ASSOCIATION OF DEPRESSION, ANXIETY, AND OBSESSIVE-COMPULSIVE DISORDER WITH SUBSTANCE MISUSE: EXAMINING THE UNDERLYING MECHANISMS WITH EPIDEMIOLOGICAL METHODS

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ABSTRACT

Internalizing disorders such as depression, anxiety disorders, and obsessive-compulsive disorder (OCD) frequently co-occur with substance use disorders (SUDs). Causes for the comorbidity remain unclear, and could be explained by several, not mutually exclusive general mechanisms. For instance, shared genetic and/or environmental factors may increase the risk of both internalizing disorders and SUDs, or the risk of SUDs might be causally increased by internalizing disorders via self-medication. The overarching aim of this dissertation was to describe the association of these internalizing disorders with substance misuse during the lifetime as well as during the important developmental period from childhood to early adulthood, and to clarify the mechanisms underlying the comorbidity using quasi-experimental research designs.

Sub-studies of this dissertation included two sources of data: Swedish nationwide registers and the Child and Adolescent Twin Study in Sweden (CATSS), a longitudinal twin cohort study. Population-based samples linked to nationwide registers were used in Studies I (n=2,996,398), II (n=1,768,516), III (n=6,304,188), and IV (n=146,114). CATSS data were utilized in Studies II (n=12,408) and III (n=9,230). To account for familial effects, we used stratified analyses within sibling and twin pairs (Studies I and II), and conducted a within-individual analysis (Study IV). We also estimated the contribution of shared genetic and environmental factors to the associations with quantitative genetic structural equation modeling (Studies I and III).

Both lifetime and childhood-onset anxiety and depressive disorders were associated with a substantially elevated risk of SUDs and substance use-related criminal offenses. OCD was also associated with an elevated risk of substance misuse, and self-reported OCD symptoms at age 18 were associated with increased alcohol and drug dependence symptoms among people who used alcohol or drugs. Shared familial liabilities contributed to the associations, but the associations were not entirely explained by familial factors. Further, we found an elevated risk of acute intoxications, accidental poisonings by alcohol or drugs, and substance use-related criminal offenses in patients with anxiety and depressive disorders during a 1-month period preceding SSRI medication treatment initiation, when compared to the reference period of more than 1 month before treatment start. On-treatment estimates were consistently lower than the 1 month pre-treatment estimate, but still elevated compared to the reference period.

In conclusion, depression, anxiety, and OCD are important correlates of substance misuse across development. Genetic factors play a major role in explaining comorbidity, but the associations were not entirely explained by familial confounding. This pattern of results suggests that the relationship between internalizing disorders and substance misuse partially reflects shared

etiology, but the findings were also consistent with (partially) direct effects between the disorders as proposed by the self-medication hypothesis. Thus, it appears that the comorbidity of internalizing disorders and substance misuse arises via several, not mutually exclusive mechanisms.

TIIVISTELMÄ

Päihdeongelmat ovat yleisiä henkilöillä, jotka kärsivät mielenterveyden häiriöistä. Aiemmissa tutkimuksissa on havaittu, että päihdehäiriöt esiintyvät usein yhdessä muun muassa masennus- ja ahdistuneisuushäiriöiden sekä pakko-oireisen häiriön kanssa, mutta komorbiditeetin, eli monihäiriöisyyden, syitä ei tunneta hyvin. On mahdollista, että komorbiditeetti heijastaa häiriöiden jakamaa geneettisistä ja/tai ympäristötekijöistä johtuvaa alttiutta. Toisaalta komorbiditeetti voi olla seurausta häiriöiden keskinäisistä syy-yhteyksistä, jotka välittyvät esimerkiksi päihteillä itselääkinnän kautta. Tässä väitöskirjassa tutkittiin masennus- ja ahdistuneisuushäiriöiden sekä pakko-oireisen häiriön yhteyttä päihdeongelmiin sekä elinaikana että kehityksellisesti tärkeänä ikäkautena lapsuudesta varhaisaikuisuuteen ja pyrittiin selvittämään komorbiditeetin taustalla piileviä mekanismeja hyödyntäen kvasikokeellisia tutkimusasetelmia.

Väitöskirjan osatöissä käytettiin kahta aineistolähdettä: ruotsalaisia kansallisia rekistereitä sekä pitkittäistä Child and Adolescent Twin Study in Sweden (CATSS) -kaksoskohorttiaineistoa. Rekisteriaineistoja käytettiin osatöissä I (n=2,996,398), II (n=1,768,516), III (n=6,304,188) ja IV (n=146,114). CATSS-aineistoa käytettiin osatöissä II (n=12,408) ja III (n=9,230). Käytimme sisarusten ja kaksosparien sisäisiä analyysejä (osatyöt I ja II) sekä yksilön sisäisiä analyysejä (osatyö IV) huomioidaksemme geneettisten tekijöiden ja ympäristötekijöiden vaikutuksia havaittuihin yhteyksiin. Lisäksi perimän ja ympäristötekijöiden roolia yhteyksien selittäjinä tutkittiin biometrisillä rakenneyhtälömalleilla (osatyöt I ja III).

Sekä elämänaikaiset että lapsuudessa diagnosoidut masennus- ja ahdistuneisuushäiriöt olivat yhteydessä selvästi kohonneeseen päihdehäiriöiden ja päihderikosten riskiin. Myös pakko-oireinen häiriö oli yhteydessä monenlaisiin päihdeongelmiin, ja 18-vuoden iässä itseraportoidut pakko-oireet olivat yhteydessä suurempaan alkoholi- ja huumeriippuvuusoireiden määrään niillä henkilöillä, jotka käyttivät päihteitä. Havaitut yhteydet selittyivät osin jaetuilla geneettisillä tekijöillä ja ympäristötekijöillä. Masennus- tai ahdistuneisuushäiriöitä sairastavilla henkilöillä akuuttien intoksikaatioiden, päihteiden yliannostusten ja päihderikosten riski oli selvästi kohonnut kuukautta ennen SSRI-lääkityksen aloittamista verrattuna aikaan yli kuukausi ennen lääkityksen aloittamista. SSRI-lääkityksen aloittamisen jälkeen riski pieneni, mutta pysyi edelleen koholla verrattuna aikaan yli kuukautta ennen lääkityksen aloittamista.

Väitöskirjatutkimuksen tulokset osoittavat, että masennus- ja ahdistuneisuushäiriöt sekä pakko-oireinen häiriö ovat yhteydessä päihdeongelmiin niin elinaikaisesti kuin pitkittäisseurannassa lapsuudesta tai nuoruudesta varhaisaikuisuuteen. Jaetuilla geneettisillä tekijöillä oli huomattava rooli yhteyksien selittäjinä, mutta ne eivät selittäneet havaittuja

yhteyksiä täysin. Tämä löydös viittaa siihen, että komorbiditeettia selittää häiriöiden osittain yhteinen etiologia, mutta mahdollisesti myös osittain suorat syy-yhteydet häiriöiden välillä. Komorbiditeetti saattaa näin ollen syntyä ainakin kahden rinnakkaisen mekanismin kautta.

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Espoo, Finland, November 2021
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1 LIST OF ORIGINAL PUBLICATIONS

I **Virtanen S**, Kuja-Halkola R, Mataix-Cols D, Jayaram-Lindström N, D'Onofrio BM, Larsson H, Rück C, Suvisaari J, Lichtenstein P, Latvala A. Comorbidity of substance misuse with anxiety-related and depressive disorders: A genetically informative population study of 3 million individuals in Sweden. *Psychological Medicine* 2020;50:1706-15.

II **Virtanen S**, Kuja-Halkola R, Lundström S, D'Onofrio BM, Larsson H, Suvisaari J, Mataix-Cols D, Lichtenstein P, Latvala A. Longitudinal associations of childhood internalizing psychopathology with substance misuse: A register-based twin and sibling study. *Journal of the Academy of Child and Adolescent Psychiatry* 2021; 60(5):593-03.

III **Virtanen S**, Kuja-Halkola R, Sidorchuk A, Fernández de la Cruz L, Rück C, Lundström S, Suvisaari J, Larsson H, Lichtenstein P, Mataix-Cols D, Latvala A. Association of obsessive-compulsive disorder with substance misuse: Two genetically informative studies. *Manuscript*.

IV **Virtanen S**, Lagerberg T, Khemiri L, Suvisaari J, Larsson H, Lichtenstein P, Chang Z, Latvala A. Association of selective serotonin reuptake inhibitor (SSRI) treatment with acute substance misuse outcomes. *Addiction* 2021, in Press.

The publications are referred to in the text by their roman numerals.

