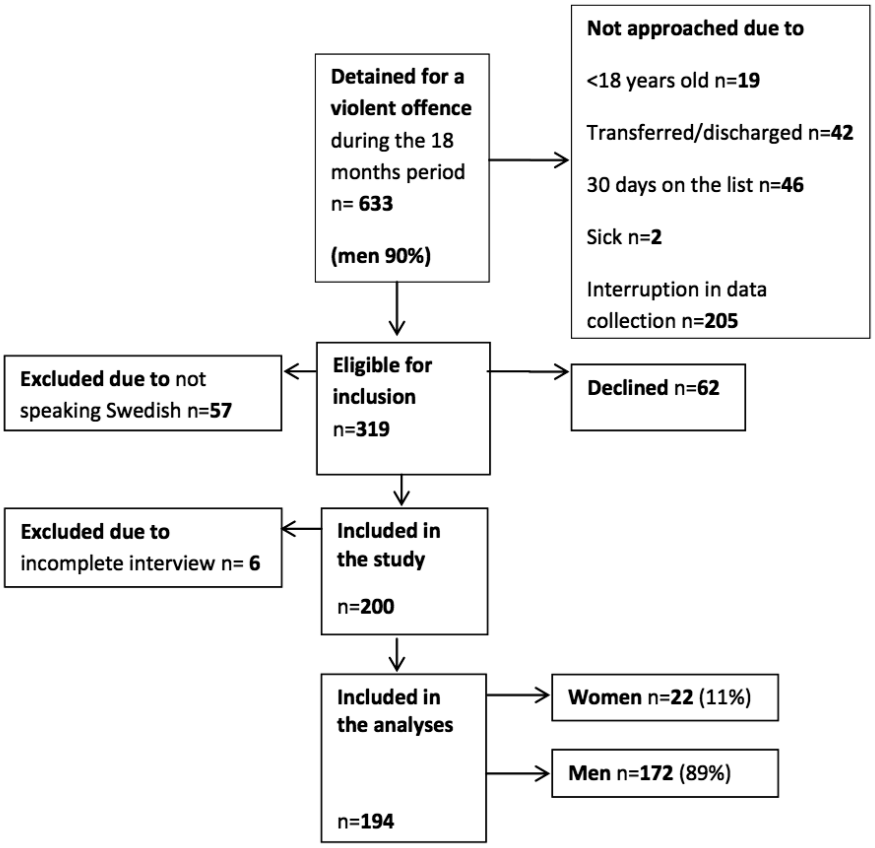
The first study is based on interviews with 3,594 substance abusers, 396 women and 3,201 men, at two remand prisons in Sweden from 2002 through 2008 as part of *The Social Medicine Remand Prison Project*, with the main purpose of preventing HIV and hepatitis. A trained nurse received a list of new custodies every day. She contacted them in their cells, and if they met the criteria for drug misuse and agreed to participate, she carried out the interview. Data from the interviews were organized in an Excel file, and even if a person had participated several times during the period, he or she would only occur once, usually with the first interview, in the file. The file also contained demographic information as well as criminal charges. Analyses concerned type of criminal act, primary drug of abuse during the past year and temporal relation between reported AAS use and the suspected violent crime.

Paper II

The second study is based on 194 interviews with remand prisoners suspected of a violent crime at Häktet Kronoberg in Stockholm (174 men, 22 women) during an 18-months period. A licensed psychologist (the author LL) received a list of new clients upon arrival at the setting once a week. Inclusion criteria were 18 years of age or older, Swedish speaking and detained for a violent crime. If an individual had been listed for 30 days and had not yet been interviewed, he or she was excluded to minimize the effect of recall bias. The mean time between the suspected violent crime and the interview was 60 days (median 18 days, range 2-1463 days). During the study period, 633 persons suspected of committing a violent crime were detained at the

remand prison (according to the Prison and Probation Administrative System). Of these, 319 were eligible for study inclusion and 200 agreed to participate. Six interviews were excluded because they were of insufficient quality (figure 2 Flow chart of recruitment*).*

Figure 2. Flowchart of recruitment paper II



Paper III

The third study is based on all male participants responding to the questions regarding use of anabolic androgenic steroids (AAS) (n=10,365) in the STAGE- survey. Women were excluded due to the rareness of both violent crime (lifetime conviction rate less than 1%) [9] and AAS use.

In The Swedish Twin Adults: Genes and Environment (STAGE), were all twins in the Swedish twin register born 1959-1985 (20-47 years old at data collection in 2005-2006) and where both siblings were alive and living in the country (n=42,224; 21,174 men, 21,050 women) invited to participate in a web-based survey. The questionnaire contained items tapping sociodemographic conditions, stressful and traumatic life events, physical and mental health, substance misuse and sexual behavior. Participants could also choose a telephone interview supplemented with a self-administered paper questionnaire for sensitive topics. Non-responders were reminded up to three times and the overall response rate for the survey was 60.1% (n=25,381).

Paper IV

The fourth study is based on suicide cases (n=18,894; 13,352 men, and 5,542 women) obtained from a forensic research register containing information on all medico-legal death investigations in Sweden from 1994 to 2009, including information on toxicological findings and manner of death. Almost all (98%) of the suicides committed in Sweden are examined by a forensic pathologist and are hence in the register. Responsible for the register is The Swedish National Institute of Public Health and Karolinska Institute. The main purpose with the register is to provide statistics on drug related death, including suicide. Based on information from the forensic pathologist the manner of death is coded according to the World Health Organisation's International classification of Diseases (ICD-10) [147] at the Cause of Death Register, and collected to the forensic research register. All decedent with diagnoses; intentional self-harm (ICD-10 codes X60-X84, table 2) and corresponding codes from ICD-9, were included in the study. The reason for not including suicides classified as events of undetermined intent, which is common in suicide research, (ICD-10 codes Y10-Y34) was that the proportion may be larger in the drug positive population than in the general population.

Table 2. *ICD-codes Intentional self-harm (suicide)*

X60-X69	Intentional self-poisoning
X70	Intentional self-harm by hanging, strangulation and suffocation
X71	Intentional self-harm by drowning and submersion
X72-X74	Intentional self-harm by firearm
X78	Intentional self-harm by sharp object
X80	Intentional self-harm by jumping from a high place
X81	Intentional self-harm by jumping or lying before moving object
X75, X76, X79, X82-X84	Other

Data collection

Paper I

The interview contained up to 81 questions related to drug abuse, sexual habits, blood borne pathogens and sexual transferred diseases, STDs (i.e., HIV and hepatitis). Issues concerning main drug of use, polydrug use, age of first injection, age of last injection, and the drug most frequently used during the past year, followed by what drug was second most frequently used, were addressed. AAS use was documented by three questions: if they had any experience from using AAS (per oral, intramuscular, or intravenous), at what age they started (not included due to high degree of missing), and when they used AAS the last time.

Paper II

The interview included demographic questions, a subjective description of the violent crime for which the participant had been remanded, and questions regarding substance intake as a potential trigger (i.e., last intake of alcohol or drugs in relation to the index crime, one week previously, and during the past year). For alcohol a question of amount of alcohol at last intake was added and the usual frequency for that amount. For benzodiazepines, the questions of whether they had used a high dose (that is, a high dose compared to usual use) and for what reason they used (the expected effect) were added. For AAS, there was an additional question about lifetime use and

purpose of using. To facilitate the memory of the requested information, a calendar was used to identify the date of the index crime and control periods. Participants also responded to four questions regarding psychiatric treatment and psychiatric diagnoses. Conduct disorder and antisocial personality disorder were assessed by the structured Mini-International Neuropsychiatric Interview [148]. Under surveillance of the interviewer, able to help and exemplify the questions, the participants also completed five self-reporting questionnaires.

Self-reported questionnaires

1) The Childhood Trauma Questionnaire (CTQ), a 28-item questionnaire with five sub-scales measuring emotional, physical, and sexual abuse and emotional and physical neglect during childhood [149].

2) The Alcohol Use Disorders Identification Test (AUDIT), ≥ 16 points equals alcohol abuse/dependence [19].

3) The Drug Use Disorders Identification Test (DUDIT), ≥25 points equals drug abuse/dependence [150].

4) The Adult ADHD Self-Report Scale volume 1.1 [151] a six-item screening instrument for adult attention deficit hyperactivity disorder, ≥ 4 item marked as significant problems was coded as screening positive for ADHD;

5) The Montgomery-Asberg Depression Rating Scale [152], ≥20 points identifies a current depression.

