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HAZARDOUS ALCOHOL USE AND ALCOHOL USE DISORDERS IN WOMEN: CHARACTERISTICS AND VULNERABILITY FACTORS

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Stockholm 2010

Picture on front page by *Agnes Magnusson*

Published by Karolinska Institutet. Printed by Larserics Digital Print AB.

ISBN 978-91-7409-98-4

ABSTRACT

The overall aim of this thesis was to study vulnerability factors associated with hazardous alcohol consumption during pregnancy and alcohol use disorders among Swedish women. Different risk-factors and characteristics were studied, and examined for their ability to discriminate or identify different subtypes (type I/late onset and type II/early onset) of alcohol dependence ("alcoholism").

In study I, an RCT at ANC in Stockholm (control, n = 156, intervention, n =147) we examined the ability of Swedish antenatal care to identify alcohol-related risk pregnancies, and the utility of some tools that could improve its performance (AUDIT, TLFB and biomarkers). In study II, a pilot cohort (n = 139) was screened for alcohol use disorders, and assessed for psychopathology, personality traits, and alcohol use during the first trimester. Subjects reporting consumption exceeding a conservative threshold for harmful use were offered a diagnostic psychiatric interview. The main findings of the pilot study were replicated using a large sample of women in the third trimester (n = 715). In study III and IV, a case-control study, detailed assessment was obtained from 200 treatment-seeking alcohol dependent women and 189 healthy population controls. All women were assessed for alcohol-related behaviors, sexual abuse history, psychiatric problems, and personality traits. Cases and controls were genotyped for markers in the *CRHR1*, *MAOA* and *OPRM1* genes. In study V, female twins from the Swedish Twin Registry (n =13 501) answered questions to establish lifetime alcohol use disorders, and subjects with alcoholism were classified for subtype. Heritability estimates were obtained, and environmental factors associated with alcoholism and its subtypes were studied.

Sixteen percent of pregnant women drank at levels that could be defined as "risk-consumption". Significantly more of these were identified by intensified screening compared to regular antenatal screening procedures (p = 0.0001), while biomarkers were of little use. Only a minority of women with hazardous alcohol consumption during pregnancy fulfilled alcohol dependence criteria. Psychiatric distress in those with risk-consumption did not differ from those with low or no consumption during pregnancy, but subjects with continued alcohol use scored higher on novelty seeking.

Among women with alcohol dependence, early onset/type II alcoholism is a valid construct. We found that alcohol dependent women classified as type II had more severe alcohol problems and significantly higher rates of illicit drug use. Family history of alcoholism was also considerably more common among type II than subjects than those classified as type I. Both alcoholism subtypes scored higher than normal on anxiety and impulsivity traits, but type II subjects scored markedly higher than either of the other groups on aggression (p = 0.00004). Despite a higher density of family history among type II subjects in the clinical cohort, our twin study did not support a difference in heritability between early onset/type II and late onset/type I alcoholism. Both genetic and environmental factors play an important role for susceptibility to alcoholism in women, in particular the early onset subtype. Childhood trauma is a category of environmental factors that plays a major role. The effect of emotional neglect and physical trauma was accounted for by familial background factors, which can be both genetic and environmental. In addition, childhood sexual abuse was an independent individual risk factor for alcohol dependence. Effects of sexual abuse were in part mediated trough psychiatric problems. Overall, treatment-seeking alcohol dependent women with a history of abuse have distinct features as compared to other alcohol dependent women.

LIST OF PUBLICATIONS

I. Magnusson Å, Göransson M, Heilig M.

Unexpected prevalence of alcohol use among pregnant Swedish women: failed detection by antenatal care, and simple tools that improve detection.
Journal on Studies on Alcohol 2005 Mar; 66(2):157-64

II. Magnusson Å, Göransson M, Heilig M.

Hazardous alcohol users during pregnancy: psychiatric health and personality traits.
Drug Alcohol Depend. 2007 Jul 10;89(2-3):275-81. Epub 2007 Mar 23

III. Magnusson Å, Göransson M, Heilig M.

Early onset alcohol dependence with high density of family history is not "male limited".
Alcohol. 2010 Mar; 44(2):131-9.

IV. Copeland W, Magnusson Å, Göransson M, Heilig M.

Testing genetic moderators and psychiatric mediators of the link between sexual abuse and alcohol dependence in females.
(Submitted)

V. Magnusson Å, Lundholm C, Göransson M, Copeland W, Heilig M, Pedersen N L.

Familial influence and childhood trauma in female alcoholism.
(Submitted).

CONTENTS

LIST OF ABBREVIATIONS

ANC	Antenatal Clinics
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AUDIT	Alcohol Use Disorder Identification Test
AUDIT – C	Alcohol Use Disorder Identification Test, Consumption
APA	The American Psychiatric Association
CI	Confidence Interval
CRH	Corticotrophin- Releasing Hormone
CRHR1	Corticotrophin Releasing Hormone Receptor 1
DSM	Diagnostic and Statistical Manuals of Mental Disorders
DZ	Dizygotic
ECA	Epidemiological Catchment Area
EOA	Early onset alcoholism
FAS	Fetal Alcohol Syndrome
FASD	Fetal Alcohol Spectrum Disorders
GAD	General Anxiety Disorder
HPA	Hypothalamic-Pituitary-Adrenal-Axis
ICD	International Classification of Diseases
LSC-R	Life Stressor Checklist
LOA	Late-Onset of Alcoholism
MAO-A	Mono-Amino-Oxidase-A
MVC	Mödravårdscentral
MZ	Monozygotic
NCS	National Co-morbidity Survey
OPMR1	Opoid Receptor Mu 1
OR	Odds Ratio
PTSD	Post Traumatic Stress Syndrome
SCL-90R	Hopkins Symptom Checklist, revised version
SCID I	Structured Clinical Interview for DSM-IV-Axis I
SSP	Swedish Universities Scales of Personality
STAGE	The Study of Twin Adults: Genes and Environment
TAU	Treatment as usual
TLFB	Timeline Follow Back
WHO	World Health Organization

1 BACKGROUND

1.1 DEFINITIONS

1.1.1 Hazardous or harmful alcohol consumption

Alcohol is a major cause of global disease burden [1]. Its consumption carries a risk of adverse health and social consequences, mediated through its ability to produce intoxication, dependence (here equated with "alcoholism"), but also direct organ damage [2]. While these properties are correlated, it is important to recognize that negative medical consequences can also occur in the absence of dependence. In general terms, hazardous alcohol consumption or risk drinking refers to a consumption level associated with a significant risk of subsequent adverse consequences, irrespectively of whether a diagnosis of alcoholism (see below) is present. The threshold for what is considered risk drinking is obviously somewhat uncertain, and recommendations vary between countries. Furthermore, recommendations are typically expressed in "standard drinks" in order to make them easier to interpret for the general public, but the definition of a standard drink differs. In Sweden, a standard drink refers to app. 12 g of alcohol, while the same term typically refers to 14 g in American literature. American recommendations define hazardous drinking as more than 4 drinks on a day or 14 per week for men and more than 3 drinks on a day or 7 per week for women [3;4]. The Alcohol Use Disorder Identification Test (AUDIT) is an instrument developed to screen for hazardous alcohol use that has been translated into, and validated in many languages, and is recommended by the World Health organization (WHO). It consists of 10 questions in three categories: consumption, dependence, and alcohol related problems, with each question scored 0-4. It has been proposed that for women, an AUDIT score of 6 or higher indicates hazardous alcohol consumption [5-7].

1.1.2 Harmful alcohol consumption during pregnancy

The concept of "risk drinking" comes into a very different light when it comes to alcohol consumption during pregnancy. Heavy alcohol consumption during this time may cause the full-blown Fetal Alcohol Syndrome (FAS), estimated to occur in approx. 1 – 5 / 1000 live births [8;9]. However, already an average consumption of as little as 70 g /week of alcohol early in pregnancy is associated with increased risk of spontaneous abortion and still-birth, decreased birth weight, and impairments of postnatal growth and intellectual development [10-13]. In addition, consumption in a binge-like pattern, i.e.

4-5 standard drinks or more on a single occasion, carries a risk of adverse consequences that is independent of average consumption level [14;15]. The term Fetal Alcohol Spectrum Disorders (FASD) has been introduced to reflect the broad range of alcohol related adverse effects at different levels of consumption during pregnancy [16]. Based on the uncertainty as to whether any safe consumption level exists, there is consensus that women should be recommended to abstain from alcohol altogether during pregnancy, and recommendations to this effect have e.g. been issued e.g. by the World Health Organization [17]. We have previously found that women who report hazardous alcohol use according to AUDIT during the year prior the pregnancy continue to drink alcohol during pregnancy to a higher degree than those who do not [18].

1.1.3 Alcohol-use disorders

Two major disease classification systems provide diagnostic criteria for alcohol related syndromes: the Diagnostic and Statistical Manuals of Mental Disorders (DSM), developed and published by the American Psychiatric Association (APA), and the International Classification of Diseases (ICD) from the WHO. Both systems have consistently been shown to be reliable and valid [19], and their criteria are reasonably similar.

According to the DSM IV, "alcohol abuse" is defined as a maladaptive pattern of alcohol use that leads to one or more among a range of specified social consequences, such as failure to fulfill a role obligation, exposure of self or others to physical risk, legal problems, or interpersonal problems. In contrast, a diagnosis of "alcohol dependence", typically equated with "alcoholism", requires the presence of "a maladaptive pattern of substance use, leading to clinically significant impairment or distress", manifested as three or more symptoms reflecting physiological dependence, increased motivation for drinking, and / or adverse consequences of alcohol use (www.psychiatryonline.com).

Alcohol abuse has traditionally been viewed as an early stage or sub-syndromal category otherwise closely related to alcohol dependence. According to this view, the presence of the latter diagnosis precludes the former. However, work in preparation for the forthcoming DSM revision (www.dsm5.org) indicates that this view is largely incorrect, and that abuse as currently defined is an imprecise construct, which can reflect both mild and severe forms of an alcohol use disorder. Furthermore, most people who receive an abuse diagnosis do so based on a single occurrence, drunk driving,

making the prevalence of this diagnosis highly dependent on traffic law enforcement. Finally, the term "alcohol dependence" is ambiguous, in that it can be taken to mean "physiological dependence", i.e. presence of tolerance and abstinence, while these phenomena are neither necessary nor sufficient to establish the behavioral syndrome the diagnosis of alcohol dependence refers to. The current draft proposal for DSM V therefore only uses a single category, "alcohol-use disorder" (alternatively and better to be labeled "alcohol addiction"), which can be moderate or severe.