ABBREVIATIONS

ADHD	Attention-deficit/hyperactivity disorder
ATAC	Autism - Tics, AD/HD and other Comorbidities Inventory
ATC	Anatomical Therapeutic Chemical classification system
AUDIT	Alcohol Use Disorder Identification Test
BOCS	Brief Obsessive Compulsive Scale
CATSS	Child and Adolescent Twin Study in Sweden
CD	Conduct disorder
CI	Confidence interval
DSM	Diagnostic and Statistical Manual of Mental Disorders
DZ	Dizygotic
DUDIT	Drug Use Disorder Identification Test
ECA	Epidemiologic Catchment Area Study
GWAS	Genome-wide association study
HR	Hazard Ratio
ICD	International Classification of Diseases and Related Health Problems
MZ	Monozygotic
NCS	National Comorbidity Survey
NESARC	National Epidemiologic Survey on Alcohol and Related Conditions
NPR	National Patient Register
OCD	Obsessive-compulsive disorder
ODD	Oppositional defiant disorder
OR	Odds Ratio
RCT	Randomized controlled trial
SSRI	Selective serotonin reuptake inhibitor
SUD	Substance use disorder

2 INTRODUCTION

Humans have a long history of psychoactive substance use. Archeological evidence suggests that many prehistoric societies all over the world were using drug plants and fermented beverages for medicinal and spiritual purposes [1]. Psychoactive substances influence the functioning of the central nervous system, which results in temporary alterations in perception, mood, consciousness, cognition, and behavior. Common recreational psychoactive substances include alcohol, cannabis, opioids (e.g., heroin, synthetic opioids, prescription pain relievers), sedatives (e.g., benzodiazepines, barbiturates), stimulants (e.g., cocaine, amphetamines), and hallucinogens (e.g., d-lysergic acid diethylamide, psilocybin). Different types of substances involve different physiological and psychological effects (e.g. disinhibition, euphoria, sedation, increased arousal, hallucinations) and can be administered via different methods (e.g., injecting, snorting, smoking, and swallowing).

Substance use is common. In 2017, an estimated 47% of the world population were current alcohol users, and the prevalence has been forecasted to increase to 50% by 2030 [2]. Alcohol is a legal substance in the majority of countries. In contrast, from the late 19th and early 20th century onwards, policies concerning other psychoactive substances have focused on criminalization, i.e., the prohibition of production, traffic, and use of drugs [3]. Despite decades of transnational efforts to suppress the drugs trade and, ultimately, to eliminate the use of drugs, the United Nations Office on Drugs and Crime (UNODC) has estimated that 269 million people used drugs globally in 2018, a 30 per cent increase compared to the estimated number in 2009 [4].

Definition of substance use disorders and substance misuse

A subset of people who use psychoactive substances develop a substance use disorder. Substance use disorders (SUDs) are psychiatric disorders characterized by persistent use of alcohol or drugs despite significant physical, social, or psychological harm or adverse consequences. SUDs are among the most common psychiatric disorders, affecting more than 100 million people world-wide [5, 6]. Further, SUDs contribute substantially to the global disease burden, and are associated with an increased risk of premature mortality [6].

Both the Diagnostic and Statistical Manual of Mental Disorders (DSM) [7] and the International Classification of Diseases (ICD) [8] include diagnoses for SUDs, with minor differences in their diagnostic criteria. Table 1 shows the diagnostic criteria for ICD-10 substance dependence, sometimes referred to as 'addiction'. Three or more symptoms should be present together for at least one month, or else repeatedly during a one-year period.

ICD-10 has several diagnoses for different types of substance use-related conditions. It includes a diagnosis of harmful use, which constitutes 'a pattern

of psychoactive substance use that is causing damage to physical or mental health' [8] - originally intended to characterize a SUD that is less severe than substance dependence, although contested in empirical studies [9, 10]. ICD also differentiates 'acute' substance-related diagnoses from 'chronic' conditions by providing a separate diagnosis for acute intoxication, described as 'a transient condition following the administration of alcohol or other psychoactive substances' [8]. However, the term SUDs usually refers to substance dependence and harmful use (or their DSM equivalents, dependence and abuse).

Table 1. *ICD-10 diagnostic criteria for substance dependence syndrome*

• A strong desire to take the psychoactive substance
• Difficulties in controlling substance-taking behavior (onset, termination, level of use)
• Physiological withdrawal if substance use is ceased or reduced; use of the substance to avoid withdrawal state
• Tolerance: increased doses are required to achieve desired effect
• Progressive neglect of alternative pleasures or interests
• Persistent use despite clearly harmful consequences

In sub-studies of this dissertation, we examined substance use problems defined in a broad sense, termed herein as 'substance misuse', which includes any substance-related behaviors that result in adverse consequences, including chronic conditions such as substance dependence as well as more acute events such as intoxications, overdoses, and substance-related criminal offenses. While nicotine is an addictive substance, this dissertation focused on alcohol and drugs, and nicotine-related problems were not included in the definition of substance misuse.

Neurobiology and learning theories of substance use disorders

SUDs are thought to develop via a multi-stage process, involving initiation, early seeking and reinforcement, formation of substance-seeking habits, and established compulsive substance use [11]. Substance use and SUDs are often conceptualized through learning theories. So-called habit/compulsion models of addiction posit that the initiation of substance use starts as goal-directed behavior. Most, if not all, addictive substances initially increase the levels of dopamine in the nucleus accumbens projected from the ventral tegmental area [12]. The release of dopamine is crucial for the initial reinforcement of substance-taking behavior [13]. Once substance-seeking is established, it is first under control of the associative striatum (caudate nucleus) via areas in

the frontal cortex [14]. At this stage, substance-related cues start forming through Pavlovian conditioning [11]. Studies suggest that when substance use becomes habitual and compulsive, there is loss of top-down control from the frontal cortex and a shift in dopaminergic activity from the associative to sensorimotor striatum (posterior putamen) [15]. Substance use is no longer goal-directed, but governed by stimulus-response habits associated with the established substance cues [11]. A competing model states that addiction is primarily driven by *excessive* goal-directed choice under negative affect, i.e., problematic substance use is not due to a switch from goal-directed to stimulus-response behavior, but because of the overvaluation of expected drug-related reward, particularly in stressful situations and/or to regulate negative affect [16]. While the development of SUDs through different stages can be described as 'progressive', not everyone who uses substances progresses through all these steps. There are large individual differences in how people respond to taking drugs and alcohol, and causes for these differences are likely to be both genetic and environmental.

Developmental origins of substance use disorders

SUDs have been suggested to have developmental origins due to the striking increase in prevalence rates from ages 13 to 18 [17]. Developmental origins of a disorder refer to psychopathology which is the result of 'normative development gone awry' due to genetic predispositions, adverse experiences during development, and their interactions over time [18]. Some studies indicate that the developing brain might be particularly vulnerable to addiction [19, 20], and that individuals who show substance use problems in adolescence are more likely to have more severe and persistent SUDs than those who develop them later in life [21, 22]. One well-supported developmental pathway to SUDs relates to an 'externalizing' risk-phenotype, which typically first emerges as a difficult temperament in infancy, followed by childhood and adolescent aggression, conduct problems, and an early onset of substance use problems [23]. However, the peak period for the onset of SUDs is in early adulthood [24, 25], and certainly not all individuals with SUDs show signs of externalizing behaviors or problematic substance use at an early age. While progress has been made in elucidating the developmental pathways to SUDs [23], much remains unclear. For instance, there is evidence of equifinality, i.e., that a common outcome such as SUD can develop over time from different starting points [23, 26], which requires further investigation.

The role of genetic and environmental influences on substance use

The role of familial influences on substance use problems has been well established for decades [27-29]. Twin and family studies have shown that the heritability, i.e., the proportion of variance explained by genetic differences between individuals within a population, of SUDs is between 40-70% [30-34]. Heritability of some drug-related disorders such as opioid use disorder falls in the higher end of the spectrum, whereas the estimate for alcohol use disorder

is approximately 40-50% [30, 33, 34]. Moreover, alcohol and drug use disorders co-occur frequently [35], which is explained in part by their substantial genetic overlap [36, 37]. Recent molecular genetic studies (GWAS; genome-wide association studies) have extended the findings of twin and family studies by investigating which specific genetic variants are correlated with SUDs and related phenotypes. Substance use-related traits are associated with at least dozens of genetic variants, most of them with a small independent effect on the phenotype [38-42]. The most robust finding is the association of alcohol dehydrogenase genes (ADH1B, ADH1C) and the aldehyde dehydrogenase 2 (ALDH2) with alcohol use disorder [39, 41, 42]. These genes have a major role in alcohol metabolism, specifically in the process of oxidizing ethanol to acetaldehyde, and catalyzing the chemical transformation from acetaldehyde to acetic acid, respectively. Certain alleles of these genes produce a protective effect against alcohol use problems by slowing down alcohol metabolism [43]. Slow alcohol metabolism results in elevated levels of oxidization products in the bloodstream, which can be extremely unpleasant, involving symptoms such as flushing, nausea, headache, and general physical discomfort. Other replicated GWAS findings include genes such as OPRM1, DRD2, DRD4, BDNF and SLC6A4 which are associated with several types of SUDs [42]. These genes are expressed in the brain, and are related to neurotransmission in the opioid, dopamine, and serotonin systems.