Paper III

Data is based on self-reported information in the STAGE survey. Lifetime use of AAS was derived from respondents' answer to the question: *Have you ever used anabolic androgenic steroids?* Alcohol abuse was defined as lifetime alcohol abuse/dependence according to DSM-IV-TR [20]. Drug use was based on lifetime use of amphetamine, cocaine, cannabis, benzodiazepines (benzodiazepines and zolpidem) and Rohypnol®. Rohypnol® use was asked for separately, since its active substance *Flunitrazepam* probably confers a higher risk of dependence and was claimed to trigger violent behavior [90]. Seven other substances were asked for in the survey and initially tested for their effect on the association between AAS and violent crime: methylphenidate, codeine, other opiates, ecstasy, LSD, gammahydroxybutyrate (GHB), and psilocybin ("mushrooms"), but not included in our analyses for reasons described under *Statistical analyses.*

For each endorsed substance including AAS, additional questions addressed age at first use, age at most frequent use and intensity during that

period, and age at last use. However, substantial non-response rates for these follow-up items would have compromised the analyses and, hence, were not used for the current study.

Current ADHD was assessed with the 18 symptom criteria from DSM-IV-TR [20], some slightly rephrased to better suit adults. Respondents endorsed the presence of symptoms persisting at least six months on a three-point scale (*0="no", 1="yes, to some extent" or 2="yes"*). From this, we created an ADHD summary score (0-36). We constructed a dichotomous measure of possible adult ADHD according to DSM-IV diagnostic cut-offs of six or more out of nine items endorsed with *yes* or *yes to some extent* in the inattention and/or the hyperactivity/impulsivity criteria subsets. Age of symptom onset, pervasiveness across settings and distress or impairment criteria were not taken into consideration.

A screen-positive result for self-reported personality disorder was defined as ≥4 points on the eleven-item IOWA Personality Disorder Screen (possible range 0-11 points; [153]. With a ≥4 cut-off, the instrument has a sensitivity of 0.77 and a specificity of 0.71[154].

Registers

The register of criminal conviction

The National Criminal Conviction Register includes all persons independently of custodial or non-custodial sentences, even when the prosecutor decided to caution or fine without a formal trial and when a defendant was judged to suffer from medico-legal insanity at the time of perpetration. Since criminal responsibility in Sweden starts at age 15 years, no offences committed before this age are recorded in the Conviction Register. It does not contain information on changes in verdict or sentences after appeal to higher courts [141]. In line with previous research, we used a broad definition of violent crime [15, 60, 65] aimed at capturing offending with the intention of causing physical or psychological harm to or coercing another individual. The following crimes were included: homicide, assault, robbery, threats and violence against an officer, gross violation of a person's/woman's integrity, unlawful coercion, unlawful threats, kidnapping, illegal confinement, arson, intimidation, and sexual interpersonal violence including rape, sexual coercion, and child molestation. Attempted and aggravated forms of these offences were included when applicable.

The Swedish Military Service Conscription Register

Swedish military was until 2010 based on national conscription, mandatory for all male citizens at about the age of 18. Enlistment included a battery of psychological and physical tests recorded in the Swedish Military Service Conscription Register.

General cognitive or intellectual capacity (IQ) was measured within the Swedish Enlistment Battery. The test consists of four subscales capturing different aspects of cognitive ability (verbal, spatial, inductive, and technological), measured on a Stanine scale (a normal distribution divided into nine categories, with mean=5 and standard deviation=2).

The scale was standardized each conscription year, so there is no change in the distribution over time. A subset of all men enlisting in 1965 were retested 1-4 years later, yielding high test-retest correlations (1 yr and 2 yrs, respectively=0.89; 3 yrs=0.80, 4 yrs=0.84) [155].

Psychological functioning was also measured as part of the assessment battery at compulsory conscription. Based on a semi-structured interview by a clinical psychologist, psychological functioning was judged on a 1-9 Stanine scale. Psychological functioning supposedly reflects stress coping during war or similar extreme stress situations [156].

The National Censuses

Population and housing censuses were performed in Sweden every five years 1960 -1990. In paper III we obtained socioeconomic characteristics from the National Censuses of 1970, -75, -80, and -85, of the household in which our study population lived in early childhood (childhood income). For each individual, we used information from the census that was closest in time to the year after their birth, meaning that their age at the census ranged from less than 1 to 10 (the latter only for individuals born 1959).

Income was based on the taxed income of the "head of household" assigned in the census (in married couples at the time, always the man). To manage skewness and inflation, income was rank coded in deciles (1-10) in each census year.

Living with a single mother was coded 1 if the family type was registered as such in the census, otherwise 0.

We used Statistics Sweden's coding of Household SEI (socioeconomic index) constructed from both parents' occupation and divided into categories reflecting the education needed for the job, associated status and payment. Since SEI coding has changed somewhat over time, we collapsed the coding into four categories: Low (skilled and unskilled workers across all fields), Medium (low- and intermediate position white collar workers), High (high-position white collar workers) and self-employed professionals and entrepreneurs. The latter included all owners of private enterprises (except agricultural), regardless of size [157, 158].

Paper IV

The Forensic Research Register

The register comprises information from two forensic registers; *Toxbase* (toxicological analyses) and *Rättsbase* (information from the forensic evaluation), containing information on all medico-legal death investigations in Sweden from 1994 to 2009, including information on toxicological findings and manner of death.

Responsible for the register is The Swedish National Institute of Public Health and Karolinska institutet. The main purpose with the register is to provide statistics on drug related death, including suicide [159].

Based on information from the forensic pathologist is the manner of death coded according to the Word Health Organisations International classification of Diseases (ICD-10) at the Cause of death register, and collected to the forensic research register.

Geographical region is based on the catchment area for the six departments of Forensic Medicine in Sweden and included in the register.

National Patient Register (NRP)

The National Patient Register is managed by the National Board of Health and Welfare and covers all psychiatric inpatient diagnoses since 1973. Information on inpatient diagnosis at last discharge from hospital was obtained from the register**.**

Statistical analyses and study design

Logistic regression was used in all four studies. Paper I, III&IV are using a cross-sectional design, investigating the likelihood for the outcome a violent crime or a violent suicide method. Paper II is using the case-crossover design where instead of comparing groups, the participants serve as their own controls when calculating the risk for a violent crime.

The Case-crossover design

The case-crossover design was introduced in 1991 by Maclure as new epidemiological study design for the purpose of investigating triggers [160], the study of brief exposures on the onset of acute events in order to answers the question "Was this event triggered by something unusual that happened just before?"

The method departs from the assumption that if there were precipitating factors these would occur more often prior to an event than during a period further from the onset. It was, as mentioned, originally used for examining

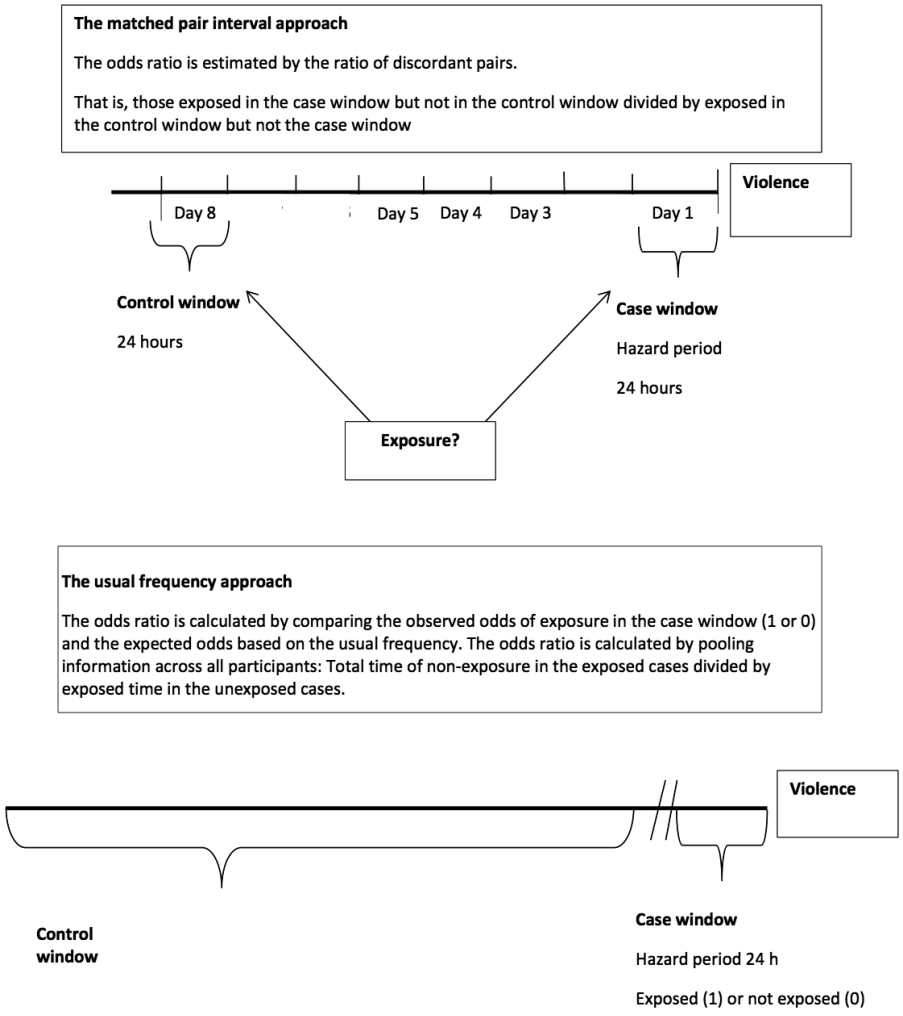
triggers of myocardial infarction, but have during the past two decades been used for an area of research [161-165] including substance abuse as a trigger for violence [15].