Alcohol dependence

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

1. Tolerance.
2. Withdrawal.
3. The substance is often taken in larger amounts or over a longer period than was 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 to obtain the substance, use the substance, or recover from its effects.
6. Important social, occupational or recreational activities are given up or reduced.
7. The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.

DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, American Psychiatric Association (APA), 1994

1.2 CONSUMPTION PATTERNS AND PREVALENCE

Across societies, alcohol consumption is consistently found to be higher among men than women. However, in developed countries, gender differences in alcohol use and in the prevalence of alcohol use disorders seem to decrease over time, paralleling increasing social gender equality [20]. One of the smallest gender gaps is found in the Nordic countries. Sweden is by international standards a country with relatively little

difference in alcohol consumption between genders. On average, Swedish men still drink more than twice the amount of women [21;22], but this gender gap continues to narrow. Between 1996 and 2002 the alcohol consumption in Sweden increased by 30%, with the total consumption estimated at 9.8 liters of pure alcohol per person aged 15 or above. The increase in alcohol consumption was reflected in a marked increase in problematic use and treatment seeking, and this trend was greater in women than in men [23].

In large US epidemiological surveys, lifetime prevalence of alcohol dependence ranged between 8.0-8.2% for females, while the combined prevalence of lifetime alcohol dependence and abuse has been calculated to 3.3% in Sweden [24]. For males in Sweden, the lifetime risk of developing an alcohol use disorder is 19.3%, 8.6% for alcohol dependence only [25;26]. Because of methodological differences, it is unclear whether the Swedish and American data are possible to compare. Of importance for the present work, several studies have found higher lifetime prevalence of alcohol dependence among younger subjects than among older cohorts, with the greatest change in women, leading to a narrowing in the gap between male and female alcohol dependence [20;27-29]. Among American women, estimates of prenatal alcohol use have ranged between 15 - 20% [30]. The reported consumption during pregnancy among Swedish women has been somewhat higher, with regular alcohol use among approximately 30 % of the females. Six percent of women in that study reported a consumption frequency that clearly placed their offspring at risk [18].

1.3 SUBTYPES OF ALCOHOLISM

Defining more homogenous alcoholism subtypes may help identify underlying etiological factors and facilitate the development of treatments tailored to the needs of the individual [31]. Since Jellinek first proposed a model with five different alcoholism subtypes, several different models have been presented [32]. An influential division of alcoholism into two major subtypes was proposed based on Swedish adoption studies [33;34]. The proposed subtypes were called ‘‘milieu limited’’ and ‘‘male limited’’, respectively, and were described to have distinct phenotypic characteristics as well as different genetic and environmental etiology. Thus, the ‘‘milieu-limited’’ form, also called type I, was described as having a later onset compared with the ‘‘male-limited’’ form, or type II. In contrast, the latter was characterized by an early onset, antisocial behavior, and a higher degree of heritability [35;36] Another two-cluster typology was

subsequently presented by Babor et al., with Type A and Type B, where Type A resembling Cloningers Type I. Type B, like Type II, was described as a more severe form with early onset and more familial alcoholism, but present in both males and females [37]. A simpler classification has also been proposed, with two subtypes of alcohol dependence, where age of onset is the key criterion; early onset alcoholism (EOA) and late-onset of alcoholism (EOA), with onset before or after 25 years [32].

However, validations of typologies with only two subtypes have suggest that more subgroups may be needed to fully characterize the clinical and etiological variation found in individuals with alcohol use disorders [38]. An example is the tree-class typology recently described by Sintov et al.: one with mild clinical characteristics and few psychiatric symptoms, a second with high probability of depression and high neuroticism, and a third class with severe psychopatalogy, early onset and high novelty seeking and with the highest rates of drug use [39]. Another recent typology used latent class analysis to empirically derive alcoholism subtypes from the population-based, nationally representative National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) dataset. This study found that the best fitting model was a five-class solution, but in fact two pairs of clusters were very similar to each other, so that this can also be viewed as a three-class model [40]. In this classification, the largest cluster, just under one third of all alcohol dependent subjects in the population, was comprised of young adults, who rarely sought help for drinking, had moderately high levels of periodic heavy drinking, relatively low rates of co-morbidity, and the lowest rate of alcoholism in the family. In contrast, two clusters that together accounted for close to another third of alcohol dependent individuals had substantial rates of family history, the most severe alcoholism, extensive co-morbid psychiatric and other drug use disorders, showed lower levels of psychosocial functioning, and had engaged in significant help-seeking. Finally, two clusters that accounted for close to 40% of alcohol dependent subjects had the latest onset, the lowest rates of periodic heavy drinking, medium/low levels of co-morbidity, moderate levels of help-seeking, and higher psychosocial functioning.

1.4 CO-MORBIDITY

Lifetime prevalence of psychiatric disorders is almost twice as high among alcohol dependent subjects compared to the general population [41]. The nature of co-morbidity is heterogeneous, and whether co-morbidity with alcohol use disorders is causal,

consequential, or attributable to some common etiological process is a major question and might of course differ between subgroups. The onset of dependence is often referred to as "primary" when it occurs prior to a co-morbid condition and "secondary", when it occurs subsequent to it [42;43], but the sequence of events is difficult to establish with certainty, in particular when this assessment rests on retrospective reports.

The US Epidemiological Catchment Area (ECA) showed that 37% of those with alcohol dependence also had at least one additional Axis I disorder. Among these, the most prevalent were anxiety disorders (19%) and affective disorders (13%). Among Axis II disorders, antisocial personality disorder was most common (14%) [25]. Similarly, in the National Co-morbidity Survey (NCS), a nationally representative household survey of people aged 15–54, 29% of those who had alcohol dependence also met criteria for a mood disorder (including major depression and bipolar disorder) [44]. Almost 37% met criteria for an anxiety disorder during the previous year. Of these, almost 12% had GAD, 4% panic disorder and nearly 8% had PTSD.

These overall co-morbidity data must be qualified in two important ways. First, the base rates of mood and anxiety disorders as well as those of alcoholism are high in the population. This alone would result in high co-morbidity rates between the two categories of disorders, even if these were otherwise unrelated. If instead the excess risk of having a co-morbid disorder is assessed, expressed as odds ratio (OR) conditional on having a diagnosis of alcohol dependence, the picture changes somewhat. The highest association is then obtained for antisocial personality disorder (OR app. 21), followed by bipolar mood disorder (OR app. 6), schizophrenia (OR app. 4), and with an OR of app. 2 for unipolar mood disorders and anxiety disorders. Second, the pattern of co-morbidity is different between men and women, such that the association with antisocial personality disorder is markedly higher among men, while the association with unipolar mood disorders and anxiety disorders is highest among women [25].

Overall, women with alcohol dependence have a significantly higher incidence of co-morbid psychiatric disorders than men with dependence: a lifetime prevalence of 65% has been calculated in women, compared to 28% in men [45].

1.5 HEREDITY AND ENVIRONMENT

Alcoholism is a heterogeneous condition, in which multiple genetic susceptibility factors interact with environmental exposure to produce the clinical disorder [46]. Like other complex diseases it involves not only discrete genetic and/or environmental causes, but also interactions between them. In fact, the phenotype arises from multiple genes, multiple environmental exposures, and multiple interactions [47].

1.5.1 Heritability

Alcoholism in the family is one of the most important factors associated with development of alcohol dependence. The risk increases 2-4 times if first degree relatives have the disease [48]. Twin-studies estimate the heritability of alcoholism to be in the 40-60% range. The degree of genetic vulnerability does not appear to differ substantially between men and women, although underlying genetic factors do not completely overlap [49-51]. Especially in early twin studies the heritability for developing alcohol dependence in women was estimated to be lower than for men. Different explanations have been suggested for the lack of agreement among these studies regarding gender differences, such as inadequate statistical power and etiologic heterogeneity [52]. Interestingly, similarities between genders have been reported for an intermediate phenotype closely related to genetic alcoholism risk, i.e. a low ataxic response to alcohol. Low responses were found in both males and females with a positive family history of alcohol dependence, compared to either males or females who were family history negative [53;54].

Although the overall role of heritable factors for alcoholism susceptibility has long been established, identifying specific genes mediating this influence has proven a more challenging task. Alcohol and aldehyde dehydrogenase genes (*ADH1B* and *ALDH2*) encode enzymes involved in alcohol metabolism, and were first established as specific genetic moderators of alcoholism susceptibility. Variants that lead to accumulation of the intermediate metabolite acetaldehyde, and the associated, highly aversive "flushing" reaction, are common among individuals of Oriental ancestry, and are protective. Subsequent studies turned to genes that influence central nervous system function, such as dopamine, gamma aminobutyric acid, opioid and serotonin systems [46;55]. The first robust, widely replicated finding in this category was *GABRA2,* the gene that encodes the alpha 2 subunit of the GABA-A receptor [56].

A candidate of interest in the context of the present thesis is the mu-opioid receptor gene, *OPRM1*. The mu-opioid receptor has a central role in both analgesic and rewarding effects of opioids. Functional *OPRM1* polymorphisms might therefore be expected to affect the sensitivity to opiates as well as the vulnerability to drugs such as alcohol and nicotine, where opioids have been postulated to be involved in mediating the rewarding properties. A strong association between a functional A118G polymorphism within the coding region of *OPRM1* and heroin as well as alcohol dependence was found in Swedish populations [57;58]. Other studies have not replicated these findings [59]. A common problem for conventional association studies is that genetic variants (alleles) are present with markedly different base frequencies in different ethnic populations. Because association studies rely on comparing allele frequencies between affected and unaffected subjects, differences in ethnic composition of these populations (ethnic admixture) are a known major source of error. It is therefore worthwhile noting that the central Swedish populations in which associations between the *OPRM1* 118G variant and substance use disorders were found are highly homogenous ethnically. A recent finding provides further support for this variant as a susceptibility factor. Possibly in support of a role for *OPRM1* 118G as a susceptibility factor, a human positron emission tomography (PET) study recently found a markedly higher mesolimbic dopamine release in response to alcohol in carriers of the 118G variant, and this was replicated in genetically modified mice carrying the human variants, as measured directly by microdialysis [60].