Heritability is a population estimate, which means that it is specific to the studied population and the timing of measurement. The dynamic nature of heritability has been demonstrated in twin studies where the role of genetic factors in explaining substance use increases throughout childhood and adolescence [44], but also depends on the environmental context [44, 45]. For instance, distal influences such as the neighborhood or availability of substances appear to moderate the degree to which genetic influences explain the risk of SUDs. In environments with limited availability of substances [46], or high levels of social control exercised by the local community (e.g., rural or religious communities) [47, 48], heritability of substance use tends to decrease. These findings highlight the need to consider both the developmental stage and environmental context when studying genetic factors in the risk of SUDs and related outcomes.

Environmental factors are undoubtedly important for the etiology of SUDs. Not only do they moderate the effect of genetic influences, but they also explain a large proportion of variance in all types of substance-related traits [34]. Besides distal environmental influences such as culture and the availability of substances, various proximal environmental correlates have been identified. These include prenatal substance exposure, early adversity such as loss of a parent or child abuse, harsh parenting, peer influences, socioeconomic status, and parental substance misuse, amongst others [49-52]. Furthermore, among the strongest correlates of SUDs are other psychiatric disorders, since the presence of virtually any type of psychiatric disorder, from schizophrenia to attention-deficit/hyperactivity disorder

(ADHD) to anxiety disorders, is associated with an increased risk of SUDs [53-57]. The topic of comorbidity is discussed in detail in section 2.1.

Sex-differences in substance use and substance use disorders

A consistent finding in the literature is the approximately two times higher prevalence of SUDs in men compared to women [17, 58, 59]. In part, this may be explained by the higher number of men using substances in general [60]. There are large historical and geographical variations in women's access to alcohol and drugs due to cultural and sociopolitical factors. At the same time, substance use is part of a 'masculine' gender role in some cultures [61], which may increase substance use among men. From the mid-20th century onwards, particularly in Western countries, sex-differences in substance use have been in decline [60-63]. This development coincided with changes in social norms which previously posed major restrictions for women's substance use. Increased access has also affected the prevalence-gap in SUDs, as less pronounced sex-differences have been found in later-born cohorts compared to earlier generations [62, 64, 65]. Substance use is clearly affected by macro-level societal influences. However, it is likely that sex-differences in SUDs are not entirely environmental in origin, but partly due to biological differences between males and females. There is a large body of literature investigating the underlying reason for the overrepresentation of 'externalizing' (e.g., ADHD, conduct disorders, SUDs) disorders in men and 'internalizing' (e.g., anxiety, depression, eating disorders) disorders in women [66]. The role of biological factors such as genetics, neuroplasticity, and hormonal factors have been supported in a number of studies [67-69]. Despite the advances in knowledge concerning sex-differences in psychopathology, SUDs included, there is an ongoing need to identify potential sex-specific causal factors to develop better prevention and treatment strategies [70].

2.1 COMORBIDITY

Comorbidity and psychiatric nosology

Comorbidity, or co-occurrence, of psychiatric disorders, either concurrently or during the lifetime, is more of a rule rather than the exception. Approximately 60% of individuals who meet diagnostic criteria for one disorder meet diagnostic criteria for another disorder, and 51% of those with two disorders meet criteria for a third, and so on [71]. The pervasive comorbidity has been problematic for psychiatric nosology, which traditionally considered psychiatric disorders as 'naturally separate' entities — an influential conceptualization introduced by Emil Kraeplin [72]. Seminal work by Thomas Achenbach was among the first to discover that psychopathology in children tended to cluster around two higher-order dimensions, so-called internalizing and externalizing [73]. The two-factor structure has since been replicated in adults and confirmed in numerous studies using different study populations

[74]. The composition of the dimensions varies based on which disorders are included in a given study, but disorders such as anxiety and depressive disorders, eating disorders, post-traumatic stress disorder (PTSD), and obsessive-compulsive disorder (OCD) are typically considered internalizing disorders, whereas the externalizing dimension involves disorders such as ADHD, conduct disorders, antisocial personality disorder, and SUDs [75, 76]. However, the substantial positive correlation between internalizing and externalizing dimensions eventually raised the question whether a two-factor structure was the correct model after all.

A more recent development in the comorbidity literature is the p-factor model, where all psychiatric disorders load on a common latent factor *p* (termed similarly to the g-factor of cognitive abilities). The p-factor is hypothesized to measure a person's overall liability to mental disorder, comorbidity between disorders (within and between the psychopathology dimensions), persistence of disorders over time, and symptom severity [71, 77, 78]. Recent family-based and molecular genetic studies have shown that all common psychiatric disorders share a set of pleiotropic genetic influences [79-81], supporting the existence of the p-factor. In addition to the general factor of psychopathology, the p-factor model also includes specific lower-order factors for internalizing (sometimes divided into 'distress' and 'fears'), externalizing, and thought disorders. However, the structure of the lower order dimensions and the interpretation of the general factor are still under debate [82-85], while some researchers remain skeptical of the p-factor model altogether for conceptual and statistical reasons [86].

The p-factor conceptualization emphasizes that the explanation for psychiatric comorbidity is that psychiatric disorders share underlying causal influences through the general factor as well as the lower-order dimensions. Causal influences are thought to be mainly familial in the case of the general psychopathology factor, and both familial and environmental (i.e., environmental influences not shared by family members) for the lower-order dimensions [78]. In this conceptualization, there are no direct causal links from one disorder to another (e.g., from depression to SUD). The p-factor conceptualization is contrasted by other proposed models such as the network analysis perceptive, which assumes dynamic, causal influences among symptoms of mental disorders and between disorders [87]. Those critical of the p-factor model have raised the issue that for any factor model with a general factor, there will be a statistically equivalent network model (and vice versa), and that it is challenging to establish the superiority of either one empirically [88]. There is support for both theoretical models, and they are not necessarily mutually exclusive. For the advancement of the study of psychiatric comorbidity, considering both points of view would be beneficial, as it facilitates testing of competing hypotheses.

Substance misuse and comorbidity: conceptual and methodological considerations

SUDs correlate strongly with each other and with other disorders within the externalizing spectrum [78]. The association of ADHD and conduct disorders with SUDs has gained considerable attention [23, 89, 90]. This work has progressed to examination of the underlying mechanisms, demonstrating that the comorbidity is partially explained by shared genetic influences, but also potentially by ADHD and conduct disorders being causal risk factors for substance use problems [91-99]. Taken together, these findings suggest that externalizing comorbidity might be the result of a 'hybrid' of different theoretical models, with both underlying shared etiology and direct causal pathways receiving support.

Importantly, SUDs are also frequently comorbid with internalizing disorders [53, 78, 100], but the causes remain largely unclear. Therefore, this dissertation examines disorders on the internalizing spectrum as potential causal risk factors for substance misuse, focusing on depression, anxiety disorders, and OCD.

As discussed previously, comorbidity can arise due to several, not mutually exclusive mechanisms, illustrated in Figure 1. First, the association of internalizing disorders with SUDs may be due to shared genetic and/or environmental etiological influences (panel A; consistent with the p-factor model conceptualization).

Second, internalizing disorders may causally increase the risk of SUDs via 'self-medication', according to which alcohol or drugs are used as stress-relief and to 'manage' symptoms of internalizing disorders, which can lead to SUDs over time (panel B). The original self-medication hypothesis proposed by Khantzian in 1985 [101] stated that substances are used selectively so that the pharmacological properties of the substance alleviate symptoms typical to the disorder an individual suffers from (e.g., use of stimulants to alleviate the lack of energy and drive in depression). The hypothesis has been controversial and with limited empirical support [102, 103], although it remains rather popular in the psychodynamic literature. More recently, most research on self-medication has focused on substance use as a coping-mechanism, without assuming that the individual's psychiatric symptoms determine the choice of drug. There are some findings in favor of the reformulated self-medication hypothesis in anxiety, depression, and PTSD [104-107]. Furthermore, epidemiological studies have shown anxiety and depressive disorders to have an onset preceding SUDs in a clear majority of individuals [108].