Maclure and Mittelman [166] defines a trigger as a more proximal and transient causal risk factor than other risk factors. According to the *sufficient component cause-model* [167] a trigger's contribution to the causal process can be understood as one of the last component causes that will make the sufficient causal process complete (sufficient component cause-model) [167]. Some exposed cases would not have occurred at that time, if they had not been exposed by the trigger immediately before [166]. The case-crossover design applies best if the exposure is intermittent and the effect on risk is transient and immediate and the outcome abrupt. All types of exposures can be studied providing the possibility to differentiate between periods of exposure and non-exposure and that the effect of the exposure is transient.

Substance use is not a necessary component for violent behavior but it might be the trigger, the last component causes, that increases the likelihood for violence.

Unlike a case-control study, the case-crossover design involves only cases that serve as their own controls. This gives the opportunity to handle static, within the individual, long-term risk factors. The comparison is made within the individual, comparing exposure at the case period (e.g., the time at the index crime) with exposures at personal control periods. The case window is a time frame of observation (the hazard period) when the trigger is supposed to have an effect on the outcome. The design resembles that of either a matched case-control study (the matched-pair approach), in which the control information is collected from a certain control period matched to the case period, or a retrospective cohort study in which the control information is from the person-time of the exposure (the usual frequency approach).
Figure 3 illustrates the two approaches.

Figure 3. The matched-pair and usual frequency approaches



Statistical analyses

Paper I

Logistic regression was performed to calculate the odds ratio for committing a violent crime in the group of AAS users. Analysis with Fisher exact test was performed for testing the observed difference in the proportion of subjects reporting benzodiazepines as the main drug of abuse during the last year and Chi 2-test was used for testing the difference between the AAS users with and without current use of benzodiazepines regarding violent

crime. Statistica 8.0 (Statsoft 2008) and Graph Pad 3.10 (Graph Pad Software.inc 2010) were employed for the analyses.

Paper II

Two types of case-crossover analysis were applied: a usual frequency approach and a matched pair interval approach. In the usual frequency approach, the relative risk can be interpreted as the ratio of the observed odds of exposure during a period of 24 hours from the violent crime to the expected odds of exposure from the control period (days of substance use during the past year). Odds ratios, estimated by Mantel-Haenszel estimator with confidence intervals for sparse data [160, 166] was used to estimate the relative risk, which can be seen as an estimation of the average incidence rate ratio.

The matched-pair interval approach was analyzed with standard methods for matched case-control studies; conditional logistic regression in which each case/event was considered as one stratum [160, 166]. The results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). SAS version 9.2 was used for case-crossover analyses and SPSS 19 for descriptive statistics.

Multiple exposures and stratified analyses

Analyses were also performed considering multiple exposures. In the usual frequency analysis, participants who were exposed to more than one substance at time of the index crime (24 hours) were excluded from the analysis. With the matched pair interval analysis, a multivariate analysis was conducted by entering all exposures into the model.

Stratified analyses were performed regarding sex, childhood trauma (reporting moderate to extreme trauma on any CTQ sub-scales), conduct problems (conduct disorder, antisocial personality disorder, ADHD), and psychiatric vulnerability (reporting ever having been treated for psychiatric morbidity). A correlation analysis of the reported frequency of alcohol consumption and AUDIT scores was performed.

Inter rater reliability

Fifteen randomly chosen interviews were tested for inter-rater reliability; a second rater (UH) was present at these interviews to score the information independently. The intra-class correlation coefficient average measures type was .75-1.0 for continuous data (i.e., time from exposure to event, person-time of exposure). For nominal and categorical data, Cohen's kappa was equal to .82-1.0, presenting good agreement [168].

Power analyses

Only half of the sample size is needed in the case-crossover study compared to the traditional case-control study. However, standard methods for power analyses cannot be applied for case-crossover studies. The possibility to detect an effect depends on the prevalence of exposure in case and control window and discordant combinations. Thus, rare exposures require a larger sample. As the prevalence of several exposures was unknown to us, we were unable to carry out power analyses prior to conducting the study.

Paper III

The association of AAS use and violent offending was analyzed with logistic regression and 95% confidence intervals calculated with robust standard errors (SAS version 9.1) taking the relatedness of twin siblings into account.

Our aim was at first to investigate the association between reported use of AAS and conviction of a violent crime. Second, we wanted to see if and to what extent other forms of substance abuse attenuated this relation. We adjusted analyses for birth year as a categorical variable.

Substance abuse analyses

First, birth year-adjusted bivariate associations were calculated separately for each substance asked for in the survey: AAS, different illicit and licit drugs, and alcohol abuse/dependence with a violent crime conviction as outcome. Second, we tested if the association of AAS and violent crime was attenuated by adjustment for other substance use, and if so which was the minimum number of substances that could explain the attenuation.

Initially, we tested if including each specific substance individually influenced the association of AAS with violent crime (data not shown). After removing those that did not yield any change (methylphenidate and codeine; less than 5% change in the regression coefficient) in the association of AAS and violent crime we entered all remaining substances (alcohol, amphetamine, cannabis, benzodiazepines, Rohypnol® other opiates, ecstasy, LSD, gammahydroxybutyrate (GHB), and psilocybin ("mushrooms"), into the model, and proceeded to iteratively remove the substance with the weakest association to violent crime from the model. If removing the substance affected the association (β-coefficient) of AAS with violent crime more than 10% it was reentered into the model, followed by removing the substance with the next weakest association. This approach was chosen in favor of, for example, a step-wise regression analysis as we wanted to examine *to what extent* each substance affected the relation between AAS and violent crime.

The variable selection procedure revealed that including any substance in addition to amphetamine and Rohypnol® did not further attenuate the association of AAS with violent crime, although several other substances where

substantially associated to violent crime. However, based on previous research and judging potential loss of power to be minor, we chose to keep four other common drugs of abuse (alcohol, cannabis, other benzodiazepines and cocaine) in the statistical analyses. Thus, we performed birth year-adjusted multivariate analyses where use of AAS, Rohypnol®, other benzodiazepines, amphetamine, cocaine, cannabis and Alcohol abuse/dependence were entered simultaneously in the model.

Potential confounders

We tested the association between AAS and violent crime controlling for the literature-based potential confounders described above. The scarcity of the data did not allow us to enter all covariates into the analyses simultaneously, and the degree of potentially informative missing on some covariates made separate analyses difficult to compare. Consequently, we limited the analyses on the association of AAS use with violent offending to participants with information on the specific covariate in four steps: 1) adjusted for birth year, 2) adjusted for birth year and specific covariate, 3) adjusted for birth year and substance abuse, and 4) adjusted for birth year, substance abuse, and the specific covariate (table 10, under results).

Paper IV

Multivariate logistic regression was performed and the relative risk with 95% confidence interval was calculated, adjusting for sex, age, geographical region and psychosis, with poisoning as reference for suicide method, and no alcohol or illicit drug as reference for substance influence.

Relative risks were calculated by dividing the theoretical proportions with outcome for the exposed and the unexposed group for each variable. The theoretical proportions were calculated using the intercept and the estimate for the variable from the logistic regression. This made it possible to use relative risks instead of odds ratios. All analyses were performed employing the software SAS version 9.2.

RESULTS

Paper I: Use of anabolic androgenic steroids in substance abusers arrested for crime.

In paper I, our aim was to examine the occurrence of AAS-use among other forms of substance abusers suspected of a variety of crimes, in order to test the relation between self-reported AAS-use and being suspected of a violent offence.

Of the 3,594 (3,201 men and 396 women) remanded prisoners, 924 (26%) reported ever using AAS (28% of the men and 5% of the women). The time since last use varied from current use to twenty years back, with a mean of four years since last intake.

Those stating any lifetime use of AAS were more likely to be suspected of a violent crime (OR=1.65 CI 95% 1.40-1.93). However, the association declined, but remained significant, after adjusting for sex and age (OR=1.28 CI 95% 1.08-1.51) as see in table 3. There were no difference between AAS users and non-users regarding primary drug of abuse during the past year, with one exception, use of benzodiazepines, which was more common among participants stating use of AAS: 7.9% (n=73) of AAS users vs. 4% (n=96) of nonusers (OR 2.30 95% CI 1.66-3.19, p<.0001 Fisher´s exact test). However, there was no difference regarding violent crime. Among the AAS experienced male with benzodiazepines as primary drug of abuse, 40% (29 of 72) were suspected of a violent crime and 36% (301 of 832) among those who had AAS experience but not benzodiazepine as their main drug (X^2=0.48 p = 0.49). It was only one of the twenty women who had the combination of AAS and benzodiazepines, and she was not suspected of violent crimes.