1.5.2 Early onset of alcohol use

To what extent early onset of alcohol use is a risk factor for subsequent alcoholism has been the subject of extensive research efforts. Epidemiological studies have shown that risk for alcoholism and illicit drug use is increased among individuals who begin to drink at an early age [61]. For example, it has been reported that among individuals who initiated alcohol use at 14 years or younger, the lifetime prevalence of alcoholism was 47%, compared to 9% among those who started to drink at 21 or older [62]. However, the age at which people start using alcohol is itself clearly not random. In fact, twin studies suggest that the association between age of drinking onset and alcoholism risk is, at least for the most part, not causal, but rather results from increased vulnerability to alcoholism, due to genetic factors and shared environment [63;64]. More recently, it has also been shown that early onset of alcohol use may additionally contribute to alcoholism risk through an interaction with genetic risk factors [65]. Shared

environmental factors have been reported to be the primary source of variance for initiation to alcohol use. Among these factors, family and peer influences have been proposed to be important, especially among females. However, the risk for transition to alcohol-related problems has mostly been found to be attributable to genetic factors [46]. Recent data from male twins have further indicated that the relative contribution of genes and environment changes over time and those genetic factors gradually increase their influence after the age of 15 [66].

1.5.3 Personality

Personality traits are central to the discussion of pathways to alcoholism. There is broad agreement that major dimensions of psychological functioning have considerable heritability [67]. Assuming that personality traits are not themselves substantially influenced by alcoholism, it seems that some of these factors increase the risk for this condition. Studies in twins suggest that shared genetic susceptibility factors underlie externalizing disorders such as alcohol dependence, illicit drug use disorders, and externalizing personality traits [68;69]. Specifically, impulsivity, a core characteristic of externalizing disorders [70], is an established risk factor for alcoholism. Impulsivity has been proposed to be involved in both the initiation and end-stage of alcohol dependence [71;72]. The frontal cortex is thought to be involved in impulsive decision-making, in which the ability to focus attention and consider outcomes is diminished. Neuroimaging studies have found abnormal function in the frontal cortex associated with substance abuse, indicating a connection to the changes of impulse-control and deficits in delay discounting described in alcohol and drug use disorders [73]. Low conscientiousness, high novelty seeking and antisocial traits are all related to impaired impulse control, and have been linked to alcohol dependence [74-77].

Antisocial traits and behavior vary along a continuum of severity. Variations in a number of dimensions of predisposing temperament characteristics and cognitive ability, each with its own genetic and environmental influences, have been described. The predisposing temperament characteristics include oppositionality, defiance and noncompliance, a foundation for physical aggression, low harm avoidance, and lack of empathy [78]. Aggressive traits vary with age, with a increase from childhood to adulthood in nonaggressive antisocial behavior, and decrease in physical aggression [78]. Antisocial behavior as impulsive physical aggression is much less frequent in women than in men, but it has been suggested that aggression may in fact be equally common in females if indirect, verbal, or social forms are included [79;80]. Subtypes of antisocial

behavior based on onset in childhood or in puberty have been described, with more severe consequences among the subject with onset of antisocial traits in childhood. Although more males than females followed this early trajectory, findings support similarities across genders with respect to developmental trajectories of antisocial behavior [81].

However, high levels of neuroticism, a trait characteristic of internalizing disorders, have also been shown to increase the risk of alcohol dependence. High neuroticism involves emotional instability and refers to an individual's tendency to respond with negative emotions to threat and frustration. Neuroticism is more than any other personality trait correlated with a wide range of mental and physical health problems, and has also been shown to increase the risk for alcohol dependence [82-86]. Studies indicate that this correlation is partly due to shared genetic factors between different mental disorders such as anxiety and depression on one hand, and neuroticism on the other [85;87-89]. Interestingly, behavioral traits related to high neuroticism and high impulsivity, respectively, have been postulated to represent extremes on a spectrum of evolutionarily conserved strategies to cope with novelty [90].

As indicated above, a complication for research on personality traits is if prolonged alcohol use alters these otherwise stable characteristics. Accumulating evidence indicates that prolonged exposure of the brain to alcohol will induce a pathological activation of brain stress and aversion systems, resulting in increased propensity for negative affect, and thus neuroticism [91]. One implication of this is that duration of excessive alcohol use must be considered in any analysis that focuses on a possible role of personality traits in alcoholism.

1.5.4 Childhood trauma

Studies from both clinical and community-based samples have shown that severe childhood adversity, and emotional, physical, and sexual abuse in particular, are associated with increased vulnerability to addiction [92-96]. The association is complex, with both genetic and environmental factors involved in transmission mechanisms [97;98].

Different forms of neglect during childhood also have an association with lower age of onset of alcohol use and heavy drinking [99-103] as well as smoking and use of illicit drugs [104], indicating a possible mechanism for the link between childhood abuse and dependence. A twin study [94] supported this connection, showing that childhood sexual

abuse increased the likelihood of early alcohol use, but not the rate of progression from initiation to alcohol dependence.

In general, it seems that the association between childhood abuse is stronger among women than among men [93]. One study examined a group with either "early onset" or "late onset" of alcohol problems [100]. Women with early onset had more childhood traumatic experiences, with a strong positive correlation between traumatic experiences within the age period of 12-18 years and severe alcohol- and drug use. No such correlation was seen among the male subjects.

Although childhood abuse and neglect has been linked to early onset of alcohol use, binge drinking and later alcohol dependence, this association might reflect familial risk or higher prevalence of dependence in the family [105-107]. However, studies have found that childhood abuse remained an independent predictor of later alcohol problems even when parental alcohol problems were taken into account. Twin studies have shown that at least in part, the association is influenced by family background factors. [94;96;102;108-111].

Not all abused women, however, develop alcohol dependence. Risk may be moderated by individual factors, including genetic vulnerability. Interactions between genes and factors in the environment contribute to alcoholism vulnerability. The hypothalamic-pituitary-adrenal-axis (HPA) regulates stress activity. The physiological response to stress is primarily mediated by the release of corticotrophin-releasing hormone (CRH). Corticotrophin-releasing hormone receptor 1 (CRHR1) is the main receptor that mediates effects of CRH to induce both endocrine and behavioral responses to stress. Genetic polymorphisms within the *CRHR1* gene have been proposed to moderate the effect of early life adversity on adult depressive symptoms [112] as well as heavy alcohol use [113;114]. This parallels findings in experimental animals that genetic variation within the CRH system moderates alcohol intake, stress sensitivity, and influence of early life adversity on alcohol intake in response to stress [115;116].

An interaction between early life trauma and genetic risk to produce early onset, severe alcoholism characterized by antisocial traits has also been described for the low activity MAO-A allele in both males and females. The MAO-A gene is located on the short arm of the X-chromosome, and encodes an enzyme that metabolizes dopamine, serotonin,

norepinephrine and epinephrine [117]. More recently, a low activity MAO-A allele was reported to interact with childhood maltreatment to produce psychopathology in males [118;119]. MAO-A variation in women was subsequently found to interact with childhood sexual abuse to mediate risk for antisocial alcoholism. Specifically, the low activity MAO-A allele was associated with alcoholism, and particularly with antisocial alcoholism, only among sexually abused subjects. Within this group, a gene-dose effect of the low-activity allele was found both for alcoholism and for antisocial symptoms [120]. Although other findings have been reported in smaller [121] or non-clinical populations [122], the findings by Ducci et al. appear consistent with, and expand on the male MAO-A findings.

1.5.5 Sexual abuse

The association between sexual trauma and psychiatric psychopathology has been well documented in the literature, in particular when exposure to sexual trauma has occurred early in life [92-96]. Sexual abuse has consistently been associated with severe alcohol problems, while it is less clear with whether less severe harmful drinking is also related to sexual abuse [123]. In general, it seems that the association is stronger among women than among males [93;123;124], and women exposed in childhood appear to have more psychological problems than those exposed as adults [100;103;125]. However, a cross-sectional community based study found no difference between women exposed during childhood or as adults, while women abused either in childhood or as adults had higher levels of psychological problems and physical symptoms [95]. Other studies have also shown that the risk for psychopathology increases with more severe forms of abuse [96;108;109;111;123].

Several studies have confirmed that sexual abuse preceded any alcohol misuse [123]. Studies have shown that risk for alcoholism and illicit drug use is increased among individuals who begin to drink at an early age [61] and it seems that different forms of neglect and sexual abuse in childhood have an association with lower age of onset of alcohol use and heavy drinking [100-103;126]. However, heavy drinking may also occur before the trauma, especially among women exposed as adults, since women who are using substances may be more vulnerable to entering a situation with a risk for sexual victimization [123;127].

Of clinical relevance, patients with addiction and a history of sexual violence have more problems across a variety of domains, with higher number of psychological symptoms and suicide attempts, as well as more medical, legal and employment problems that affect treatment outcome [124;128;129].

1.6 SOCIAL AND CULTURAL DIFFERENCES

Interaction with social norms and the ways in which society controls drinking differ across times and societies. Different cultural aspects may differentially influence male and female alcohol consumption and drug use [130-132]. One hypothesis is that the degree of gender equality is an important factor when it comes to differences in drinking habits among men and women. The Nordic countries consistently rate the highest on scales measuring gender equality and it is also here the smallest gender gap with regard to alcohol use is found [21;133].