Finally, it is also possible that SUDs causally increase the risk of internalizing disorders, e.g., as a consequence of neurobiological effects of repeated intoxication and withdrawal (panel C). Laboratory studies have demonstrated that drugs and alcohol can induce anxiety and low mood (which are also typical withdrawal symptoms), and observational studies suggest that for some individuals SUDs precede the onset of anxiety and depressive

disorders [109-111]. However, in this dissertation, the focus is on evaluating the first two scenarios.

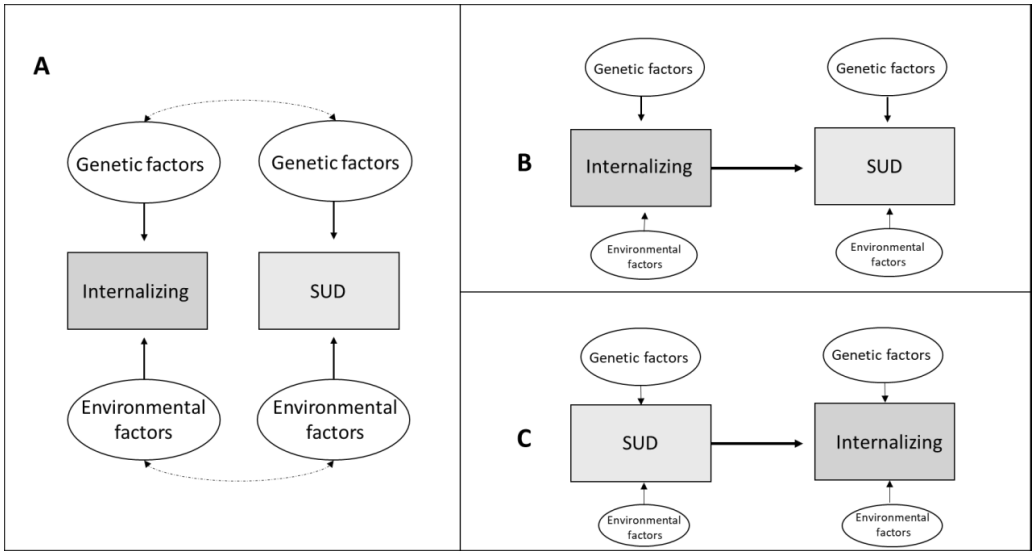


Figure 1 Potential explanations for the comorbidity of internalizing disorders with SUDs

Much of the literature on the link between internalizing disorders and SUDs rely on correlational study designs. Establishing an association is an important first step, but a purely correlational study design does not allow for investigating the underlying mechanisms. Rigorous testing of competing causal hypotheses is important not only from a theoretical perspective, but because of different mechanisms having different implications for prevention and treatment efforts. Treatment and prevention would be most successful if targeted to the factors causing the outcome, but investigating causality is methodologically challenging. The gold-standard of causal research is the experimental design, where participants are randomly assigned to experimental and control conditions. In human research investigating psychopathology, experiments are often not feasible and/or ethical. For instance, it is virtually impossible to randomly assign individuals to depressed and non-depressed groups and then observe which group is more likely to develop SUDs. However, causality can theoretically be inferred from observational data using a standard between-subjects design and regression modeling [112], if the following requirements are met:

1) The study sample is probability sample, i.e., appropriate for formal statistical inference

2) There is an association between the exposure and outcome

3) The exposure precedes the outcome in time

4) Any given causal variable can be manipulated independently of any other causal variable and independently of the error terms

5) The statistical model is correctly specified

6) The association between the exposure and outcome is not explained by confounding or omitted variable bias

Clearly, the assumptions for causal inference using observational data are highly stringent, and unlikely to be fulfilled in most studies. A particularly difficult problem in observational research is unobserved confounding [113]. This is not to say that causal inference with observational data is impossible and should not be attempted, but that a more realistic approach would be to use *triangulation* of evidence. Triangulation in this context means that a hypothesis is tested with different methods that are able to rule out alternative explanations (e.g., rule out confounding). Since these methods often have different sets of assumptions, strengths, and limitations, similar findings from a number of studies increase the confidence that the observed association may be causal [114]. Methods that are able to rule out unobserved confounding factors are often called 'quasi-experimental' designs. They are observational studies which do not randomly assign individuals to conditions, but use design features to rule out plausible alternative explanations for an observed association [115]. Quasi-experimental studies include, for instance, the use of instrumental variables, within-individual designs, regression discontinuity designs, or co-relative designs. The following sections review findings from ordinary and quasi-experimental observational studies investigating the association of internalizing disorders with SUDs.

2.1.1 DEPRESSION AND SUBSTANCE MISUSE

Epidemiological studies in adult samples

Landmark epidemiological survey studies conducted in the adult population of the US had a major role in establishing the pervasive comorbidity between internalizing disorders and SUDs. These studies include the Epidemiologic Catchment Area Study (ECA) in the 1980's, the National Comorbidity Survey (NCS) in the 1990's, and the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) in the 2000's. The association of depressive disorders with SUDs has been demonstrated in all of the aforementioned surveys. Depression (major depressive disorder) is a common mental health disorder characterized by persistent feelings of sadness and lack of interest or

pleasure, which interferes with daily functioning. Depressive disorder is an umbrella term which refers to different forms of depression that develop under specific circumstances. For instance, dysthymia is a mild but persistent depressive disorder with an insidious onset (i.e., depression is not severe enough to fulfill criteria for major depressive episode within the first two years of the disturbance). A person may have episodes of major depression along with periods of less severe symptoms, but symptoms must last for at least two years. In postpartum depression, the onset of major depressive disorder typically occurs shortly after giving birth.

ECA found people with lifetime depressive disorders (dysthymia, major depressive disorder) to have 1.3-1.7 times higher odds of lifetime alcohol use disorder, and 3.8-3.9-fold odds of any drug use disorder compared to those without depressive disorders [116]. In the NCS, depressive disorders were associated with 2.3-2.5 times higher odds of alcohol use disorder [117], and 2-fold increased odds of drug use disorders [118]. Findings from the NESARC showed lifetime major depressive disorder to be associated with a 1.7-fold increased odds of lifetime alcohol use disorder [119]. Further, those with lifetime depressive disorders had 2.9-3.6 times higher odds of any lifetime drug use disorder compared individuals without depressive disorders [120]. Similar surveys from other countries have further confirmed the high rate of comorbidity of SUDs among individuals with depressive disorders [108, 121-125].

Lifetime associations are important for establishing that comorbidity exists, but cannot tell much about the direction of the association. Longitudinal studies, on the other hand, can elucidate whether internalizing disorders predict future SUDs, which is an essential criterion for causality. The NESARC participants were followed-up for 3 years, and major depressive disorder at wave 1 was associated with a significantly increased risk of SUDs at wave 2. Importantly, the association persisted even after controlling for *all other* wave 1 psychiatric diagnoses [126].

Although mainly capturing the treatment-seeking population, register-based studies have the advantage of including individuals who are less likely to participate in voluntary surveys, such as people with severe mental health disorders [127]. Further, register-based data are prospective, and not biased by retrospective recall [128]. Very few studies have investigated the association between depression and SUDs using nationwide register data. A Danish study of nearly 6 million individuals found that patients with a mood disorder had over a 10-fold increased risk of subsequent SUDs compared to unaffected population controls [129]. However, depressive disorders were not investigated separately, and therefore it is uncertain how much of the association was driven by bipolar disorder which was included in the definition of mood disorder. Another Danish register study showed that the prevalence of SUDs was 25% among patients treated for depression in psychiatric specialist services [130]. The relative risk was not estimated as there was no control group.

Epidemiological studies in children and adolescents

In children and adolescents, depressive disorders are also associated with an elevated risk of SUDs. In the NCS Adolescent Supplement of 13—18-year-olds, having major depressive disorder within the past 12 months was associated with a 4.2-fold increased risk of having a SUD during the same time period [131]. Longitudinal studies in children and adolescents can be particularly useful if the follow-up starts at an early age, preceding the typical age of substance initiation. In such a study design, reverse causality is unlikely to explain any emerging association. A meta-analysis of longitudinal studies in child and adolescent samples found depression to be associated with over a two-fold increased risk of subsequent SUDs [132]. However, not all included studies had follow-up from an age preceding the typical onset of substance use, and a longitudinal design does not rule out the possibility that the observed association was explained by unmeasured confounding.

Sex-differences in comorbidity

Sex-differences in the association between depression and SUDs remain inconclusive: in a Danish register-based study, the association was similar in men and women [129], whereas the NESARC study found women with depression to have a higher relative risk of some specific drug use disorders (cannabis, opioids) than men, but there was no evidence of sex-differences in the association with drug use disorders overall [120]. A consortium study of epidemiological surveys from several countries found no consistent sex-differences in the association of depression with SUDs, but in some instances the magnitude of comorbidity tended to be greater for women [108]. In studies of children and adolescents, no consistent sex-differences have emerged [131, 132].