No temporal relation between use of AAS and the suspected violent crime was found, table 3.

Table 3. *Time since last using AAS and users vs. non-users regarding suspected crime.*

	Time since last use AAS				**Ever vs. never used AAS**			
Crime	AAS past months n=67	AAS past year n=215	AAS use in the 1-5 years n=282	AAS use >5 years ago n= 360	Ever used AAS n=924	Never used AAS n=2673	OR Crude (CI95%)	OR Adjusted for sex and age (CI95%)
Violent crime	25 (37%)	82 (38%)	105 (37%)	123 (34%)	335 (36%)	687 (26%)	1.65 (1.40-1.93)	1.28 (1.08-1.51)
Sexual crime	2 (3%)	2 (1%)	3 (1%)	7 (2%)	14 (2%)	47 (2%)		
Weapon offence	1 (2%)	4 (2%)	9 (3%)	9 (3%)	23 (2%)	28 (1%)		
Drug related crime	14 (21%)	52 (24%)	64 (23%)	77 (21%)	208 (23%)	781 (29%)		
Crime against property	10 (15%)	51 (24%)	68 (24%)	80 (22%)	208 (23%)	667 (25%)		
Other	15 (22%)	24 (11%)	33 (12%)	64 (18%)	136 (15%)	463 (17%)		

Paper II: The triggering effect of alcohol and illicit drugs in a remand prison population: A case-crossover study

In paper II, we examined the triggering effect of alcohol, illicit drugs, benzodiazepines and anabolic androgenic steroids on violent crime. Of the 194 participants, 118 (61%) were exposed to one or more substances within 24 hours of the index crime. Table 4 shows information on education, living and income during the past year. Mean age for men and women were about 30 years and of the men, 17% had not finished 9 years of mandatory school.

Table 4. *Education, living and income the past year*

	Male	**Female**
Sex	172	22
Age	30.51 (sd 10.88)	30.68 (sd 9.64)
Highest education		
Less than 9 years	30 (17%)	0
9 years compulsory school	70 (41%)	10 (45%)
High school	61 (35%)	9 (41%)
University	11 (6%)	3 (14%)
Housing (past year)		
Own apartment	64 (37%)	14 (64%)
With parents/friend	80 (47%)	3 (14%)
Other	15 (9%)	2 (9%)
Homeless	13 (8%)	3 (14%)
Income (past year)		
(self)employed	68 (40%)	8 (37%)
Social security	29 (17%)	5 (23%)
Student	12 (7%)	2 (9%)
Criminality	23 (13%)	0
On sick-leave	9 (5%)	3 (14%)
Retired	6 (3%)	0
Other	25 (15%)	4 (18%)

Clinical Assessments

Clinical Assessments and self-report revealed that 30-40% met the criteria for substance abuse/dependence, about 30% were screening positive for ADHD, 29% met the criteria for Conduct disorder and 19% for ASPD. Table 5 presents the overall clinical assessments, separate for male and female participants.

Table 5. *Clinical assessments*

Assessment	All (n=194)	Men (n=172)	Women (n=22)
	No (%)	No (%)	No (%)
Alcohol abuse/dependence[1]	58 (30%)	52 (30%)	6 (27%)
Substance abuse/dependence[2]	74 (38%)	70 (40%)	4 (18%)
Screening positive for ADHD[1]	61 (31%)	56 (33%)	5 (23%)
Depression Moderate/severe (current)	105 (54%)	92 (53%)	13(59%)
Conduct Disorder	57 (29%)	52 (30%)	5 (23%)
Antisocial Personality Disorder	39 (20%)	38 (22%)	1 (5%)
Any childhood trauma moderate/severe/extreme[3]	97 (50%)		
Emotional abuse		31 (18%)	5 (23%)
Physical abuse		50 (30%)	4 (18%)
Sexual abuse		17 (10%)	6 (27%)
Emotional neglect		39 (23%)	5 (23%)
Physical neglect		43 (25%)	5 (23%)
Psychiatric treatment during childhood[3]	68 (35%)	63 (37%)	5 (23%)
Psychiatric treatment as adult	55 (28%)	49 (28%)	6 (27%)
Psychiatric diagnosis lifetime	55 (28%)	38 (22%)	5 (23%)

[1] Information missing for 4 persons
[2] Information missing for 12 persons
[3] Information missing for 8 persons

Index crime

Proportion of suspected index crime is presented in table 6 separately for male and female participants and for the 62 that declined and 57 that did not speak Swedish. Assault was overall the most common suspected crime.

Table 6. *Proportion of suspected crime in the group eligible for inclusion n=319*

Index crime	Men 172	Women 22	Declined 62	Not speaking Swedish 57
Assault	58 (34%)	11 (50%)	23 (37%)	26 (46%)
Homicide, manslaughter	15 (9%)	3 (14%)	6 (10%)	5 (9%)
Sexual crime	16 (9%)	3 (14%)	6 (10%)	14 (25%)
Robbery, unlawful threat, intimidation	44 (26%)	2 (9%)	9 (15%)	4 (7%)
Gross violation against a woman's integrity	24 (14%)	-	9 (15%)	4 (7%)
Kidnapping, illegal confinement, illegal coercion	9 (5%)	2 (9%)	4 (6%)	3 (5%)
Arson	6 (3%)	1 (4%)	-	1 (2%)

The six excluded participants were suspected of robbery (3), arson (1), homicide (1) and assault (1).

Substance use as a trigger for violence

Table 7 displays the ORs for the association between alcohol/substance use and violence.

We also attempted to carry out stratified analysis for sex, conduct problems (CD, ASPD and ADHD), psychiatric problems (endorsing psychiatric treatment or diagnosis) and childhood trauma (any childhood trauma moderate, severe, extreme). However, this was only possible for alcohol, cannabis and benzodiazepines due to low power and the results did not yield any substantial differences. Sex differences were only possible for alcohol (table 8).

Alcohol

There was an increased risk of a violent crime within 24 hours after alcohol consumption OR 4.28 (95% CI, 2.77-6.61) with the usual frequency approach and OR 4.70 (95% CI, 2.30-9.61) with the matched-pair interval approach adjusted for multiple exposures. Results adjusting for amount of alcohol at last intake and multiple exposures yield an increased risk of OR 15.63 (95% CI, 8.45-28.91). The amount of consumed alcohol 24 hours from the index crime varied from one drink (i.e., 12 g pure alcohol) to 40 drinks (mean= 8.9, standard deviation = 7.8). Reported alcohol use showed a strong correlation with AUDIT scores (Spearman's rho = .71; P = .0001).

Benzodiazepines

The association between benzodiazepines and violence appears to be explained by those participants reporting intake of an unusual high dose OR 36.32 (95% CI, 7.18-183.65). When participants reporting unusual high intake and multiple exposures were excluded from the analysis, the result indicated a reduced risk of violence when under the influence of regular doses of benzodiazepines OR 0.42 (95% CI, 0.10-1.74). The most common expected effects of using benzodiazepines were reduced anxiety and "to feel better". Eight persons reported this high intake (10-50 tablets) they were all male, six of them were suspected of robbery and two of aggravated assault.

Other common drugs of abuse

Cocaine intake in the 24 hour period prior to the index crime was associated with a significantly increased risk of violence OR 6.24 (95% CI, 2.66-14.63). The effects were consistent between the two types of analytic approaches and after adjusting for multiple exposures; however, the matched-pair approach yielded a statistical non-significant result. The effect of amphetamine was elevated, albeit not significantly, and declined after adjusting for multiple exposures. Opiates and cannabis use did not reveal any triggering effects on violence after adjustment for multiple exposures. Only one person was exposed to AAS in the 24 hour period prior to the index crime, while 20% of male participants, no females, reported having used at some

point during their lifetime. The most commonly reported reason for using was “to exercise”, “get stronger”, “nice looking body”, two persons reported concealing other forms of substance abuse (alcohol and amphetamine).