2 OUTLINES OF THE THESIS

Until recently Swedish midwives assumed that most Swedish women abstained from alcohol during pregnancy [134]. However, in an anonymous screening of drinking habits among pregnant women, it appeared that approximately 30% continued to drink during pregnancy [135]. The study also indicated that simple screening instruments could help the midwifes to identify women with hazardous alcohol consumption. In **study I** the question of whether screening could be conducted during face-to-face registration at the antenatal clinics (ANC) was examined. Screening instruments and blood test were evaluated for their ability to detect hazardous alcohol use on admission at the ANC. The results showed that using screening instruments is feasible, and that these identify considerably more women with at risk consumption than the currently used method, a question routinely asked based on the ANC medical records. This more effective screening has been evaluated and implemented at ANC [18]. In study I we also identified a group of women with a more complex picture, with alcohol use during pregnancy accompanied by drug use and a history of psychiatric complains. In **study II,** we carried out a pilot study in early pregnancy at the ANC and an anonymous interview with pregnant women in late pregnancy, in order to better characterize the group of women who continued to use alcohol during pregnancy. The hypothesis was that psychiatric morbidity, rather than alcohol use disorders, would be over-represented within this group. However, we found that none of these factors were common. Instead, our results showed that alcohol use during pregnancy was associated with impulsive personality traits, or novelty-seeking. Since similar personality traits had been reported in women with fully developed alcohol dependence, especially in those with a more severe form, the next study, **study III**, explored subtypes of alcoholism in a case-control study of treatment seeking alcohol dependent women. A classification of alcoholism into two major subtypes was proposed based on Swedish adoption studies [33;34]. Type I was described as having a later onset, compared to type II, with an early onset. Type II was furthermore characterized by antisocial behavior and a higher degree of heritability (the proportion of phenotypic variation in a population due to genetic variation), and was also described as “male limited” [35;36]. We found that sub-typing treatment seeking alcohol dependent women according to type I/II criteria based on age of onset and presence of social complications generated groups that differed in several clinically meaningful characteristics, resembling those originally described for males. Among

these characteristics, density of family history was markedly higher in type II women, possibly suggesting a higher heritability in this group. In **study IV,** we examined the association between sexual trauma and alcohol dependence in the population originally described in study III. We found a strong association between alcohol dependence and sexual abuse, whether experienced in childhood or adulthood. We examined in further detail the role of heritable- and environmental factors for female alcoholism in a cohort of female twins from The Swedish Twin Registry in **study V**. We used classical twin modeling to quantify the proportion of phenotypic variance due to genetic and environmental factors in alcohol dependence, and analyzed the association between childhood trauma (exposure to emotional neglect, physical trauma or sexual trauma during childhood) and alcoholism or its subtypes. We found that heritability of alcoholism in females was comparable to that previously found in men, and did not find evidence for a difference in heritability between the different subtypes of alcohol dependence. The twin study also provided evidence for a role of severe childhood abuse, of sexual as well as physical nature, in susceptibility to alcoholism, especially of the early onset / Type II category.

3 METHODS

3.1 OVERALL AIM

The overall aim of this thesis was to study vulnerability factors leading to hazardous alcohol consumption during pregnancy as well as alcohol dependence among Swedish women. Different risk factors and characteristics were studied. We also examined if specific characteristics could discriminate or identify different subtypes (type I/late onset and type II/early onset) of alcohol dependence.

3.2 STUDY AIMS

3.2.1 Study I

Pregnant women at antenatal clinics in Stockholm, Sweden were evaluated using some potentially useful tools for detection of alcohol use, in order to collect data on hazardous alcohol consumption prior pregnancy and measuring the consumption during pregnancy. The research questions were:

- What is the prevalence of risk consumption among pregnant women in present-day urban Sweden?
- Would an intensified screening strategy better identify hazardous alcohol use during pregnancy compared with current antenatal care?

3.2.2 Study II

Study II was a study in two stages at antenatal clinics in Stockholm. In stage one, pregnant women in early pregnancy where interviewed, while in stage two, women in late pregnancy answered anonymously to screening instruments. The research questions were:

- Do women who consume significant amounts of alcohol during pregnancy have alcohol use disorders and / or psychiatric co-morbidity?
- Are there differences in personality traits between women with hazardous consumption during pregnancy and those without it?

3.2.3 Study III

In Study III we obtained detailed phenotypic data (socio-economical data, alcohol use, illicit drug-use, personality, family density of alcohol dependence) from a large sample of treatment-seeking alcohol dependent women in present day Sweden. The research question was:

- Is type II alcohol dependence, a subtype characterized by an early onset, antisocial behavior and a higher degree of heritability, previously described in men, also a useful and valid subtype in this female treatment seeking population?

3.2.4 Study IV

The same sample as in study III was used. The following research questions were asked:

- Is sexual abuse in childhood and/or as adult associated with alcohol dependence?
- Do psychiatric disorders mediate a possible association between sexual abuse and alcohol dependence?
- Do genetic markers within genes that have that have been reported to be associated with alcohol dependence (*OPRM1*) or with stress-related risk for alcohol problems (*MAO-A* and *CRHR1*) moderate the influence of early life adversity and alcoholism in our sample?
- Do female alcoholics with a history of sexual abuse differ in alcohol severity, drug-use, psychiatric co-morbidity, personality traits or subtype of alcoholism, from other alcohol dependent women?

3.2.5 Study V

In Study V, a population based female twin sample from the Swedish twin register was used. The research questions asked were:

- What is the lifetime prevalence of alcohol abuse and dependence in this female Swedish twin sample?
- What is the role of heritable and environmental factors for female alcoholism, taking in account possible differences between early onset/type II and late onset/type I subtypes of this disorder, with focus on the association between different forms of childhood trauma and alcohol dependence?

3.3 OVERALL PROCEDURES, PARTICIPANTS AND INFORMATION

3.3.1 Study I

Study I was a randomized controlled study. The study was based on data from ANC in Stockholm County, obtained from pregnant women typically in early pregnancy in conjunction with their first admission to the ANC clinic. The subjects were asked by

the admitting midwife, after the admission exam, to meet the interviewer for oral and written information, consent and randomization to intervention or treatment as usual. All 156 subjects randomized to treatment as usual (TAU) accepted i.e. allowed access to their antenatal care records for subsequent extraction of data. Among 150 subjects randomize to screening procedure, 147 accepted (drop-out 2%).

3.3.2 Study II

The study was made in two stages, with a randomized pilot study, and a replication study with case-control methodology. The pilot sample in study II was based on pregnant women from Stockholm County and data were obtained at their first visit to ANC. The women were given oral and written information by their regular antenatal care midwife to whom they also gave their informed consent. The participating midwifes were randomized into two groups, intervention and control (treatment as usual). All 153 subjects in the control condition agreed to participate, i.e. allowed access to their antenatal care records for extracting data. Among 162 subjects in the intervention condition, 139 accepted, yielding a drop- out rate of 14%.

The replication cohort was obtained by targeting all women in the third trimester (pregnancy week 30 or later) who signed up for parental education routinely offered at an antenatal clinic in central Stockholm, and attended by the vast majority of pregnant women. During the recruitment period, 950 subjects were offered parental education and 735 signed up. Complete data were returned by 715 individuals, yielding a drop-out rate of 3%. The midwife giving the parental education class gave oral information as approved by the ethics committee, and handed out the questionnaires. These were filled out during a break, and returned at the end of the session. Subjects gave their consent by anonymously returning the forms.

3.3.3 Study III

Study III was a case-control study. Women seeking treatment for alcohol dependence at two outpatient clinics in Stockholm, Sweden, participated. All female subjects received brief information about the study and were asked if they could be contacted later for additional information. On second contact, both oral and written information was given to the women and informed consent was obtained. Among 246 subjects with presumed alcohol dependence that were given information about the study, 202 accepted to participate. Of 248 healthy controls recruited through the same two-stage process

among women who attended routine gynecological health examinations in Stockholm, 203 accepted to participate. This yielded a dropout rate of 18 % and 19 % respectively.

3.3.4 Study IV

The same sample as in study III was used in study IV.

3.3.5 Study V

The sample in study V was based on the females in the cohort from "The Study of Twin Adults: Genes and Environment" (STAGE). The target group was contacted with an invitation letter containing information about the project. Of 21 369 possible female subjects from monozygotic (MZ) and same- and opposite-sex dizygotic (DZ) twins born in Sweden 1959–1985, 66.0 % (n = 14 114) responded to the interview by telephone or by the internet. The study population was restricted to subjects answering the questions about alcohol consumption and alcohol use disorder (n=13501, 63.2 %). A total of 457 (3.3%) subjects failed to respond to the questions about alcohol abuse and 613 to the questions about alcohol dependence (4.5%). The non-responders to these questions were significantly younger, less likely to be married, and had a lower education than responders. There were also internal non-responders to the questions about childhood trauma. The numbers varied somewhat between the different questions with the highest amount of non-responders in the question about "emotional neglect" (non-responders with alcohol dependence 206, 31% and healthy subjects 3310, 26%, p =0.004).

3.4 QUESTIONNAIRES AND INSTRUMENTS

3.4.1 Addiction Severity Index, ASI

The ASI is a semi structured interview designed to obtain a history from, and measure problem severity in patients with substance use disorders [136]. The family history questions from the ASI were used in order to assess family history of alcohol dependence and other psychiatric disorders.

3.4.2 Alcohol Use Disorder Identification Test, AUDIT

The AUDIT is a self-report questionnaire developed by a World Health Organization study group to identify hazardous alcohol use [5]. It has good performance in general populations [6]. Its 10 questions, each scored 0-4, fall into three categories: consumption,

dependence and alcohol-related problems. The questionnaire and manual for its administration are freely available for download [137]. In the Swedish version of the AUDIT, the definition of a standard drink (originally 12 g ± 10%) has been adjusted to local conditions and refers to 1 bottle (33 cl) beer in tax class II (3.5% v/v, sold outside of the state monopoly), 1 small (25 cl) beer in tax class III (approximately 5% v/v, sales restricted to monopoly stores), 1 glass of wine or 4 cl of distilled spirits. It has been proposed that the cut-off score for detecting hazardous alcohol consumption (i.e., consumption that has led to, or in the future might lead to, adverse health consequences) in women should be adjusted to 6 [7] and this level was used.

3.4.3 Alcohol Consumption Questions, AUDIT – C

The AUDIT-C is a modified version of AUDIT. It includes only the quantity/frequency items (Item 1–3) from AUDIT, a subscale that has a reasonable validation to detect significant alcohol use and to detect alcohol use disorders [137].

3.4.4 Classification into type I or type II alcoholism

Based on revised Cloninger and Bohman criteria, a subject is classified as type II if both of the following criteria are present: onset of alcohol problems before the age of 25 years and/or seeking treatment before the age of 30 years; and two or more social complications (such as drunk driving, loss of job, incarceration, so on). Otherwise the subject is classified as type I by exclusion [75].

3.4.5 Hopkins Symptom Checklist, revised, SCL-90R

This is a self-report symptom inventory with 90 questions and nine subscales, designed to estimate recently experienced physical and psychiatric distress. SCL-90R does not establish a formal psychiatric diagnosis, but gives both global and domain specific measures of current psychopathology for which normative population data are available in Sweden, allowing generation of *T*-scores [138;139].

3.4.6 Life Stressor Checklist, LSC-R

LSC-R is a self-report measure that assesses traumatic or stressful life events over the course of the lifetime. The LSC yields estimates of the frequency of traumatic events similar to other standard assessment measures of traumatic exposure and has demonstrated good predictive validity [140].

3.4.7 Swedish Universities Scales of Personality, SSP

SSP is a self-report inventory with extensive normative data in the Swedish population. SSP is a refinement of the Karolinska Scale of Personality. It has 13 subscales with a total number of 91 items. SSP has been evaluated and has been found to be easy to understand and administer, regardless of the patient's age, gender or diagnosis. It generates measures of personality traits that are closely correlated with those obtained using questionnaires with widespread international use, such as the NEO-PI [141].