Genetically informative and quasi-experimental studies

Twin studies have shown a significant genetic overlap in lifetime depressive disorder and alcohol use disorder [133-136], as well as depression and drug use disorders [137-140]. In most studies, both genetic and non-shared environmental factors contributed to the association, with little support for the role of shared environmental influences (e.g., the rearing environment). Recent GWA studies provide further support for the genetic correlation between depression and SUDs [141-143]. Longitudinal studies suggest that the association between depression and SUDs is not entirely accounted for by shared familial factors, with is consistent with the hypothesis of depression causally increasing the risk of subsequent SUDs [144-146]. Further, a recent study using an instrumental variable approach (Mendelian randomization) found evidence of a causal pathway from depression to alcohol use disorder [147]. However, there are several studies that do not support the causal hypothesis, indicating that the association is instead explained by familial confounding or reverse causality [137-140, 148]. Many of the studies investigating the direct effect of depression on SUDs used the co-twin control

design with dichotomous variables and a sample size of a few thousand participants at best. Due to the at least moderate heritability of both traits and the use of dichotomous measures with unbalanced distributions, such design would require a very large sample size, as it tends to increase imprecision in the estimates [149, 150]. Imprecise estimates are difficult to interpret, and in such a situation, relying heavily on p-values to conclude the presence or absence of an effect is not advisable [151]. Larger samples with a longitudinal study design are needed to clarify the issue.

Summary
To summarize, there is strong evidence that depression is associated with an elevated risk of SUDs, both concurrently and longitudinally. Register-based studies would further strengthen this conclusion by including data on individuals who are less likely to participate in voluntary surveys. More studies are needed to clarify whether sex-differences in the association exist. There are some studies showing results consistent with the hypothesis of depression having a causal role in the development of SUDs, but many studies with quasi-experimental designs have methodological limitations which deter from drawing strong conclusions.

2.1.2 ANXIETY DISORDERS AND SUBSTANCE MISUSE

Anxiety disorders are characterized by persistent and uncontrollable feelings of anxiety or fear, which interferes with daily functioning. Common anxiety disorders include generalized anxiety disorder (GAD; persistent worry/fear about everyday matters, not focused on any one object or situation), specific phobias (uncontrollable fear of a specific object or situation), panic disorder (repeated, unexpected panic attacks), agoraphobia (fear of places where escape might be difficult or embarrassing, such as crowds or open spaces), social anxiety disorder (fear of social situations). ICD and DSM also include anxiety disorders with onset specific to childhood. These involve disorders such as childhood separation anxiety (fear of separation from parental figure) and social anxiety (wariness of strangers and social apprehension; only included in ICD), which must be unusually severe or persistent when accounting for the child's developmental stage.

Epidemiological studies in adult samples
Epidemiological surveys have shown an elevated risk of SUDs in adults with anxiety disorders compared those without anxiety disorders [117, 152]. There are large variations in the strength of the associations across studies and types of anxiety disorders, with Odds ratios (ORs) ranging from 1.5 to more than 10 [117, 120]. A consistent finding across different studies is the lower risk of SUDs in people with specific phobias compared to other anxiety disorders [116, 117, 120]. Some studies indicate that panic disorder may have the

strongest association with SUDs out of anxiety disorders [117, 120], although this finding is not consistent across samples [117]. In the ECA and NESARC, anxiety disorders had weaker associations with SUDs than did depressive disorders, but in other epidemiological surveys the associations were similar in magnitude [108, 117, 120]. Importantly, anxiety disorders also predict SUDs longitudinally. In the NESACR, all types of anxiety disorders at wave 1 were associated with an increased risk of SUDs three years later, although the associations became non-significant once wave 1 comorbidities were adjusted for [126].

As is the case with depressive disorders, there are few studies investigating the link between anxiety disorders and SUDs with register-based data. In a Danish study, neurotic disorders were associated with over a 10-fold increased risk of subsequent SUDs [129]. Neurotic disorders included a wide range of anxiety, somatoform, and stress-related conditions, and thus it remains unclear what the specific contribution of anxiety disorders was. Another Danish study using a sample of all patients treated for psychiatric conditions in specialist services found a 25% prevalence of SUDs in people with anxiety disorders [130]. While the data are scarce, there is little evidence that anxiety disorders are associated with a lower risk of SUDs than depressive disorders in register-based studies.

Epidemiological studies in children and adolescents

In the NCS Adolescent Supplement study, lifetime anxiety disorders were associated with a significantly increased risk of substance use and transition to SUDs. All types of anxiety disorders were associated with an elevated risk of SUDs, with the exception of generalized anxiety disorder [153]. A meta-analysis of longitudinal studies found a significant association between childhood/adolescent anxiety disorders and subsequent drug use disorders, but not alcohol use disorder or SUDs overall [132]. It should be noted that there was heterogeneity in results across different studies, possibly explained by differences in the measurement, severity, and type of anxiety disorder.

Sex-differences

Findings concerning sex-differences in the association of anxiety disorders with SUDs are mixed. In the NESARC, specific phobias and social anxiety disorder had stronger associations with sedative use disorder in women compared to men. The association between panic disorder and sedative use disorder was stronger in men [120]. Further, lifetime social anxiety disorder was found to be associated with a very small increase in the prevalence of alcohol abuse in men but was associated with a 50% increased risk in women [154]. Men with generalized anxiety disorder were more likely than women to self-medicate their symptoms with alcohol [155]. Other cross-sectional epidemiological surveys, and one register-based study found no clear sex-differences in the association of anxiety disorders with SUDs [108, 129]. A

meta-analysis of longitudinal studies in children and adolescents also showed no evidence of sex-differences [132].

Genetically informative and quasi-experimental studies

The underlying mechanisms for the association of anxiety disorders with SUDs are not as well understood as for depression and SUDs. Twin and family studies suggest that the association is at least partially explained by shared genetic factors [136, 156-160], but many of these studies examined anxiety-like traits or internalizing symptoms in general instead of anxiety disorders specifically. Further, the majority investigated alcohol consumption or alcohol use disorder, whereas data on other substances remains sparse. Most twin studies report that both genetic and non-shared environmental factors contributed to the association, with no clear evidence of shared environmental influences. A Norwegian longitudinal twin study found that the association between anxiety disorders and alcohol use disorder in adulthood was entirely explained by shared genetic factors, with the exception of social anxiety disorder, for which the study found evidence of a direct environmental effect (i.e., social anxiety causally increasing the risk of alcohol use disorder) [159]. Emerging studies using molecular genetic methods have further revealed genetic correlations between anxiety disorders and substance use-related traits [161-163], but studies examining the association with SUDs specifically are yet to be published.

In addition to the Norwegian study discussed above, there are a few studies examining the longitudinal association of anxiety with substance use in child and adolescent samples. In contrast to studies measuring anxiety with clinical diagnoses, non-clinical measures of social anxiety were associated with a *decreased* risk of subsequent substance use. A Finnish twin study found a negative association between teacher-rated social anxiety at age 12 and the initiation of drug use at age 17, and the association was primarily explained by familial confounding [164]. Peer-rated social anxiety at age 12 was negatively associated with alcohol dependence in adolescence and early adulthood. The association was evidently not explained by familial factors, but the results were inconclusive as most of the within-twin pair correlations were low and non-significant [165], possibly due to measurement error and/or statistical power issues.

Summary

In conclusion, there is clear evidence from cross-sectional studies that anxiety disorders are associated with an elevated risk of SUDs. A longitudinal association is also supported, at least in adults, but it is possibly explained by the comorbidity of anxiety with other psychiatric disorders. Future studies should account for psychiatric comorbidity to clarify whether anxiety disorders have an independent association with SUDs. Moreover, the association of anxiety disorders with SUDs may depend on the severity of anxiety and the type of anxiety disorder, with some disorders being less

strongly related to SUDs than others. Sex-differences in the associations remain unclear. The underlying mechanisms for the comorbidity of anxiety disorders and SUDs are not well understood, but prior studies suggest familial influences may play a role. More genetically informative studies with sufficient sample sizes and clinical measures for anxiety disorders are needed.