Table 7. *Odds ratio for a violent crime 24 hours after exposure to different substances among 194 suspected offenders*

Exposure	**Number of exposed cases in the 24 hours prior to crime**	**Usual frequency**	**Matched pair interval**
		OR (95% CI)	**OR (95% CI)**
Alcohol	95	6.41 (4.24-9.67)	4.60 (2.32-9.11)
Adjusted[1]		4.28 (2.77-6.61)	4.70 (2.30-9.61)
Adjusted[2]	95	15.63 (8.45-28.91)	-
Benzodiazepines	25	4.06 (1.90-8.67)	5.50 (1.22-24.80)
Adjusted[1]		0.42 (0.10-1.74)	4.63 (0.92-23.21)
High doses of benzodiazepines[3]	8	36.32 (7.18-183.65)	Not asked for
Cannabis	28	1.25 (0.61-2.60)	1.40 (0.44-4.41)
Adjusted[1]		0.40 (0.14-1.15)	1.25 (0.34-4.57)
Amphetamine	12	1.51 (0.52-4.41)	2.00 (0.18-22.05)
Adjusted[1]		-	0.85 (0.05-15.78)
Cocaine	10	6.24 (2.66-14.63)	7.00 (0.86-56.90)
Adjusted[1]			5.25 (0.50-54.74)
Opiates	6	4.52 (1.03-19.90)	1.50 (0.25-8.98)
Adjusted[1]		-	0.48 (0.06-4.18)
AAS	1	1.53 (0.17-13.76)	Not asked for

[1] Exposure to more than one substance in the 24 hour period prior to the index crime was adjusted for in two ways; for the usual frequency approach, cases being exposed to other substances was excluded from the analyses, and in the matched pair approach multivariate logistic regression analyses was performed with simultaneously including all substances

[2] Adjusted for amount of alcohol intake and multiple exposures of other drugs

[3] Also included in the crude OR in Benzodiazepines

Table 8. *Stratified analyses on* conduct problems *(CD, ASPD and ADHD), psychiatric problems (endorsing psychiatric treatment or diagnosis) and childhood trauma (any childhood trauma moderate, severe, extreme on CTQ).*

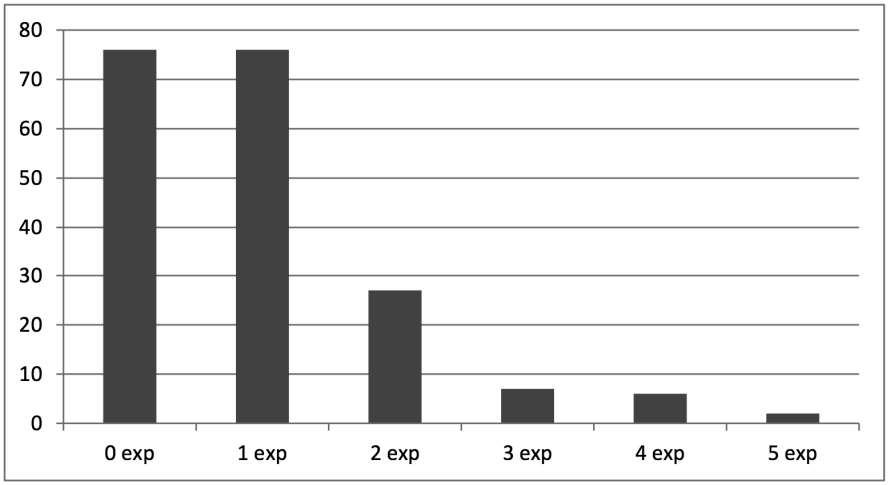
Exposure	**Stratified variable**	**Usual frequency**	**Matched pair**
	Men	6.29 (4.06-9.73)	4.56 (2.21-9.73)
	Women	7.56 (2.24-25.51)	5.00 (0.58-42.79)
Alcohol	Childhood trauma		
	1	9.19 (4.19-20.16)	7.00 (1.59-30.8)
	0	5.57 (3.44-9.02)	4.00 (1.84-8.68)
	Psychiatric vulnerability		
	1	6.54 (3.58-11.94)	5.75 (1.99-16.63)
	0	6.99 (3.90-12.55)	4.40 (1.67-11.62)
	Conduct/ behavioral problems		
	1	5.61 (3.02-10.41)	5.50 (1.90-15.95)
	0	7.23 (4.26-12.26)	3.83 (1.56-9.41)
Cannabis	Childhood trauma		
	1	1.37 (0.49-3.87)	*
	0	1.15 (0.41-3.22)	4.67 (1.34-16.24)
	Psychiatric vulnerability		
	1	1.56 (0.70-3.47)	13.0 (1.70-99.35)
	0	0.33 (0.04-2.98)	3.50 (0.73-16.85)
	Conduct/ behavioral problems		
	1	1.24 (0.58-2.65)	17.0 (2.26-127.74)
	0	1.46 (0.12-17.82)	1.50 (0.25-8.98)
Benzodiazepines	Childhood trauma		
	1	6.46 (1.79-23.26)	*
	0	2.73 (1.01-7.37)	2.50 (0.49-12.87)
	Psychiatric vulnerability		
	1	3.08 (1.37-6.90)	7.00 (0.86-56.89)
	0	38.54 (3.13-475.29)	3.00 (0.31-28.84)
	Conduct/ behavioral problems		
	1	5.81 (2.15-15.65)	4.00 (0.85-18.84)
	0	2.36 (0.70-7.90)	*

* No discordant pairs

Multiple exposures

Of the 194 participants, 76 (39%) were not exposed to any substance within 24 hours from the suspected violent offence, while 2 were exposed to five different substances, of whom one was suspected for robbery and one for aggravated assault. Figure 4 displays number of participants and exposures.

Figure 4. Number of participants with different numbers of exposure



Paper III- Anabolic androgenic steroids and violent offending: Confounding by polysubstance abuse among 10,365 general population men

In paper III we wanted to examine the link between AAS use and violent crime in a population-based sample while controlling for polysubstance abuse and additional suggested risk factors for violence. Data on self-reported use of AAS, alcohol and other substances, ADHD and personality disorder symptoms were linked to nationwide longitudinal register information on criminal convictions, IQ, psychological functioning and childhood SES covariates.

AAS substance abuse and violent crime

A total of 4.9% of 10,365 participants (n=511) had been convicted for a violent crime and 0.7% (n=76) reported AAS use. There was no difference in age at first conviction between AAS users and non-users (p>0.80). As suggested from table 9, violent offenders more often reported AAS use (2.7% vs. 0.6%, odds ratio [OR] 5.0 (95% CI: 2.7-9.3). This association was substantially reduced and lost statistical significance after adjusting for other lifetime substance abuse. Similarly, associations decreased considerably also for the five non-AAS forms of lifetime drug abuse, but less so for DSM-IV Alcohol abuse/dependence when adjusting for co-occurring substance use. However, associations remained significant for Rohypnol®, amphetamine, cannabis and alcohol abuse/dependence. Adjusting only for Rohypnol® and amphetamine was sufficient to attenuate the association of AAS with violent crime to a nonsignificant OR of 1.7 (95% CI: 0.9-3.3) (data not shown).

Table 9. *Self-reported lifetime substance use and risk of any violent crime conviction of among 10,365 20-47-year old men in the Swedish general population*

Violent crime	**Yes**	**No**	**Bivariate**	**Multivariate**
Substance	**(n=511)**	**(n=9,854)**	**Odds Ratio[a]**	**Odds Ratio[b]**
AAS	14 (2.7%)	62 (0.6%)	5.0 (2.7-9.3)	1.6 (0.8-3.3)
Rohypnol	40 (7.8%)	104 (1.1%)	9.0 (6.0-13.7)	2.1 (1.2-3.7)
Other benzodiazepines	56 (11.0%)	358 (3.6%)	3.3 (2.4-4.5)	1.1 (0.7-1.6)
Amphetamine	97 (19.0%)	365 (3.7%)	6.9 (5.3-8.9)	2.7 (1.9-4.0)
Cocaine	55 (10.8%)	228 (2.3%)	5.8 (4.2-8.0)	0.9 (0.6-1.5)
Cannabis	208 (40.1%)	1820 (18.5%)	3.2 (3.1-4.6)	1.8 (1.5-2.3)
DSM-IV Alcohol abuse/ dependence	159 (32.1%)	1155 (12.0%)	3.8 (3.1-4.6)	2.7 (2.2-3.4)

Potential confounders

Table 6 shows the influence of potential confounders beyond co-occurring substance abuse on the association of AAS use and violent offending. Overall, the association between AAS use and violent offending declined slightly, albeit not significantly so, when we investigated the influence of intelligence and psychological functioning, respectively. Only marginal changes were found for the remaining covariates. Importantly, none of the measured confounders contributed to additional change following adjustment for co-occurring substance abuse. As described under materials measured covariates differed in response rate, there for each row in Table 10 provides anal-

yses based on the number of participants with information on the specific covariate. These analyses yielded similar ORs (adjusted for birth year) for the association of AAS and violent offending for participants with information on intelligence, psychological functioning and socioeconomic positions as presented in Table 9 (based on all 10,365 participants). Analyses based on participants with information on personality disorder symptoms (Iowa) and ADHD, both with low internal response rates (52% and 66%, respectively), yielded lower, non-significant ORs between 2.1 and 2.4.