3.4.8 Sex in Sweden

Questions were adapted from the standardized questionnaire used in a survey of sexual behavior in Sweden "Sex in Sweden" [142]. The interview asked about various forms of sexual abuse, from being forced to watch someone masturbate to being forced into anal or vaginal intercourse and also about the age of first abuse, number of separate incidents and relationship to abuser.

3.4.9 Structured Clinical Interview for DSM-IV, SCID I

The SCID I is a semi-structured interview for establishing the major Axis I DSM-IV diagnoses. It includes an introductory overview followed by nine modules, seven of which represent the major axis I diagnostic classes. The SCID has been found to yield highly reliable diagnoses for most axis I disorders [143].

3.4.10 Timeline Follow Back, TLFB

The TLFB is a systematic interview method to obtain a day-by-day account of a person's actual alcohol consumption. In non-pregnant subjects, it yields estimates of drinking that have been validated for up to 6-12 months [144].

Instruments used in the different studies.

Study I

AUDIT and TLFB.

Study II

Pilot cohort:

On all subjects: AUDIT, SCL-90, SSP, TLFB,

On subjects positive on AUDIT and/or TLFB: SCID- I, part F.

Replication Cohort:

AUDIT-C, SSP.

Study III

ASI, AUDIT, Classification in type I and type II, SSP, SCID-I and TLFB.

Study IV

ASI, AUDIT, Classification in type I and type II, SSP, SCID-I, Questions from "Sex in Sweden" and TLFB.

Study V

Classification in type I and type II, SCID-I part F and LSC-R.

3.5 DATA ANALYSIS AND STATISTICS

3.5.1 Study I

In Study I Statistica 6.0 (StatSoft Inc., Tulsa, Oklahoma) was used for all analyses. Frequencies were compared using $\chi 2$-test with Yates's correction.

3.5.2 Study II

Statistica 6.0 (StatSoft Inc., Tulsa, Oklahoma) was used for all analyses. Within the pilot cohort, possible differences between consumption positive and negative subjects on SCL-90 *T*-scores were evaluated using one-way ANOVA. Within each of the cohorts, SSP subscale scores were subjected to factor extraction using the principal component method. In each case, following normalized Varimax rotation, this yielded

three factors with eigenvalues >1.0, similar to what has been published previously. Differences between consumption-positive and negative subjects on SSP factor scores were analyzed using one-way ANOVA. Since there were trend level differences for age and education between the consumption-positive and negative groups, these two variables were entered into the analysis as co-variates to assess the independent contribution of consumption status.

3.5.3 Study III

Statistica 8.0 (StatSoft Inc., Tulsa, Oklahoma) was used for all analyses. Difference between the groups (healthy controls, type I and type II) in age, number of children, severity and family density of alcohol dependence were analyzed using ANOVA/ ANCOVA, with Neuman- Keuls post-hoc test. Age was evaluated as a covariate in subsequent analyses and controlled for when relevant. Frequency differences between groups in drug use were compared using Fisher's exact test.

To reduce the dimensionality of the SSP data, factor analysis using principal component extraction was carried out. To account for the highest possible proportion of the variance, individual factor scores on the respective factor (neuroticism, sensation-seeking and aggression) were computed using all loadings and were compared between groups (healthy controls, type I and type II) using ANOVA.

3.5.4 Study IV

All analyses were performed using SAS 9.2 (SAS Institute Inc, Cary, North Carolina). For the moderation analysis, logistic regression was carried out using PROC LOGISTIC. Case-control status was regressed on demographic covariates, genotype status, sexual abuse status, and a genotype by abuse interaction term. With this procedure, a Wald Chi-square test was used to evaluate each of the predictors. The same analytic approach was used for all analyses involving a dichotomous outcome (case-control status). A few of the analyses without covariates were run with the PROC FREQ procedure using the CHISQ option (chi square statistic). A few cases involved continuous outcomes and the PROC GLM procedure was used to run ANCOVAs.

For the factor analysis of personality measures obtained using SSP, the same method as described in study III was used and finally, the Sobel test was used for the calculation

of the mediation effect (i.e., to determine if a statistically significant indirect path existed between physical, psychological or sexual abuse and alcohol dependence through the psychiatric disorder)

3.5.5 Study V

We used structural equation modeling to quantify the proportion of phenotype variance due to genetic and environmental factors in alcohol dependence and its subgroups, type I and type II among females. This was followed by analyses of the association between the environmental factor childhood trauma and alcohol dependence in the female population.

To quantify genetic and environmental effects we used the basic twin model assuming the individual differences in liability to a trait to originate from 3 sources: Additive genetic effects (A), Childhood Shared environmental effects (C) and Non-Shared environmental effects (E), the ACE model. All genes as well as shared environment are shared by MZ twins. DZ twins share one-half of the genes and all the shared environmental. Two more assumptions are included in the twin method; no assortative mating that could influence the range of variation, and the equal environment assumption, which states that environmental exposure is shared to the same extent by MZ and DZ twins. We used structural equation modeling, comparing the similarity of MZ and DZ same sex twin pairs, to provide estimates of each source's contribution to the population variance in liability to a disorder [145].

In order to investigate whether childhood trauma is associated with the development of alcohol dependence, we first analyzed the study group as a cohort (*n*=13501). Childhood trauma was specified, as described above, as exposure to emotional neglect, physical or sexual trauma during childhood. Dependent variables were alcohol dependence and the subgroups Type I and Type II. The analyses were adjusted for age. In this first step, we used a generalized estimating equation model with the logit link (SAS procedure GENMOD) correcting for the twin structure of the data (within pair correlations) to estimate odds ratios with 95% confidence intervals.

In order to examine whether the association between childhood trauma and alcohol dependence was confounded by familial factors, we performed a co-twin control analysis, using both MZ and DZ pairs. Twin pairs discordant for alcohol dependence were analyzed as a case control study, where the healthy co-twin was used as a matched

control for the affected twin. We performed a conditional logistic regression analysis, with the same variables as described in the cohort analysis. When odds ratios from the co-twin analyses are lower than those resulting from the cohort analyses, familial influence on the associations between exposure and outcome is suggested, either from early environment or genetics [146].

To test whether results from the cohort analysis differed significantly from the co-twin analyses, we tested for a possible difference in exposure (childhood trauma) between the co-twins of alcohol dependent twins and the general twin population. Two sets of controls were used; 1) Twins unrelated to the cases were randomly selected from the study population, five controls for each case, matched by age and 2) the co-twins of the cases. We then compared the external and the co-twin control subjects. A higher prevalence of childhood trauma among the co-twins of the cases would indicate a familial confounding by childhood environment and/or genes. Statistical analyses were performed using SAS software version 9.2 (SAS Institute Inc, Cary, North Carolina).

3.6 ETHICAL CONSIDERATIONS

Studies I-IV were approved by Stockholm South Human Subject Committee, with the following registration numbers: Study I 199/00, Study II 288 /00, 25/02, Study III and IV380/03, 2005/694-32, 2006/41-32. Study V was approved by the Research ethics committee of the Karolinska Institutet, with the registration number 306, 03-224.

3.6.1 Study I

An ethical consideration in this study was whether pregnant women would find the more detailed questions in the screening questionnaire intrusive, and also whether they may be worried about the blood sampling. A second ethical consideration was whether subjects would be, or perceive being, unduly coerced into participation out of loyalty with their clinical care provider, or out of concern that a decision to decline participation would influence their clinical care.

To minimize this risk, the treating midwife acted only as an intermediary between the woman and the research midwife. The woman was informed by the research midwife and then randomized to the interview or control group. She was also informed that her treating midwife had not been told which group she had been randomized to, and was

asked whether she was willing to participate in the study. This design meant that the women could not feel obliged to participate out of loyalty with their midwife or concern about consequences for clinical care.

The benefit of this study is improved detection of hazardous alcohol use during pregnancy, a major preventable risk factor for the offspring. The Swedish antenatal care system is charged with identifying such use, and questions about alcohol consumption have been routine at the ANC for many years. If successful, this study would result in improved identification of women with hazardous alcohol consumption during pregnancy. An earlier and improved identification of women at risk was considered to outweigh the risks of the more detailed screening when carried out with appropriate precautions as described above.

3.6.2 Study II

Similar to study I, an initial ethical consideration in this study was whether the women attending ANC would be unduly coerced to participate because they would feel a loyalty towards "their" midwife and towards the group to which she had been randomized, or because they would be concerned that their clinical care would be affected by a decision to decline participation. These considerations applied only to the pilot part of study II, because the replication was an anonymous survey.

In carrying out the risk – benefit analysis for this study, we could build on the experience from study I. The screening procedure at the ANC had not worried the pregnant women. Instead, they had reported that they found the discussion and information about alcohol and pregnancy positive. The few subjects that had more severe alcohol problems were offered adequate follow up for this. In the pilot part of study II, the midwives were randomized, and were those giving information to the pregnant women. Written information was distributed to the pregnant women, and this information stated that they were in no way obliged to participate, and that their care would not be affected if they declined to participate. This information was also given to the woman orally by the midwife.

These procedures minimized the risk, which was considered to be outweighed by the benefit of improving methodology for early detection of hazardous alcohol consumption during pregnancy.

The replication study was anonymous. Consent was implied by returning the questionnaire, and identity of individual respondents was not revealed. This part of study II was considered to be associated with minimal if any risk, while contributing generalizable knowledge.

3.6.3 Study III and IV

The main ethical considerations for these studies were as follows:

- The assessment interview was relatively extensive, with focus on psychiatric health and personality, and also included highly personal questions about trauma and sexual experiences. This could be perceived as intrusive.
- Subjects were in treatment for alcohol use disorders, and participation could be perceived to influence treatment provision.
- Sensitive personally identifiable information was disclosed, which if revealed in inappropriate ways could be damaging.

To minimize risk, written as well as oral information was given to all subjects that they were in no way obliged to participate, and that the care they were offered would not be affected if they declined to participate. This information was therefore given in several steps. Treatment staff acted only as an intermediary between the woman and the researchers, and it was the researchers who gave the detailed written and oral information about the study. It was possible for subjects to discontinue the interview at any point, and it was also possible to do the interview but not the blood tests, since some subjects were afraid that venipuncture would be painful. If we received some previously unknown information of clinical relevance, subjects were offered further diagnostic evaluation and treatment, and were given the choice of whether treatment staff could be informed. Sensitive information was protected using established procedures.