2.1.3 OBSESSIVE-COMPULSIVE DISORDER AND SUBSTANCE MISUSE

Compulsivity as an endophenotype

OCD is a disorder characterized by persistent, unpleasant thoughts (obsessions) and/or the need to perform certain rituals or routines repeatedly to neutralize or counteract the obsessions (compulsions), which causes distress or impairs daily functioning. In the field of neuroscience, there is accumulating evidence that OCD and SUDs share similar neurobiological correlates, as both conditions are thought to involve deficits in reward and punishment processing, negative reinforcement in limbic systems, cognitive and behavioral inflexibility with diminished prefrontal control, and habitual responding with imbalances between ventral and dorsal frontostriatal recruitment [166]. Some researchers have hypothesized that both disorders are related to a 'compulsivity' endophenotype, which increases the risk of all types of addictive/compulsive behaviors (e.g., OCD, SUDs, gambling disorder, eating disorders, trichotillomania) [166, 167].

An endophenotype (or 'intermediate' phenotype) is a heritable quantitative trait, often a cognitive process, which increases vulnerability for developing a clinical disorder. The compulsivity endophenotype is hypothesized to involve over-reliance on forming stimulus-response habits [167, 168], which may help to explain why some people can use substances and not develop an addiction, while others cannot. Indeed, one study found that obsessive-compulsive traits were significantly higher in individuals with cocaine dependence, compared to cocaine users who were not dependent [169]. In fact, the non-dependent cocaine users had similar levels of compulsive traits as the non-cocaine using control subjects. The study also revealed that compulsive traits (and orbitofrontal abnormalities associated with these traits) were similarly elevated in non-cocaine dependent siblings of the dependent individuals, which implies that the origins of compulsivity were familial and not the consequence of substance use. While the results suggest that obsessive-compulsive traits may be linked to cocaine use escalating into dependence, the laboratory-based study was cross-sectional and had a limited sample size, and the finding is yet to be replicated in other studies.

The hypothesis of compulsivity endophenotype as a causal risk factor for addictive behaviors is somewhat ambiguous concerning the type of relationship OCD and SUDs would be expected to have [167]. Several different scenarios are possible: first, significant comorbidity between OCD and SUDs

might be expected because they share a causal risk endophenotype. But as discussed earlier in the Introduction, direct links from one disorder to another should not be automatically ruled out either. Comorbidity may arise, for instance, because the compulsivity endophenotype increases vulnerability to OCD, which in turn increases the risk of SUDs via self-medication. Second, compulsivity might be an endophenotype with multifinality, whereby it can lead to different types of developmental outcomes (i.e., OCD vs. SUD). In this scenario, a high rate of comorbidity is not necessary or even expected.

Epidemiological studies on the association between obsessive-compulsive disorder and substance use disorders

The evidence for the association between OCD and SUDs is mixed. In clinical samples, there are inconsistencies regarding the prevalence of SUDs in patients with OCD: some studies show SUDs to be highly prevalent [130, 170, 171], while others report a very low prevalence [172]. Cross-sectional epidemiological surveys show OCD to be associated with an elevated risk of SUDs compared to people without OCD, with ORs ranging from 2.5 to 9 [116, 173-177]. Similar findings were reported in a community sample of adolescents [184]. Some case-control studies found no association between OCD and SUDs [178, 183]. In contrast, other studies suggest that people with OCD might even be *less* likely to use substances than the general population because of health-anxiety and low levels of impulsivity associated with OCD [179, 180]. One proposed hypothesis states that people with OCD might be less likely to initiate substance use but are particularly vulnerable to addiction once they start using [180, 182], although there is little empirical evidence to support this. Most studies have not examined sex-differences, with the exception of a study among adolescents, which found no sex-differences in the association of OCD with heavy drinking and drug use [184]. Even though most of the epidemiological surveys had large samples, many of them included a limited number of individuals who had OCD (in some cases, only a few dozen), resulting in imprecise estimates. As OCD is a relatively rare disorder, studies with very large samples are required to clarify its association with SUDs.

There are also inconsistencies in the order of onset: a clinic-based study found that the majority of OCD patients experienced the onset of OCD prior to SUD [170]. Conversely, the NCS data show that the majority of individuals reported the onset of SUDs to precede OCD [177]. The onset of disorders was reported retrospectively in both studies, and thus can be biased by retrospective recall. At the moment, there are no longitudinal studies on the association between OCD and SUDs which is a major gap in the literature. Aforementioned epidemiological studies suggest that there is an increased risk of SUDs among people with OCD, but the cross-sectional study designs do not allow for making strong conclusions about the direction of the association.

Genetically informative and quasi-experimental studies

While the heritability of both SUDs and OCD [185, 186] is well established, the contribution of familial influences to the association between them remains largely unclear. There are a few family studies, although with a limited sample size, which found no familial co-aggregation of SUDs in close relatives of individuals with OCD [178, 183]. In contrast, a family study with a larger sample did find an elevated risk of OCD among first degree relatives of individuals with alcohol dependence [187]. Literature search revealed no twin studies on the topic. A recent study using GWAS summary statistics reported a negative genetic correlation between OCD and SUDs, but the correlation was not statistically significant [188]. If there was a shared causal endophenotype in OCD and SUDs, we would expect to see a positive genetic correlation between the two traits. On the other hand, if OCD causally increases the risk of SUDs (e.g., via self-medication), the effect would be detected as a non-shared environmental correlation, independent of possible shared genetic effects. Quantitative genetic studies would be ideally suited for testing these competing hypotheses.

Summary

In summary, many open questions remain concerning the link between OCD and SUDs. There is a need for large-scale, prospective population studies with a sufficient number of individuals with OCD. Such studies would help to clarify the magnitude and direction of the association, and the existence of potential sex-differences. Further, since very little is known about the underlying mechanisms for the association, twin studies and other quasi-experimental designs are needed to test different competing hypotheses.

2.2 COMORBIDITY AND PHARMACOLOGICAL TREATMENT

Psychiatric comorbidity is a major challenge for a clinician, as it is associated with increased symptom severity, treatment resistance, and diminished daily functioning [189, 190]. As discussed earlier in the Introduction, a large proportion of patients with anxiety and depressive disorders will also have a SUD, and problematic substance use patterns are common even in the absence of a formal SUD diagnosis [191]. As a common clinical presentation, comorbid substance use problems are an important factor to consider when planning treatment. Treatment planning is complicated by the fact that concurrent use of psychiatric medications with alcohol or drugs can be dangerous to the patient's health, and in the worst-case scenario, even fatal [192-195]. SSRIs are the first-line treatment for anxiety and depression. Because of their safety-profile and comparatively low risk for toxic interactions with alcohol and drugs [194-196], they might be a good treatment option also in situations where SUD comorbidity is present.

SSRIs are effective in reducing anxiety and depression, but clinical trials have typically excluded patients with comorbid SUDs [197, 198]. Studies that investigate the effectiveness of SSRIs in patients with SUDs show more heterogeneous results in the estimated effect sizes, but suggest that SSRIs are likely to be effective in reducing anxiety and depressive symptoms in this patient group [199-201]. If substance use problems were mainly caused by self-medication, reductions in anxiety and depression would be expected to also reduce substance use. Randomized controlled trials (RCTs) have suggested that SSRIs used as monotherapy [202], or in combination with Naltrexone [203], may reduce alcohol consumption and relapse rates in patients with depression and alcohol use disorder. In contrast, numerous meta-analyses of all available RCTs have revealed disappointing results, with little evidence of SSRIs having any effect on substance use [200, 204-208]. Yet, the conclusions from the meta-analyses are constrained by methodological problems in the RCTs, such as low statistical power, short follow-ups, high dropout rates, and excessive placebo response in the control groups [200, 204, 207].

Pharmacoepidemiological studies provide an alternative for examining whether substance use is affected by SSRI treatment. Observational studies cannot confirm causality, but using health record data allows investigating non-selected, large samples of patients with long-term follow-up, often not feasible in RCTs [209]. Thus, pharmacoepidemiological studies can be useful in triangulating evidence for the real-world effectiveness of SSRIs, while avoiding methodological issues typical for RCTs. The use of within-individual designs comparing medicated and non-medicated periods, treating each patient as his or her own control, increases validity compared to traditional observational studies by eliminating confounding by factors which remain constant over time within the individual [210]. Further, a within-individual design is well-suited for pharmacoepidemiological research because it is not confounded by indication, as opposed to a between-individual design which compares individuals who are on SSRI medication to those who are not. However, a within-individual design can lead to misleading results if potential dynamic treatment-initiation processes and other time-varying factors are not accounted for. For instance, one study found an increased risk of substance misuse events during SSRI treatment in patients with ADHD [211]. The authors speculated that the increased risk on-treatment was unlikely to represent an actual adverse effect of SSRI, but rather reflected time-varying confounding. The period shortly preceding SSRI treatment initiation might have been associated with a particularly high risk for substance-related problems, which would not have completely resolved once treatment was initiated, producing a spurious positive association. Dynamic treatment-initiation processes have been reported for other outcomes, such as suicide attempts [212, 213].