Table 10. *Influence of potential confounders on the association of any lifetime AAS use with any violent crime conviction among 10,365 20-47-year-old men in the Swedish general population.*

Covariate	**No. of individuals with covariate**	**Association between AAS use and violent crime, adjusted for**			
		Birth year only	**Birth year and specific covariate[a]**	**Birth year and co-occurring substance abuse**	**Birth year, co-occurring substance abuse and specific covariate[b]**
General intelligence (IQ)	8,835	5.3 (2.7-10.4)	4.4 (2.2-9.0)	1.8 (0.9-3.9)	1.6 (0.7-3.6)
Psychological functioning	8,349	5.9 (2.9-11.8)	4.4 (2.0-9.7)	2.1 (0.9-4.8)	1.9 (0.8-4.7)
DSM-IV ADHD	6,867	2.4 (0.8-7.0)	2.1 (0.7-6.2)	1.0 (0.3-3.5)	0.9 (0.3-3.3)
Possible personality disorder	5,257	2.3 (0.7-8.0)	2.3 (0.6-7.9)	0.8 (0.2-3.3)	0.9 (0.2-3.5)
Childhood family income	8,339	4.6 (2.2-9.8)	4.9 (2.4-10.2)	1.8 (0.8-3.8)	1.9 (0.9-4.0)
Childhood SEI	9,412	5.0 (2.5-9.7)	4.8 (2.4-9.6)	1.8 (0.9-3.9)	1.9 (0.9-4.1)
Single mother family during childhood	10,075	4.7 (2.5-9.0)	4.9 (2.6-9.2)	1.6 (0.8-3.3)	1.6 (0.8-3.4)

Notes:
Each row presents analyses among participants with information on specific covariate. Associations are expressed as odds ratios; figures within parentheses are 95% confidence intervals based on robust standard errors accounting for relatedness between twin siblings. The scarcity of the data did not allow for all covariates to be entered simultaneously in a total model.
a) Indicates each specific covariate at the beginning of each row, respectively.

Paper IV- Acute influence of alcohol, THC and central stimulants on violent suicide-A Swedish population study

In paper IV we investigated suicide method in relation to acute intoxication of alcohol, THC and central stimulants, based on information from 18,894 medico-legal death investigations. Of the decedents, 23% were positive for alcohol, 1.3% for central stimulants and 0.7% for THC. The overall most commonly used method was hanging; 38% followed by poisoning; 27%. When comparing each substance group with the group negative for alcohol and illicit drugs as reference, there was a lower relative risk for all violent methods, (compared with the nonviolent method poisoning) in the alcohol positive suicide decedents. There was a significantly increased risk for suicide by jumping from a height in the THC positive group; RR 1.62 (95% CI: 1.01-2.41) after adjusting for confounders. The central stimulant positive decedents had an elevated risk for several violent methods (i.e., hanging, sharp force, jumping from a height) that, however, did not reach statistical significance (table 11). None of the potential confounders, age, sex, treated for psychosis and geographical region, contributed any substantial change in the association substance influence and suicide method.

Table 11. *Suicide method and toxicology.*

	Alcohol	**THC**	**Central - stimulants**	**Not affected (ref)**
	n=4,280	**n=142**	**n=239**	**n=14,233**
Hanging	1,457	53	114	5,503 (39%)
	(34%)	(37%)	(48%)	
RR Crude	**0.80***	0.90	1.12	ref
(CI)	**(0.76-0.83)**	(0.73-1.06)	(0.99-1.23**)**	
RR Adjusted	**0.67***	0.81	1.17	ref
(CI)	**(0.63-0.71)**	(0.60-1.03)	(0.98-1.35)	
Drowning	200	3	3	1076
	(5%)	(2%)	(1%)	(8%)
RR Crude	**0.49 ***	**0.27***	0.23	ref
(CI)	**(0.43-0.57)**	**(0.09-0.78)**	(0.07-0.65)	
RR Adjusted	**0.56***	0.51	0.34	ref
(CI)	**(0.47-0.66)**	(0.16-1.62)	(0.10-1.08)	
Firearms	635	7	14	1583
	(15%)	(5%)	(6%)	(11%)
RR Crude	0.95	**0.45***	0.67	ref
(CI)	(0.87-1.02	**(0.22-0.85)**	(0.41-1.03)	
RR Adjusted	**0.78***	**0.36***	0.63	ref
(CI)	**(0.69-0.89)**	**(0.16-0.84)**	(0.33-1.18)	
Sharp force	48	4	13	469
	(1%)	(3%)	(5%)	(3%)
RR Crude	**0.22***	0.71	1.66	ref
(CI)	**(0.17-0.30)**	(0.27-1.74)	(0.99-2.64)	
RR Adjusted	**0.24***	0.70	1.53	ref
(CI)	**(0.17-0.32)**	(0.25-1.93)	(0.82-2.81)	
Jumping from height	135	17	15	857
	(3%)	(12%)	(6%)	(6%)
RR Crude	**0.41***	1.43	1.12	ref
(CI)	**(0.34-0.49)**	(0.93-2.08)	(0.69-1.70)	
RR Adjusted	**0.44***	**1.62***	1.12	ref
(CI)	**(0.37-0.53)**	**(1.01-2.41)**	(0.67-1.77)	
In front of a moving object	174	10	19	858
	(4%)	(7%)	(8%)	(6%)
RR Crude	**0.52***	0.95	1.34	ref
(CI)	**(0.44-0.61)**	(0.53-1.60)	(0.88-1.92)	
RR Adjusted	**0.61***	0.84	0.92	ref
(CI)	**(0.54-0.69)**	(0.53-1.16)	(0.67-1.17)	
**Other ** **	87	4	7	334
	(2%)	(3%)	(3%)	(2%)
RR Crude	**0.62***	0.97	1.34	ref
(CI)	**(0.49-0.78)**	(0.37-2.36)	(0.64-2.60)	
RR Adjusted	**0.53***	0.89	1.09	ref
	(0.42-0.67)	(0.32-2.35)	(0.50-2.29)	
Poisoning	1,544	44	54	3,553
(REF)	(36%)	(31%)	(23%)	(25%)

Adjusted for sex, age, diagnosis of psychosis, and geographic region.
*Significant with a 95% confidence interval.
**Methods not specified elsewhere.

Descriptive statistics

The nonusers were significantly older than the alcohol and illicit drugs positive decedents. The alcohol positive were older than the central stimulants and male THC positive suicide victims. Mean age in the drug positive group (central stimulants and cannabis) was 34.2 years, in the alcohol positive group, 46.9 years, and the negative group 53.6 years. Mean age by substance group and gender is depicted in table 12 and last admission as inpatient with a psychiatric diagnosis in table 13.

Table 12. *Mean age for men and women in each substance group*

	Men	**Women**
Alcohol	46.9[1] sd 15.72 (15-94)	46.8[1] sd 12.56 (15-69)
THC	34.6[2] sd 10.62 (17-66)	41.6 sd 13.85 (22-63)
Central stimulants (CS)	34.8[3] sd 9.9 (15-84)	32.2[3] sd 12.3 (15-69)
Not affected (NA)	53.6 sd 19.72 (8-99)	53.2 sd 19.5 (12-102)

[1] Mean age differ significant ($p<0.001$) from THC, CS and NA
[2] Mean age differ significant ($p<0.001$) from Alcohol and NA
[3] Mean age differ significant ($p<0.001$) from Alcohol and NA

Table 13. *Last admission as inpatient with a psychiatric diagnosis in 18, 894 suicide decedents per results from toxicological analysis*

Diagnosis n (Column %)	Alcohol n= 4,280	THC n= 142	Amphetamine n= 217	Cocaine n=22	Not affected n=14,233
Substance abuse (including alcohol)	599 (14%)	22 (15%)	65 (30%)	3 (14%)	851 (6%)
Psychosis due to intoxication	21 (0.5%)	3 (2%)	11 (5%)	-	41 (0.3%)
Psychosis	70 (2%)	6 (4%)	6 (3%)	-	851 (6%)
Depression	294 (7%)	11 (8%)	10 (5%)	1 (5%)	2097 (15%)
Anxiety	148 (3%)	7 (5%)	9 (4%)	-	672 (5%)
Personality disorder	62 (1%)	5 (4%)	9 (4%)	-	242 (2%)
Other	74 (2%)	3 (2%)	6 (3%)	-	292 (2%)
Total	1,268 (30%)	57 (40%)	114 (53%)	4 (18%)	5,046 (35%)

SUMMARY OF FINDINGS

I Lifetime use of anabolic androgenic steroids is related to an increased likelihood of being suspected of a violent crime, albeit no temporal relation between use and the violent offence was found.

II Intake of alcohol or high doses of benzodiazepines is triggers for violent crime in a selected sample of remand prisoners with high prevalence of other static risk factors.