The benefit of these studies is generalizable knowledge about characteristics of female alcoholism, with potential to improve prevention, diagnosis and treatment. This benefit was assessed to outweigh the risks listed above, once every reasonable effort to minimize those had been made as described.

3.6.4 Study V

The main ethical consideration in this study was protection of sensitive, personally identifiable information. In the course of assessment, personal questions about psychiatric symptoms, personality and use of alcohol and other drugs were asked.

Risk was minimized by information that participation was voluntary, and by protecting the identity of participants using established procedures (every individual in the registry was represented by a number and the personal identity were not in the files).

The benefit of this study is generalizable knowledge about the role of environment and heredity in alcoholism and its subtypes in women. This knowledge has a potential to improve prevention, diagnosis and treatment, a benefit assessed to outweigh risk.

4 SUMMARY OF FINDINGS

4.1 STUDY I

Interviews were conducted on initial admission to the ANC for pregnancy. The results showed that despite the fact that the women were not anonymous when screened for alcohol consumption, screening and interviews did not pose any difficulties. TLFB showed some self-reported alcohol consumption during the first trimester of pregnancy in 87% of the women. In a vast majority of these cases, however, consumption was marginal, but 24 women (16%) drank at levels that could be defined as "risk-consumption" during pregnancy. (TLFB was "consumption -positive" if consumption exceeded 70 g/week during any 2 or more weeks and/or if there was a heavy episodic drinking pattern, 60 g/episode, on 2 or more episodes). The AUDIT had a moderate sensitivity (54%) to identify these subjects, but in the control group, only 4 (3%) were identified as using alcohol, indicating a probable underestimation of alcohol use by regular antenatal screening procedures ($p = 0.0001$).

For alcohol consumption that continued during pregnancy, blood chemistry biomarkers were of very little use. Most women with pathologically elevated values turned out to have medical conditions rather than high consumption of alcohol. Two women had hazardous alcohol consumption and elevated test results, but both these were also identified by the screening questionnaire. The screening procedure identified a group of women (9%) who differed from the others in a troubling way. They screened positive both for hazardous use before pregnancy (AUDIT) and for continued consumption at levels documented to be harmful for the fetus during pregnancy (TFLB). Other indicators support that the group identified in this manner is a high risk population. Thus, these women have a history of seeking contact with psychiatric services more often than others, and both smoke and have used illegal drugs at higher rates than the general pregnant population. Furthermore, they have significantly higher alcohol consumption with regard to number of occasions, amount and binge drinking.

4.2 STUDY II

We analyzed alcohol use disorders, co-morbid psychiatric symptoms and personality traits in women with self-reported alcohol use during pregnancy at levels which have been shown to increase adverse pregnancy outcomes in epidemiological studies. In the

pilot study, interviews were conducted with women on initial admission to the ANC, while the replication study was performed anonymously in late pregnancy.

Seventeen percent of the subjects in the pilot sample reported significant consumption according to TLFB during early pregnancy, according to the definition provided above under "study I". Only a minority of those fulfilled alcohol dependence criteria, or had scores on AUDIT typically associated with such a diagnosis. Recently experienced psychiatric distress did not differ from those with low or no consumption during pregnancy.

Among personality traits, there was no difference between the groups with regard to neuroticism or aggressiveness. In contrast, there was a significant difference on the novelty seeking factor (p =0.01). The results were robustly confirmed in the replication study, where low prevalence of alcohol dependence among consumption positive subjects also was found while high novelty seeking was confirmed with a high degree of statistical significance (p <0.0001).

4.3 STUDY III

We examined whether the construct of type II of alcoholism, originally proposed to be ''male limited'', would also cluster female alcohol dependent patients in a meaningful way. We found that alcohol dependent women provisionally classified as type II had more severe alcohol problems and significantly higher rates of illicit drug use than female alcoholics classified as type I. In both alcohol dependent groups, family history of alcoholism was present with a higher density than among healthy controls, but in addition, this measure was considerably higher among type II than among type I women. Finally, the pattern of personality traits distinguished the groups. Both alcoholism subtypes scored higher than normal on anxiety (neuroticism) and impulsivity traits (sensation seeking), but aggression was the trait that robustly discriminated between the two sub groups. Measures of this trait in Type I patients were indistinguishable from healthy controls, while type II subjects scored markedly higher than either of the other groups on this dimension (p =0.00004).

4.4 STUDY IV

Sexual abuse was overrepresented in alcohol dependent females. This association, however, was limited to the most severe category of sexual abuse, involving anal or

vaginal penetration. Of those reporting any sexual abuse, 65.0% (*n*=67) reported an onset of sexual abuse in childhood (before age 18). Both child- and adult-onset abuse were associated with alcohol dependence and the strength of the association was similar for both groups (child-onset: OR= 3.89; 95% CI=2.14, 7.09; adult-onset: OR= 3.98; 95% CI=1.81, 8.76). The association between sexual abuse involving penetration and alcohol problems may be accounted for, fully or in part, by an intermediary psychiatric condition. Of the five psychiatric disorders tested, anxiety, anorexia nervosa, and bulimia met criteria as potential mediators of the abuse-alcohol dependence association; however, no evidence was found for mediation by either affective disorders or PTSD. Sexual abuse continued to have an independent effect on alcohol dependence status even after accounting for these potential mediators. Thus, sexual abuse involving penetration is associated with later alcohol problems directly and through its effect on psychiatric problems. Among alcohol dependent subjects, those with a history of sexual abuse with penetration had elevated severity of alcohol problems, psychiatric co-morbidities, and novelty-seeking. Sexual abuse was not associated with an earlier onset of regular drinking or a higher density of family history of alcohol dependence. None of the candidate genetic moderators of the sexual abuse-alcoholism association, *OPMR1* A118G, *MAOA* or *CRHRI*, met statistical criteria as moderators.

4.5 STUDY V

In a population-based cohort of female twins, we found a lifetime prevalence of alcohol dependence of 4.9%, with 74% of the alcohol dependent subjects classified as type I, and 26% as type II alcoholics. Heritability was 52% in the whole alcohol dependent sample, similar to that previously reported in men. No difference in heritability was found between early and late onset alcoholism, with heritability estimated to be 59% in type I and 64% in type II. Data suggested a greater influence of shared environmental factors in type II subjects (15.0 %) compared to type I (3.3 %). We found evidence for a role of severe childhood abuse, both of sexual and physical nature, in susceptibility for early onset alcoholism among women, since childhood physical trauma and sexual abuse had a strong association with early onset alcoholism compared to late onset alcoholism (OR 2.36, CI 1.49, 3.75 and OR 2.17, CI 1.31, 3.58 respectively). Emotional neglect was also related to early onset alcoholism, when it was reported as "frequent" (OR 2.01, CI 1.18, 3.44).

A co-twin control analysis indicated that childhood trauma is a major component of the environmental factors early in life especially important for Type II alcoholism. Because sexual abuse was a significant risk factor for alcohol dependence in the co-twin control analysis, we found evidence for a direct association between this form of childhood trauma and alcohol dependence, independent of other forms of shared childhood environment. In summary, we conclude that childhood trauma is likely to be both a marker of familial susceptibility factors and an individual specific risk factor *per s*e.

5 METHODOLOGICAL CONSIDERATIONS

5.1 STUDY I

The major strength of this study is that it obtained data on actual alcohol use during early pregnancy. We used the TLFB, which provides a day-by-day estimation of actual alcohol intake. This allowed us to set screening thresholds to directly identify subjects whose consumption in early pregnancy exceeded what has been demonstrated to increase the incidence of FASD. The use of TLFB was particularly important since AUDIT detected problem drinking prior to pregnancy. Even though pre-pregnancy substance use to some degree predicts alcohol use during pregnancy [135], not all women who drink during pregnancy are problem drinkers [147]. A possible limitation of our results is a lack of comparative data on performance or on resource demands for AUDIT and/or the TLFB, versus shorter instruments specially developed for use during pregnancy. Furthermore, the subject population may not be representative of the general Swedish population of pregnant women. For instance, demographic measures indicate that this may be a sample enriched for affluent, well-educated subjects. It is unclear whether this potential bias might over- or under-estimate risk in the general population.

5.2 STUDY II

The strength of this study is that we used different methods to identify subjects with significant consumption during pregnancy, TLFB in the pilot study and AUDIT-C in the replication. It is possible that the AUDIT–C has been too simplified, and that this method was less sensitive than the face-to-face TLFB interviews used in the smaller pilot study, since a lower proportion of the replication cohort fell in the consumption positive category. Furthermore, the replication study was carried out much later in pregnancy. As expected, the proportion of those consuming significant amounts was found to be lower at that time, indicating that, in many cases, engaging in antenatal care or other processes that evolve after pregnancy is confirmed led to reduction or cessation of consumption. However, the core group who continued significant consumption up to this late stage shared characteristics with those reporting this in early pregnancy, i.e. little if any alcohol use disorders, but elevated impulsivity or novelty seeking. A limitation was that being cross-sectional, our study did not address a possible causal link between high novelty seeking and alcohol use.

Finally, in considering the external validity of these findings, we note that the principal results were replicated in two different cohorts, independently recruited during two different periods. It would therefore appear that, at a minimum, our findings can be generalized to women in a metropolitan region such as the greater Stockholm area. Whether generalization beyond this is justified is unclear, since women in other countries, or outside metropolitan areas, may have different alcohol use habits both prior to and during pregnancy.

Another limitation is that in the pilot study, we were unable to carry out full structured diagnostic interviews in only approximately 30% of our consumption positive subjects. This attrition may be systematic, such that subjects with more severe alcohol problems were more likely to decline participation. The true prevalence of alcohol dependence may therefore have been somewhat higher than observed. However, this is made less likely by the low number of subjects with AUDIT scores typically associated with alcohol dependence, an observation replicated in the larger, anonymous replication cohort.

5.3 STUDY III AND IV

The cross-sectional nature of this study, and its recruitment among treatment seeking individuals poses some important limitations. First, the study relied upon retrospective assessment of abuse status, alcohol behaviors, psychiatric problems and other variables. As such, subject reporting may be affected by forgetting or recall bias associated with current status. Second, as the alcohol dependent subjects were treatment-seeking, they likely display higher levels of impairment and psychiatric co-morbidity than alcohol dependent women in the community. It is unclear how treatment-seeking status may affect mediator and moderator analyses, and these analyses would benefit from being retested in population representative samples. Related to this, the higher density of family history of alcoholism that was found in our type II subjects must be interpreted with caution. This finding could reflect either a higher heritability in this group, or shared environmental factors. Due to the design of this study, it was not possible to distinguish between these possibilities.