To conclude, because of their favorable safety-profile, SSRIs might be a good pharmacological treatment option for patients with anxiety/depression

and concurrent substance use problems, but their effectiveness in reducing substance use remains unclear [214]. Pharmacoepidemiological studies could offer new insights into real-world effectiveness of SSRIs treatment. Furthermore, assuming that SSRIs reduce anxiety and depression but do not directly influence substance use, a within-individual study comparing substance use problems on- vs. off-treatment would allow for testing of the self-medication hypothesis.

3 AIMS

The overarching aim of this dissertation was to examine the association of depression, anxiety, and OCD with substance use problems. Specifically, the dissertation aimed to 1) describe the association of these internalizing disorders with substance misuse during the lifetime as well as during the important developmental period from childhood to early adulthood, and 2) to clarify the mechanisms underlying the comorbidity using quasi-experimental designs.

Specific study aims

Study I: To examine the lifetime association of substance misuse with anxiety-related and depressive disorders in the general population, and to estimate the extent to which the associations were explained by shared genetic and environmental factors.

Study II: To investigate whether childhood anxiety and depressive disorders were associated with subsequent substance misuse, and whether the associations persist once shared genetic and environmental factors were accounted for.

Study III: To estimate the association of OCD with substance misuse in late adolescence and during the lifetime, and to examine whether OCD was related to a higher risk of developing substance dependence in those who used alcohol or drugs. The second aim was to estimate the contribution of shared genetic and environmental factors to the association between OCD and substance misuse.

Study IV: To test whether SSRI medication treatment was associated with a reduced risk of substance misuse among individuals with anxiety and depressive disorders by conducting a longitudinal within-individual analysis, where the risk for acute substance misuse outcomes was compared during periods when on vs. off SSRI medication.

4 METHODS

4.1 DATA SOURCES AND MEASURES

Sub-studies of this dissertation included two sources of data: Swedish nationwide registers and the Child and Adolescent Twin Study in Sweden (CATSS). Studies I and IV utilized register-based data exclusively, whereas Studies II and III combined register-based data and the CATSS data. Data sources for each sub-study are summarized in Table 2.

In all register-based samples, we excluded individuals who had died or emigrated before the start of the follow-up. In sub-studies I-III we also excluded individuals whose parents could not be identified from the Multi-Generation Register, which is required for identifying sibling clusters within the sample.

Table 2. *Data sources and cohort description for each sub-study*

STUDY	DATA SOURCE	DESCRIPTION
I	Register-based	Population-based sample born in Sweden 1968–1997 (n=2,996,398). Follow-up between January 1997 and December 2013.
II	1) Register-based 2) CATSS cohort	1) Population-based sample born in Sweden 1984–2000 (n=1,768,516). Follow-up from 13th birthday until December 2013. 2) CATSS twin study participants born 1992-1998 (n=12,408). Follow-up from 13th birthday until December 2013.
III	1) Register-based 2) CATSS cohort	1) Population-based sample born 1932-1997 (n=6,304,188). Follow-up from 1997 or 15th birthday until December 2013. 2) CATSS twin study participants born 1993-2001 who endorsed using alcohol or drugs at age 18 assessment (n=9,230). Follow-up from age 18 to 24.
IV	Register-based	Individuals with a newly dispensed SSRI prescription between July 2006 and December 2013, and an ICD-10 diagnosis of anxiety/depressive disorder registered between 1997 and the first SSRI treatment initiation (n=146,114). Follow-up between June 2005 and December 2013.

4.1.1 SWEDISH NATIONAL REGISTERS

A ten-digit personal identity number assigned to every resident at birth or after immigration has been in use in Sweden since 1947. The personal identity number allows for linkage of several different administrative registers [215]. Data linkage has been approved by the Stockholm Regional Ethical Review Board. The requirement for informed consent was waived because the data have been anonymized for research purposes. The sub-studies of this dissertation had register follow-up available until December 31st 2013.

Total Population Register

The Total Population Register includes information on birth dates, place of residence, civil status, and migration of Swedish residents from 1968 onwards [216]. The register was used to collect information on demographic covariates in all sub-studies, as well as dates for emigrations and deaths to define censoring in time-to-event analyses.

The Swedish Twin Register

The Swedish Twin Register, hosted at the Department of Medical Epidemiology and Biostatistics at the Karolinska Institutet, was established in the 1960's to collect information on all twin individuals in Sweden. It now contains information of more than 87,000 twin pairs with confirmed zygosity, based on an intra-pair similarity algorithm, or single nucleotide polymorphism (SNP) markers [217].

Multi-Generation Register

The Multi-Generation Register links all Swedish residents with their parents, which allows identification of different types of family pedigrees within the population [218]. The register has linkage for individuals born 1932 onwards and living in Sweden since January 1, 1961. Linkage is available for immigrated persons only if they immigrated together with their parents before age 18. Information on family relatedness was used in Studies I, II, and III to identify clusters of full siblings and half-siblings.

National Patient Register

The National Patient Register (NPR) includes information on somatic and psychiatric inpatient care from 1964 and 1973 onwards, respectively [219]. The data concerning psychiatric care has nationwide coverage since 1987. Outpatient specialist care information is available from 2001 onwards with nationwide coverage. The NPR includes dates for admission and discharge, and ICD-diagnoses for the conditions the patient was treated for. In Sweden, the ICD-8 diagnostic system was in use between 1969 and 1986, ICD-9 in 1987-1996, and ICD-10 since 1997.[1]

[1] List of Swedish ICD-10 codes by the Swedish National Board of Health and Welfare (Socialstyrelsen): https://klassifikationer.socialstyrelsen.se/ICD10SE/

Table 3 describes the diagnostic codes of the main exposure (anxiety and depressive disorders, OCD) and outcome (substance-related disorders) measures in the sub-studies. We also included other diagnoses from the NPR as covariates. Covariates in Study I included any parental ICD-8, ICD-9, or ICD-10 mental or behavioral diagnosis. In Study II, we collected ICD-9/10 diagnoses for ADHD (314, F90), and conduct disorders (314, F91). Study III covariates included ICD-10 anxiety (F40-F41) and depressive (F32-F39, excluding F34.0) disorders.

Table 3. *ICD diagnostic codes for the exposure and outcome measures.*

STUDY	EXPOSURE	OUTCOME
I	**ICD-10** Anxiety disorder (F40-F43) Depressive disorder (F32-F34, F38-F39)	**ICD-10** Substance use disorder (F10-F16, F18-F19)
II	**ICD-9** Childhood-specific anxiety disorder (309.31, 313.2) Anxiety disorder (300, except 300D and 300E) Depressive disorder (296B, 311) **ICD-10** Childhood-specific anxiety disorder (F93.0, F93.2) Anxiety disorder (F40-F41, F44-F45, F49) Depressive disorder (F32-F34, F38-F39)	**ICD-9** Substance use disorder (291, 303, 304, 305) **ICD-10** Substance use disorder (F10-F16, F18-F19)
III	**ICD-10** Obsessive-compulsive disorder (F42)	**ICD-10** Substance use disorder (F10-F16, F18-F19) Drug-related poisoning (T40) Alcohol poisoning (T51) Somatic condition caused by alcohol (E24.4, G62.1, I42.6, K29.2, G31.2, G72.1, K70.1, K70.9, K70.3, K70.0, K70.2, K70.4, K85.2, K86.0) Other alcohol-related diagnosis (O35.4, Y57.3, X65, Y90, Y91, Z50.2, Z71.4, Z72.1)
IV	**ICD-10** Anxiety disorder (F40-F41) Depressive disorder (F32-F39, excluding F34.0) Substance use disorder (F10-F16, F18-F19, excluding acute intoxications) *Note: Diagnoses were used to define the study population, exposure was SSRI medication*	**ICD-10** Acute intoxication (F10.0-F16.0, F18.0-F19.0) Accidental poisoning by alcohol or drugs (X41, X42, X45, X46)

The Cause of Death Register

The Cause of Death Register includes information concerning deaths of Swedish residents, with nationwide coverage since 1961. The date and the

contributing cause of death according to the ICD diagnostic system is included in the records. In Study III, we collected information on individuals who had died due to substance use-related causes (using the same ICD codes as reported in Table 3).

Crime registers

Underdiagnosing and low treatment utilization is common in SUDs, resulting in many individuals with substance use problems not being present in the NPR. Therefore, we included substance use-related criminal offenses as an outcome measure to ensure a better coverage of substance misuse in the population. The Crime Register includes nationwide district court convictions among people aged 15 and older (age of criminal responsibility in Sweden) since 1973. Studies I, II, and III included convictions for driving under the influence of alcohol/drugs, and violations of the Narcotic Drugs Act such as possession, manufacturing, trafficking, or sales of illicit drugs. In Study IV, we included convictions for driving under the influence of substances, as well as suspicions of use or possession of illicit drugs from the Register of People Suspected of Offences (coverage 1998 onwards).