III The elevated risk for being convicted of a violent crime in general population men with a (lifetime) self-reported use of anabolic androgenic steroids seems to be confounded by other forms of substance abuse.

IV Among the 18,894 suicide decedents; 23% were positive for alcohol, 1.3% for central stimulants and 0.7% for THC. The results revealed that acute influence of THC was related to using the violent suicide method; jumping from a height (RR 1.62; 95%CI 1.01-2.41). Alcohol intoxication was not related to any violent method.

DISCUSSION

Substance abuse is related to an enhanced risk for interpersonal violence [12] and suicide [64].

The aim of the present thesis has been to investigate the relation between a "suspected substance", anabolic androgenic steroids and violent offending. To disentangle to what extent intake of different substances has a triggering effect on violent crime and examining the risk for violent suicide when under the influence of common substances of abuse.

Below are the main findings and methodological considerations discussed.

Comments to the main findings

AAS and violent crime

In a highly selected sample of substance abusers arrested for crime (paper I) and in a large general population sample of male twins (paper III), a significant association between self-reported use of anabolic androgenic steroids and being suspected or convicted of a violent crime was found. However, in paper III, the association declined and lost significance after adjusting for other forms of substance abuse, and in paper I, no temporal relation between AAS use and the violent crime was found. Further, the crude association was not as large in the sample of substance abusers as in the general population sample. These results indicate that AAS is not a proximal risk factor for interpersonal violence and that polysubstance abuse is a stronger risk factor for violence than AAS use *per se.*

The observed decline in the association AAS and violent crime, when adjusting for other forms of substance abuse, may also be related to other risk factors associated with an increased risk for violence and substance abuse. However, adjusting for potential individual-level confounders in paper III, including IQ and psychological functioning, ADHD, personality disorder symptoms, and childhood sociodemographic characteristics, respectively, did not substantially alter the pattern of findings differences. Hence, since prior research posits that these confounders covary with substance abuse, it seems that pharmacological, psychological or social effects related to substance abuse *per se* contribute most of the risk for violent offences.

Previous studies suggest that AAS users are more verbally and indirectly aggressive and irritable [169], and more often suffer from cluster B personality disorders (Anti-social, borderline, narcissistic and histrionic personality disorder) [170, 171]. The absence of changes in results when controlling for psychologist-rated personality functioning at mandatory conscription or self-reported personality disorder symptoms in paper III, could indicate that AAS use-related personality changes do not manifest themselves in actual violent crimes. Population based studies confirming the relation between AAS and violence has been based on self-reported aggressiveness and involvement in violent behavior [172, 173]. While in a selected sample of all tested for AAS, no relation between being tested positive for AAS and convicted for a violent crime was proven [107].

AAS as part of a poly substance abuse pattern have been suggested previously [116, 117, 174, 175] and is also confirmed in the present studies. Even with our conclusion that the relation with violent offending is confounded by substance abuse, animal research has found exacerbated risk for aggressive, competitive and dominance behavior after intake of alcohol or amphetamine in animals pretreated with AAS [176, 177]. So even if AAS as a proximal risk factor does not seem relevant, we have not ruled out the possibility that use might cause future sensitivity to intake of other substances.

Adjusting only for Rohypnol® and amphetamine in paper III was sufficient to attenuate the association of AAS with violent crime to a nonsignificant OR of 1.7 (95% CI: 0.9-3.3). Amphetamine and Rohypnol® respectively, had a strong association with violent crime, which remained significant after adjusting for other substances.

Flunitrazepam (the active substance in Rohypnol®), a benzodiazepine with high potential for the development of dependence, became rather popular in the late 1990s. It was used quite widely as a drug of abuse and based on interviews with highly selected samples with juvenile offenders, it was even suggested that Flunitrazepam induced violent behavior [89]. Rohypnol® is not available on the legal market in Sweden since 2004, and Flunitrazepam is nowadays only rarely prescribed for anxiety and sleeping disorders.

Amphetamine use may have serious side effects such as irritability and paranoia that could increase violence risk [178].

The overall lifetime prevalence of AAS use reported by 20-47-year old men in paper III was 0.7%, similar to other population studies [23, 173]. In contrast, the prevalence in the remand prison population was 28% among the male participants and 5% among the female. The high prevalence in the females was unexpected, but has recently been validated in a study on female prisoners in Sweden were 6% of 157 women claimed ever tried AAS [179].

In paper II only one person had a current use of AAS at the time for the suspected violent crime, while 20% of the male (none of the female) participants reported a life-time use. The most common reported reason for using

AAS in paper II was “to exercise”, “get stronger”, “nice looking body”, thus, the same reasons as for non-criminals. Two persons reported concealing other forms of substance abuse.

Finally, contrary to what would have been expected if there were a difference in criminal trajectories between AAS users and non-users, we found no difference in age at first conviction in paper III.

The triggering effect of substance intake on violent crime

Of the 194 remand prisoners in paper II, 61% had used one or several substances within 24 hours from the suspected violent crime. As expected alcohol intake was associated with an increased risk for violent crime and a further elevated risk was found when adjusting for amount of alcohol. The results for alcohol as a trigger for violence corroborate previous findings in similar populations using the same method [15] and correspond to a strong association between alcohol and violence described in previous research [17, 18]. These findings also confirm that large amounts of alcohol at the same occasion increases the risk of violent behavior.

The mean amount of alcohol consumed was 8.9 glasses (one glass is defined as a standard glass that equals 12 g pure alcohol), which is the equivalence of almost two bottles of wine. More than five glasses for men and four glasses for women at the same occasion is regarded as harmful drinking [19], so called binge drinking, with an increased risk for violence and injuries as well as mental and somatic effects [86]. Reported amount of alcohol showed a strong correlation with AUDIT scores and 30% of the participants met the criteria for alcohol abuse/dependence. Thus, high intake may have different individual impact due to developed tolerance.

High doses of benzodiazepines appear to explain the elevated risk of violence associated with the substance. The expected effects of benzodiazepines are reduced anxiety and sleepiness, and regular doses of benzodiazepines without any other exposures present suggested a preventative effect regarding violent behavior. A question about expected effect was added for those reporting use of benzodiazepines, in order to capture if a paradoxical reaction was desired. That was not the case; reduced anxiety and “feeling better” were the most commonly reported reasons for using benzodiazepines. High doses are self-reported (for the person an unusual high dose) and varied between 10-50 tablets. This imperfect measure does not contain any information on size or type of benzodiazepine in each tablet. Nevertheless, it seems to capture a misuse pattern important for the risk of violence. The majority of those reporting intake of high doses were suspected of robbery, which suggests a form of more instrumental violence

Overall, all other measured risk factors for violence were highly prevalent in the remanded population and the case-crossover design used in the study,

in order to handle static within the individual confounding is further discussed under methodological considerations.

The risk for suicide by jumping from a height when under the influence of THC

In paper IV, we used a large sample of 18,894 suicide cases (98% of all suicides in Sweden 1994-2009) to investigate if there were an association between acute influence of alcohol, amphetamine, cocaine (central stimulants) or THC (cannabis) and suicide by a violent suicide method. We hypothesized that if substance use is related to violence in general, it might also be related to a violent suicide method. That was not the case, the only significant risk for using a violent method was testing positive for THC and jumping from a height, in comparison with the method poisoning and those not under the influence of neither alcohol nor illicit drugs. The risk is not large; however, 12% in the THC positive group used this method, the highest proportion of any group in this study. The proportion of suicide decedents jumping from a height in the alcohol and illicit drug negative group was 6%.

Cannabis is mostly used for its relaxing effect, but the drug has several psychiatric side effects. Jumping from a height is a method related to psychopathology and cannabis is associated with confusion and drug related psychosis [95, 180]. There are clinical anecdotes describing impulsive jumps through windows and bridges under acute influence of cannabis. Our finding indicates the need of further studies with other methods to investigate this relation, for example psychological autopsies.

Alcohol was present in 23% of the decedent, wish corroborates previous findings regarding acute alcohol intoxication in suicides [118]. Alcohol is the substance for which a triggering effect on violence toward others is most documented [13, 15]. However, in contrary to our hypothesis, alcohol intoxication was related to a significantly decreased risk of using a violent suicide method compared with the alcohol/illicit drugs negative cases, meaning that suicide by poisoning was more common in the alcohol positive cases.

The central stimulant positive decedents had an elevated, albeit non-significant, risk for several violent methods.

Given that very little is known about suicide and acute intoxication, the study does contribute with prevalence figures and reveals significant differences in age between the alcohol positive, illicit drugs positive and the unaffected suicide victims.

Methodological considerations

In all four papers substance use is the exposure and violent crime or violent suicide the outcome. The studies are cross sectional, but to be able to draw firmer conclusions regarding causality, we used the case-crossover design in paper II.