A lesser limitation of this study was that the alcohol dependent subjects and controls were not fully matched. Specifically, the alcohol dependent subjects were less often married and less well educated. These differences in social function could reflect

underlying susceptibility factors that overlap with those for alcoholism, but could also be a consequence of this disorder itself. However, it is in our view unlikely that the robust differences found within the alcohol dependent group itself, between the two alcoholism subtypes, are secondary to alcohol dependence. In fact, these differences remained once severity of alcohol problems was controlled for.

5.4 STUDY V

In general, a strength of this twin study was that it made it possible to determine the relative influence of genetic and environmental factors for alcohol dependence among females. The breakdown of alcohol dependent subjects into subgroups made it possible to examine the role of heredity as well as specific environmental factors for categories of alcohol dependent women with different alcoholism severity. The co-twin control analysis allows the role of specific environmental factors such as physical and sexual abuse to be disentangled from non-specific effects of familial background.

One of the limitations in this study of female twins was the high number of non-responders. Only 66% of possible subject took part in the study. Not all of the subjects answered the questions about alcohol habits, yielding a response rate for this part of 63%. This can introduce a selection bias that might complicate the interpretation of the study findings. Characteristics that differed between non responders and participating subjects without alcohol consumption were younger age and lower level of education.

Finally, despite the Swedish Twin Registry being the largest in the world, the study was still underpowered in some cases. This was particularly the case for the group with early onset/type II alcoholism.

6 GENERAL DISCUSSION AND CONCLUSION

Around 16% of the pregnant women in a suburban area in Sweden drank amounts of alcohol during the first trimester that could lead to adverse effects on the fetus. The majority of these women reported that they became abstinent after their first visit to ANC, but 4% continued to drink significant amounts through pregnancy. Almost half of the women in the ANC sample in study I with consumption at levels harmful to the fetus were not "hazardous alcohol users", but we also found a group of women (9%), a high risk population, with both hazardous use before pregnancy and continued consumption at levels documented to be harmful for the fetus during pregnancy. Some characteristics of this group, like higher AUDIT scores, more psychiatric contacts and use of illicit drugs are signs of more severe problems, and perhaps risk for developing alcohol dependence later in life.

However, as shown in study II, the prevalence of present alcohol use disorders was low among the pregnant women. It is possible that the numbers of subject with alcohol use disorder was slightly underestimated, due to reporting bias. In the population based twin study (study V), lifetime prevalence of alcohol use disorder was higher (6.8%), but lifetime and present prevalence are difficult to compare. Furthermore, the suburban, well-educated ANC sample is not fully comparable with the population based twin sample. Most importantly, the purpose of the new screening method at ANC was not to diagnose alcohol use disorders, but to examine if an intensified screening strategy would better identify hazardous alcohol use during pregnancy. This objective was clearly achieved.

Instead of alcohol dependence we found increased novelty seeking in the pregnant risk users. High novelty seeking may predate the development of alcohol use disorders, but the relationship between novelty seeking and alcoholism is not consistently found. The presence of *one* risk factor does not necessarily lead to disease, since the risk of an outcome usually depends on an interaction between multiple determinants [148]. It has recently been proposed that impulsivity does not directly mediate the association with alcohol use disorder, but rather moderates it, or interacts with parental alcohol dependence [149].

Different combinations of determinants can probably lead to different clinical pictures and the classification of alcohol dependence in different subgroups illustrates this. We classified the treatment seeking women in the clinical sample as well as the female twins from the Swedish twin register in two subgroups: late onset/type I, and early onset/ type II, according to the subtypes proposed by Cloninger and Bohman [33;35;75]. Defining more homogenous alcoholism subtypes does not only help identify underlying etiological factors but also facilitates development of treatments tailored to the needs of the individual.

We found that approximately 40% of the treatment-seeking alcohol dependent women (study III) and 26 % of the women with alcohol dependence in the population based twin sample (study V) fall into a category closely resembling that described as early onset/type II alcoholism. A core characteristic described in type II is a higher degree of heritability compared to late onset/type I [33;35;150] and density of family history was also markedly higher in type II women in the clinical treatment-seeking sample. However, high density of alcohol dependence in the family does not necessarily reflect genetic influence alone. In fact, in the twin study, no difference in heritability was found between early and late onset alcoholism. The difference in both total numbers of subjects classified as type II and the distinctly higher family density of alcoholism is probably due to selection bias in the clinical study. Assessing the importance of genetic and environmental risk factors using self-selected samples of treatment seeking individuals is fraught with important limitations. Specifically, early onset/type II alcoholism is typically accompanied by a greater severity of clinical symptoms [39], and this alone is sufficient to result in the systematic selection. In the twin sample, where it is possible to control for the influence of shared environment (e.g. growing up in a family with alcohol dependent parents), heritability estimates were very similar between type I and type II alcohol dependent women. Instead, we found an indication for a role of shared environment in type II, but not in type I subjects.

Another typical feature described in men classified as type II is antisocial traits [75;151]. Our findings were indirectly compatible with this also being the case in female alcoholics. Impulsivity or novelty seeking was present to a higher degree in both type I and type II females compared to controls in the clinical treatment-seeking sample in study III, while elevated measures of aggression distinguished type II subjects from both healthy controls and type I alcoholics.

From an evolutionary perspective, it has been discussed whether impulsive or noncompliant traits may carry any fitness advantages. Specifically, it has been proposed that risk-taking behavior under some circumstances can lead to benefits for the group, while the costs are mainly borne by the individual [152;153]. We found several negative individual consequences in the current studies. Most importantly, besides the association with alcohol dependence, impulsive traits were also associated with alcohol consumption during pregnancy.

Furthermore, impulsivity was higher among subjects who had been sexually abused. Our data clearly do not allow us to determine whether this association reflects a causal link. Nevertheless, alcohol dependence is likely to be a mediator of this association, since it is well-established that sexual abuse places women at risk for later alcohol problems [93;123]. Some studies have noted a concentration of alcoholism risk in those exposed to sexual abuse in childhood or earlier in childhood [94-96;125], while others failed to support this role of when abuse occurred [108;111]. In our treatment-seeking clinical sample, women exposed to severe sexual abuse with penetration, either as a child or as an adult, had 10-fold higher odds of alcohol dependence compared to those with no such history. Sexual abuse was associated with later alcohol problems directly, but also through its effect on psychiatric problems, with anxiety and eating disorders as mediators.

Sexual abuse and its association with alcohol dependence were also studied in the twin sample. Similar to the clinical treatment seeking sample, sexual abuse remained an independent individual risk factor also after controlling for confounding familial factors. This differed from other forms of childhood adversity, such as physical trauma and emotional neglect, whose association with alcohol dependence was largely accounted for by familial factors, both genetic and environmental.

In the twin study, the association between sexual and physical trauma on one hand, and alcoholism on the other was stronger in early onset/type II- than in late onset/type I - alcoholism. This was in contrast with findings in the clinical treatment seeking sample in study III, where the strength of the association with sexual abuse did not differ between the two subtypes of alcoholism. Severity of alcoholism was generally higher, irrespectively of subtype, in the treatment seeking sample, indicating that a higher strength of association between sexual abuse and alcoholism may be a function of alcoholism severity rather than subtype *per se.* Of note, dependence on other substances

and elevated alcohol severity according to AUDIT, were more common in the alcohol dependent females in the clinical sample exposed to severe sexual abuse. These characteristics were more common among subjects with type II alcoholism, but also reflect higher alcoholism severity.

In conclusion, early onset/type II appears to be a valid construct also in women with alcohol dependence. It can be described as a more severe form of alcoholism than late onset/type I. The different trajectories and clinical presentation of the two alcoholism subtypes are likely to result from differential interactions between genetic susceptibility factors and environmental exposure. In the latter category, physical and emotional early life adversity appears to be of general importance as a risk factor, possibly as a marker of familial background factors, while sexual abuse seems to be an important, specific individual risk factor in particular for early onset/type II alcoholism. These observations point to the heterogeneity of alcoholism among women, implies that women with different forms of alcoholism are likely to have unique treatment needs, and highlights that treatment approaches to alcoholism need to be individualized.

7 SUMMARY IN SWEDISH

7.1 BAKGRUND

Med riskfylld alkoholkonsumtion menar man vanligen ett konsumtionsmönster där en individ relativt frekvent dricker stora mängder alkohol, vilket på sikt kan leda till både fysiska och psykiska skador. Enligt de amerikanska rekommendationerna definieras riskdrickande vanligen som14 standardglas per vecka eller 4 glas vid ett tillfälle för män, medan kvinnornas nivåer satts till 7 glas per vecka eller 3 glas vid samma tillfälle (ett standardglas är 14 g) . Under graviditet blir denna definition dock missvisande, eftersom studier visat att skador uppstår vid betydligt lägre nivåer. En genomsnittlig veckokonsumtion på ca 5-6 glas (60-70g) har visats leda till ökad missfallsfrekvens, ökad förekomst av dödfödda barn, samt minskad tillväxt på fostret.

Alkoholmissbruk är en diagnos som sätts då en person har ett alkoholmönster som leder till sociala och eventuellt legala problem, medan alkoholberoende innebär tillkomst av fysiska tecken på beroende, tolerans och sug efter alkohol.

Den vuxna befolkningen i Sverige (över 15 år) dricker i genomsnitt knappt 10 liter 100 % alkohol per person och år. Männen dricker ungefär dubbelt så mycket som kvinnorna. Trenden har dock varit att kvinnornas konsumtionsandel ökar. Särskilt tydligt är detta när man tittar på yngre åldersgrupper, där skillnaden mellan könen minskar.

En anonym studie på gravida kvinnor i sen graviditet visade att ca 30 % fortsatte att dricka under hela graviditeten, därav 6 % på sådana nivåer att det skulle kunna påverka graviditetsutfallet. Få av dessa kvinnor hade en diagnos av alkoholmissbruk eller beroende, men visade på personlighetsdrag som kan öka risken för att i framtiden utveckla dessa tillstånd.

Ur klinisk synvinkel finns det ett behov att dela in alkoholberoende i undergrupper, eftersom den kliniska bilden, förlopp och prognos kan variera mycket. En sådan indelning, som ursprungligen bygger på adoptionsstudier, är typ I och typ II alkoholism, där typ II framförallt beskrevs hos män. Typ I debuterar sent, efter 25 år och har få sociala komplikationer, medan typ II debuterar tidigt, före 25 års ålder, och karakteriseras av antisociala drag och högre grad av ärftlighet.