The case-crossover design

When using the case-crossover design all participants are selected on the outcome, thus, in our study, all were suspected of a violent crime. The major advantage with the design is the possibility to use the participant as its own control. It is challenging to match a control group on all possible static risk factors and follow up data often suffer from a high degree of missing in these vulnerable populations.

The design is used to measure the strength between a suggested trigger and the outcome. The motive to study and identify proximal and transient risk factors is to identify any component of the causal web that is closer to the onset than any other causes under consideration [166], and thus, give us the possibility to target the *trigger* in treatment and risk prediction.

The more abrupt the outcome is, the more amenable is the design, because a time of onset is needed. A violent offence may differ in duration and nature, normally it was not a problem for the participant to describe the time for onset of the event, but in some cases, were the crime included repeated offences, often domestic violence or sexual assault toward family members, it was necessarily to pick one occasion, if possible the last one or the one that lead to the detention was defined as the event.

The induction time was estimated 24 hours from the onset of the event, thus, the case window was decided to 24 hours for all substances. Substance intake was the only trigger measured in the study and there could be unmeasured triggers present in relation to the violent event. However, questions regarding co-exposures may become demanding for the participant to answer. Multiple exposures of substance intake were adjusted for, as well as amount of alcohol. Unfortunately we did not have enough power to calculate the triggering effect of certain combinations of substances.

Measures of exposures

Paper I-III is based on self-reported use and paper IV on toxicological analyses at autopsy. In paper I information of main drug of abuse during the past year and life-time use of AAS and number of months since last using was asked for. This is fairly rough information and the participants, all with a confirmed substance abuse, did not have any observable benefit from adjust-

ing or be less inclined to share this information. However, memory difficulties, especially regarding time since last use cannot be ruled out.

In paper II exposures were self-reported substance use at the suspected violent offence and control information based on usual frequency during the past year and a control window one week prior to the event. The participants were not aware about the 24h case-window. The matched-pair interval and usual frequency approaches yielded similar results overall, which is usually regarded as a sign of validity of the control information. The matched-pair interval approach generally yields wider confidence intervals because the analysis is based on discordant pairs, and consequently not all exposed cases contribute to the analysis.

The aid of the calendar and redundant information during the interview was helpful for validating time and frequency of exposure. For example if a person claimed an everyday drinking pattern for the past year and then mentioned a month of hospitalization, that would reduce the usual frequency with 30 days.

Further, the interview was carried out, for the majority, less than three weeks after the suspected violent crime to minimize the risk for recall bias. Several factors may influence the information on substance intake; the person may have memory difficulties due to heavy substance misuse or denial. In general, social desirability would lead to underestimate use, but in relation to a suspected crime, one might want to exaggerate the exposure at the time of the index crime to explain the behavior, and consequently lead us to overestimate the risk.

The risk of information bias has been of major concern using the case-crossover design with self-reported retrospective information, however, empirical tests have shown that it is less than expected [181].

Paper III is a general population based sample and substance use is self-reported. Linkage with Swedish national registries has shown that STAGE non-responders do not differ from responders regarding age, birth weight or inpatient treatment for neurological disorders. Nevertheless, non-responders were more often male, criminally convicted, and treated for psychiatric conditions. They were also less educated, and had somewhat lower general cognitive ability (IQ) at mandatory conscription (males only) at the age of 18 (all p-values <0.001)[182]. Thus, responders are a more well-functioning, this might have lead us to underestimate the relation AAS and violent crime.

For each endorsed substance including AAS, additional questions addressed age at first use, age at most frequent use and intensity during that period, and age at last use. However, substantial non-response rates for these follow-up items would have compromised the analyses and were not used for the current study. Thus, paper III lack information on temporal relation.

Finally, exposure in paper IV is based in toxicological analyses in blood, no limit in alcohol concentration was used. Analyses were carried out at the department of Forensic Chemistry in Linköping, which serves all six departments of Forensic Medicine in Sweden, employing methods described in detail previously[183]. During the study period alcohol was analysed in 95-98% of all medico-legal death investigations and illicit drugs in slightly less than one third of the cases. The accuracy of the forensic pathologists in requesting analyses for illicit drugs was controlled at the Department of Forensic Toxicology, Linkoping, by screening for illicit drugs in all cases where the performing forensic pathologist had not ordered such screening during a one-year period. The study showed that 95% of all illicit drug positive cases were included in the initially requested screening (not published, full details can be provided by the author). Due to discrepancy in detection window, time from intake to suicide may differ between the decedents. We have argued that this above all concerns THC, which has a wide detection window in heavy users. Further the register is organized in a hierarchic order where central stimulants dominate THC and illicit drugs dominate alcohol. This means that the THC-cases have no other illicit drug present and cases having only alcohol were classified as alcohol cases. The reason for this classification in the register is related to the lethality of the drugs [184]. We accepted this with the motivation that we could get as close as possible to the unique effect of each substance, but we are also aware that this classification is rendering obvious limitations, we may underestimate the presence of THC, as their might be decedents positive for THC in the central stimulant group. Similar there might be co-occurrence of alcohol in the two illicit drugs groups.

Measures of outcomes

In paper I&II the outcome is a suspected violent crime. In paper I the crime was not of primary interest in the data collection within the Swedish Remand Prison Project and is just recorded from the crime classification when the person was remanded.

In paper II the participants are selected on the outcome, remanded of a violent crime, but in addition to the crime classification the participants gave a description of what had lead them to be remanded, in order to agree on the date for the event. Thus, in paper II, the suspected crime might in some cases not lead to convictions but they all capture a violent event.

In paper III the outcome measure is convicted for a violent crime in lower court. A valid measure regarding violent crime, but does not capture all violent offences. Far from all violent acts lead to conviction or are even reported to the police. Based on surveys, about 25% of interpersonal violence is reported to the police, the lowest rate is for sexual crimes where only 13% are reported. Severity of violence and hospitalization increases the likelihood

for a crime to be reported, while repeated offences or a young perpetrator decreases the likelihood [39]. Further, in mean, 53% of the crimes against a person lead to what is called a *solved crime*, which means that either an identified person is prosecuted or the case is closed due to lack of evidence or an under aged perpetrator [185]. Thus, far from all violent crimes are to be found in the crime register, but it probably catches more severe crimes.

In paper IV we limited the suicides to ICD-diagnoses Intentional self-harm (X60-X84) due to the risk of misclassification if including events of undetermined intent (ICD-10 codes Y10-Y34. Normally in suicide research events of undetermined intent are included, and 70-75% are estimated to be intentional self-harm [4]. But, as self-poisoning might be more common in in the illicit drug suicides, we made this limitation.

ICD-diagnosis of manner of death is based on information from the forensic pathologist and coded at the Cause of Death Register by a specially trained staff. In order to differentiate an accidental intoxication from self-poisoning all available information is evaluated by the forensic pathologist.

Potential confounders

As pointed at in the introduction several factors are related to substance abuse as well as violence. In paper I additional information was sparse and we were limited to adjust for sex and age in the analyses.

In paper II the case-crossover design handles static within the individual confounding. However, potential dynamic risk factors that would confound the results are not taken into account.

In paper III our main interest was to investigate to what extent intake of other forms of substances affected the association between AAS and violent crime. Actually, it was sufficient to adjust for amphetamine and Rohypno® to reach the presented decrease in the association, even though each substance was related to violent crime and overall, the association between each of the six non-AAS types of substance abuse and violence declined after adjusting for other co-occurring substance abuse. Given the imperfect nature of our measures of substance abuse, it is likely that the associations would have been even more attenuated with better measures.

Further, the association of AAS use with violent offence in the subsample with full information on ADHD and personality disorder symptoms was weaker than in the full sample (non-significant odds ratios at 2.1-2.4). One possibility is that the higher degree of missing data resulted from responders choosing the telephone interview not returning the separate, self-administered paper questionnaire with mental health questions equally often

as those who took the full internet-based survey (and hence did not have to separately fill out and send in the paper questionnaire). It is likely the choice of response format is not completely random. If the difference is not due to chance, it is possible that the subgroup of more well-functioning participants that provided full data caused the crude association of AAS and violent crime to be slightly lower.

In paper IV, adjusting for sex, age, geographical region and inpatient treatment with a psychiatric diagnosis, resulted in very minor differences.

Ethical considerations

All studies were approved by ethic committees.

Conclusion

The results of this thesis suggested that AAS use in itself is not a proximal risk factor for violent crime; the observed risk is probably due to the co-occurrence of abuse of other substances. Alcohol is a strong triggering risk factor for violent crime, constant across males and females as well as individuals with or without behavioral and psychiatric vulnerability. Intake of *high* doses of benzodiazepines is associated with an increased risk for violent crime. Cannabis use is associated with an increased risk of using the lethal suicide method of jumping from a height. I conclude that mapping substance abuse patterns may inform violence risk assessment and treatment planning.

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