Liksom vid andra komplexa sjukdomar beror den individuella sårbarheten för att utveckla alkoholberoende på en interaktion mellan arv och miljö. Studier på manliga tvillingar har visat att ärftligheten står för cirka 40-60%. Andra riskfaktorer är tidig

alkoholdebut, samsjuklighet med andra psykiska sjukdomar, vissa personlighetsdrag, trauma i barndomen och sexuella övergrepp.
Det är framförallt ångest och depression som förekommer samtidigt vid alkoholberoende och denna samsjuklighet är vanligare hos kvinnor. De personlighetsdrag som associerats till ökad risk för alkoholberoende är ”neuroticism” (en ökad ängslighet och låg frustration för negativa känslor), impulsivitet och även antisociala drag. Trauma i barndomen, inte minst sexuella övergrepp har i flera studier visat ett tydligt samband med alkoholberoende, även sexuella övergrepp efter 18 år har i vissa studier visat på samma samband. Sambandet har framförallt visats på kvinnor.

7.2 ÖVERGRIPANDE SYFTE

Det övergripande syftet har varit att kartlägga förekomsten av riskfaktorer som kan leda till alkoholkonsumtion under graviditet, samt alkoholberoende hos kvinnor. Vi har också studerat eventuella skillnader mellan två undergrupper av alkoholberoende, typ I/sen debut och typ II/tidig debut.

De specifika syftena i respektive artikel var.

- **I.** att studera förekomsten av riskfylld alkoholkonsumtion under graviditet, samt undersöka om utökad screening vid MVC hittar fler kvinnor med riskfylld konsumtion än sedvanlig diagnostik.
- **II.** att undersöka om kvinnor med riskfylld alkoholkonsumtion under graviditet har alkoholberoende eller högre förekomst av andra psykiatriska besvär, samt om de har specifika personlighetsdrag, jämfört med gravida som ej dricker skadliga mängder.
- **III.** att se om typ II, väl beskriven hos män och karakteriserad av tidig debut av alkoholberoende, antisociala drag och högre ärftlighet också är en väl definierad undergrupp hos alkoholberoende kvinnor.
- **IV.** att studera associationen mellan sexuella övergrepp och alkoholberoende hos kvinnor i behandling för beroende och undersöka möjliga länkar (psykiatriska sjukdomar, gener), samt se vilka karakteristika som förekommer hos de kvinnor som utsatts jämfört med dem som ej har utsatts för sexuella övergrepp.
- **V.** att hos en populationsbaserad grupp kvinnliga tvillingar undersöka betydelsen av ärftlighet och miljö (delad och individuell) för alkoholberoende, samt kopplingen mellan trauma i barndomen och alkoholberoende uppdelat i typ I/sent debuterande och typ II/tidig debuterande alkoholism.

7.3 METODER

Studie I var en randomiserad studie på två mödravårdscentraler i Stockholm. Kvinnornas alkoholkonsumtion året före graviditet screenades med ”The Alcohol Use Disorder Identification test” (AUDIT), ett frågeformulär med 10 frågor kring konsumtion, beroendekarakteristika och eventuella skador. För att fånga vilka mängder fostret exponerats för kartlades det dagliga intaget av alkohol under graviditeten (vanligen första trimestern) med ”Timeline Follow back” (TLFB). Alkoholmarkörer i blod (ASAT, ALAT, MCV och CDT) kontrollerades också.

Studie II var uppdelad i två steg. Steg 1 var en randomiserad, kontrollerad studie på en MVC i Stockholm. Kvinnorna screenades med AUDIT och TLFB och de med riskfylld alkoholkonsumtion intervjuades om sin beroendediagnos, med ”Structured Clinical Interview for DSM-IV-Axis I” (SCID I). Kvinnorna fyllde i två självskattningsformulär, ett om personlighet (Swedish Universities Scales of Personality, SSP) och ett om aktuella psykiska besvär (The Hopkins Symptom Checklist, revised version, SCL-90R). Steg 2 genomfördes anonymt i sen graviditet i samband med att gravida i Stockholm deltog i en förlossningsförberedande utbildning. De screenades med en kortversion av AUDIT, AUDIT-C, för sin aktuella alkoholkonsumtion, samt fyllde i SSP.

Studie III och IV, var fall/kontroll studier, där intervjugruppen rekryterades från två öppenvårdsmottagningar för kvinnor med alkoholberoende och kontrollerna från mödravården dit friska kvinnor kom för hälsokontroll. Med en strukturerad intervju (SCID I) diagnosticerades psykiska besvär och beroende, typ I- respektive typ II-alkoholism klassificerades. Deltagarna intervjuades om förekomst av beroende i familjen (Addiction Severity Index, ASI, frågor om familjehistoria) och senaste tidens alkoholkonsumtion kartlades (TLFB). De fyllde i självskattningsformulär vad gällde personlighet (SSP) och utsatthet för sexuellt trauma (Questions from “Sex in Sweden”) samt grad av alkoholproblem (AUDIT).

Studie V baserades på ett material på kvinnor mellan 20 och 47 år, från det svenska tvillingregistret. Kvinnorna svarade på frågorna via webben eller via telefon. Beroendediagnostik och klassificering i typ I- och typ II-alkoholism skedde på samma sätt som i tidigare studier. För frågor om trauma i barndomen användes ett traumaformulär (Life Stressor Checklist, LSC-R.).

7.4 RESULTAT

I **studie I** fann vi att 16 % exponerade fostret för potentiellt farliga nivåer av alkohol under första trimestern. Signifikant fler kvinnor med riskfylld alkoholkonsumtion hittades med den utökade intervjubaserade screeningen, medan alkoholmarkörer i blod inte var till hjälp för detektionen.

I **studie II** framkom att de kvinnor som dricker riskfyllda mängder under graviditet inte är alkoholberoende eller har högre förekomst av psykiska besvär än kvinnor med ingen eller låg konsumtion under graviditeten. Däremot var de kvinnor som hade riskfylld konsumtion personlighetsmässigt mer riskbenägna.

Studie III visade att typ II är en kliniskt urskiljbar undergrupp av alkoholberoende kvinnor. De hade högre grad av alkoholproblem, missbrukade illegala droger i större utsträckning, samt hade högre förekomst av beroende i familjen jämfört med typ I. Vad gällde personlighetsdrag hade både typ I och typ II högre grad av neuroticism och impulsivitet/äventyrslystnad jämfört med kontroller, medan typ II hade signifikant högre förekomst av aggressivitet jämfört med kontroller och typ I.

Studie IV visade att sexuellt trauma var avsevärt vanligare hos kvinnor med alkoholberoende än hos friska kontroller. Detta gällde dock enbart svårare former av sexuellt trauma (analt eller vaginalt). Både trauma före och efter 18 år var associerat med alkoholberoende. Utöver ett direkt orsakssamband mellan sexuellt övergrepp och alkoholberoende, sågs också en effekt av ångestsjukdomar och ätstörningar. De alkoholberoende kvinnor som utsatts för sexuella övergrepp hade svårare alkoholproblem, högre grad av psykiatrisk samsjuklighet och mer impulsiva personlighetsmässiga drag.
Ett antal gener som associerats till alkoholberoende eller till stressrelaterad risk för alkoholberoende testades också, men ingen fyllde kriteriet som statistiskt säkerställd förmedlande länk (eng. ”moderator”).

I **studie V** sågs att ärftligheten har lika stor betydelse för kvinnor som tidigare beskrivits för män. Detta gällde både för typ I och typ II alkoholism. Delad miljö hade större betydelse för typ II alkoholism. Trauma i form av emotionell försummelse, psykisk och sexuell misshandel i barndomen var tydligt associerat med

alkoholberoende, och specifikt typ II alkoholism. En familjär effekt, både genetisk och miljöbetingad, sågs för emotionell försummelse och fysiskt trauma, medan sexuellt trauma också var en direkt individuell riskfaktor för alkoholberoende.

8 ACKNOWLEDGEMENTS

I wish to express my warm and sincere gratitude to everyone who has supported me during the work with my thesis. I particularly want to thank -

My supervisor **Markus Heilig,** who introduced me into the research area of Addiction and who believed in me the whole time while I was working on my thesis. He also supported me when I most needed it, with an almost scary timing. My two co-supervisors; **Mona Göransson,** best friend and fellow traveler both in research and reality, for giving the research work a feeling of joy as well as a meaning and a sense of "me being at home"; and **Nancy Pedersen**, for teaching me about twin methodology and giving me the opportunity to try and explore this area on my own.

Professor **Ulf Rydberg**, for stimulating my interest in alcohol and pregnancy.

The staff at the Antenatal (ANC) and the Addiction Clinics, without whose support my studies would have been difficult to accomplish. The midwives at Eken, for their courage to have a psychiatrist introduced at the ANC! To the management and all the staff at the Out-patient Clinic at "Maria Beroendecentrum" and "Livslinjen Terapi & Konsult", especially **Inger Roslin, Siv Karlsson, Ing-Marie Welin** and **Anneli Bäcke.**

All the brave women who participated in our studies.

My colleagues who shared my life as a Ph.D. student and helped me with large as well as small issues, **Christina Arlinde, Lillebill Nordèn, Kristina Wahlberg**, **Cecilia Dhejne** and **Pouran Almstedt.**

My colleagues and friends at 'Psykiatri Sydväst' and 'Beroendecentrum Stockholm', with special thanks to Director **Stefan Borg** and **Lena Harland**.

My co-authors, Biostatistician **Cecilia Lundholm** at the Department of Medical Epidemiology and Biostatistics, for always helping me when I got lost in my calculations and for sharing her knowledge with me. **William Copeland** for the very nice collaboration when working on our joint articles.

My friends at the board of the Swedish Society of Addiction Medicine, with special thanks to **Bengt Sternebring** and **Jörgen Engel**.

To **all my friends and family**, for your constant support; **Marie Gladh** for always calling when I most needed it; **Örjan Bartholdson** for questioning EVERYTHING; **Kristina Magnusson** for her great moral support; **Gunnar**, my beloved husband who continued to edit my tables after I'd fallen into deep sleep; **Agnes,** my daughter, for her wise and sometimes crazy ideas; **Zakarias,** my son, for his kindness and playfulness; and **Cilla** for her warmth and open mind.

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