The Prescribed Drug Register

The Prescribed Drug Register contains information on dispensed prescription medications of Swedish residents nationwide since July 1, 2005, including the type of medication (classified according to the Anatomical Therapeutic Chemical [ATC] classification system), dosage, and prescription and dispensation dates [220].

In Study IV, we retrieved all dispensed prescriptions of SSRIs between July 1 2006 and December 31 2013 for individuals aged 15 or older. We restricted the sample to individuals who had at least one year with no record of dispensed SSRI prescriptions before their first treatment initiation. The primary exposure was time-varying SSRI treatment status (i.e., on- vs. off-treatment). We defined on-treatment periods based on elapsed time between dispensed prescriptions. In Sweden, the '90-day-rule' allows for dispensing of oral psychiatric medications for a maximum of 90 days at a time. Therefore, when defining on-treatment periods we assumed that two dispensed prescriptions falling within 120 days of each other belonged to the same, continuing treatment period. We added 30 extra days to the 90 days to account for possible treatment non-adherence. For the last dispensed prescription in a treatment period, we defined the end of treatment by adding the median number of days between previous prescriptions to the date of dispensation. Time periods of 120 days or more without dispensed prescriptions were considered off-treatment.

We also included other medication as covariates to account for polypharmacy: benzodiazepines, non-SSRI antidepressants, and other psychotropic medications (see Table 4 for drugs and ATC codes). For the other medications, we defined on-treatment periods similarly to the SSRI

medication periods, with the exception that the end of a treatment period was estimated by adding 30 days to the date of the last dispensation.

Table 4. *Drugs and ATC codes*

Drug	ATC-code
Main Exposure	
SSRIs	N06AB
Covariates	
Non-SSRI antidepressants	N06A, excluding N06AB
Benzodiazepines	N05BA
Antipsychotics	N05A
Anxiolytics	N05B, excluding N05BA
Hypnotics/sedatives	N05C
Psychostimulants	N06B
Drugs for addictive disorders	N07B
Opioids	N02A
Antiepileptics	N03A
Antidementia drugs	N06D

Census records

We used parental socioeconomic status and highest achieved education as covariates in Study I, and we retrieved the data from census records available for years 1960, 1970, 1980, and 1990. The variables were constructed based on information from the years the parent had reached at least the age of 15. The parental socioeconomic status variable was based on the recorded profession, in accordance with the classification provided by Statistic Sweden: 1) low, 2) medium, 3) high, 4) unknown (if information was unavailable). For study participants born before 1990, we obtained the highest parental education level from census, classified as 1) primary school, 2) high school, 3) university, 4) doctorate, 5) unknown (if information was unavailable).

The Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA)

LISA register includes information concerning, e.g., education, employment, and income since 1990. In Study I, we used LISA register to obtain the highest achieved parental education level for participants born 1990 and after, classified as described in the previous section.

4.1.2 CHILD AND ADOLESCENT TWIN STUDY IN SWEDEN (CATSS)

The Child and Adolescent Twin Study in Sweden (CATSS) is an ongoing longitudinal study focusing on developmental aspects of social, physical, and psychological well-being [221]. The aim of CATSS is to recruit all twins born in Sweden since July 1 1992. From the beginning of the study in 2004, all 12-year-old (born 1992–1995) and 9-year-old (born July 1 1995 and after) twins have been identified through the Swedish Twin Register and their parents have been asked to participate in a telephone interview and to fill out questionnaires regarding their children's well-being. Families are contacted again when the twins reach the age of 15, 18, and 24. During the follow-up assessments, both twins and their parents provide information via web-based questionnaires. Twin zygosity is determined with 48 single nucleotide polymorphisms, or if DNA information is unavailable, by an algorithm based on a questionnaire on twin similarity. Information Swedish registers can be linked with the CATSS participants using the personal identity number. The CATSS study was approved by the Stockholm Regional Ethical Review Board. At age 9/12, parents provided consent for their children to participate, and the twins themselves provided informed consent from age 15 onwards.

Sample and measures in Study II

The sample in Study II consisted of 12,408 twin individuals born 1992–1998 whose parents participated in the CATSS age 9/12 telephone interview. The response rate of this sample was 76%, with the mother being the informant in most families.

The main exposure measures, anxiety and mood problems, were assessed at age 9/12 telephone interview with the Autism - Tics, AD/HD and other Comorbidities Inventory (A-TAC)[2]. The ATAC is a validated instrument covering common psychiatric disorders in childhood, and it includes separate scales for anxiety and mood-related problems [222, 223]. The A-TAC items represent symptoms of psychiatric disorders according to the DSM-IV. Parents rated their children's symptoms on a dimensional scale: 0=item does not apply; 0.5=applies to some extent; and 1=applies in full. The interviewer proceeded to ask whether the symptoms had led to 1) dysfunction at school, among peers, or at home, and 2) suffering on the part of the child, if the parent fully or partially endorsed at least one of the items. The sum of the dysfunction and suffering items (range 0-2) formed a 'problem load score', with a cut-off at ≥ 1 indicating that at least one of the problem questions was fully endorsed or that both were endorsed to some extent, i.e., the problems were considered to have caused significant distress [223].

Anxiety-related problems were assessed with items describing symptoms such as panic attacks, fearfulness, generalized anxiety, and social withdrawal. Mood-related problems included depressed mood, feelings of worthlessness,

[2] The questionnaire is available online: https://www.gu.se/en/gnc/gncs-resources/screening-questionnaires/a-tac-screening-questionnaire

lack of self-confidence, psychosomatic symptoms, and self-harm. We used binary variables for anxiety and mood problems derived from the corresponding problem load score (with the cut-off of ≥ 1) to better capture severe or debilitating forms of psychopathology (coded: 0=no symptoms causing significant distress, 1=symptoms causing significant distress).

To account for comorbidity of internalizing psychopathology with externalizing problems, we included the A-TAC scales on symptoms of ADHD, ODD, and conduct disorder as covariates (used as continuous variables describing symptom severity). The substance misuse outcome measure was derived from the national registers (see Table 3 and "Crime registers" section).

Sample and measures in Study III

The sample in Study III consisted of CATSS participants (born 1993–2001) who provided information regarding obsessive-compulsive symptoms and substance use problems at the age 18 assessment. Participants with missing values were excluded. The final sample included participants who endorsed using alcohol or drugs (n=9,230). A subset of participants had also provided data on substance use problems at age 24 (n=3,404). The sample from age 18 assessment included 2,056 monozygotic and 2,250 dizygotic twins whose co-twin also participated in the study. There were 3,277 opposite-sex dizygotic twins, 221 twins with unknown zygosity, and 524 monozygotic and 902 dizygotic twins without their co-twin in the study, who were excluded from the quantitative genetic analyses, but contributed to the estimates of individual-level associations.

Obsessive-compulsive symptoms

At age 18, the twins completed a 15-item symptom checklist, the Brief Obsessive Compulsive Scale (BOCS), which is based on the clinician-administered Yale-Brown Obsessive-Compulsive Scale. The BOCS scale has good validity and reliability [224]. In the BOCS questionnaire, participants are asked to rate each symptom item as either 'never', 'past' or 'current'. In accordance with previous studies [225], we combined the two symptom endorsing categories (i.e., 'past' and 'current' was coded as 1, 'never' was coded as 0), and excluded three items related to hoarding, dysmorphic concerns, and self-harm, because they do not represent the core OCD phenotype, but measure related psychopathology. The sum of the 12 included items was used as the main exposure variable. The internal consistency of the resulting 12-item scale was good (α=0.76). The variable for OCD symptoms was standardized for the analyses to ease interpretability.

Substance use

Substance use problems were measured with self-reported Alcohol Use Disorders Identification Test (AUDIT) and the Drug Use Disorders Identification Test (DUDIT) at ages 18 and 24.

AUDIT is a 10-item questionnaire developed to identify persons with risky or hazardous alcohol consumption and alcohol use disorder [226]. Items 1-3 relate to consumption of alcohol (typical frequency and quantity, binge drinking), whereas items 4-10 measure alcohol dependence and harmful use (i.e., loss of control, withdrawal, neglect of other pursuits, continued use despite clear harm caused by alcohol). Previous research supports a two-factor structure for the AUDIT, where factor 1 consists of items 1-3 (level of consumption), and factor 2 of items 4-10 (dependence and harmful consequences) [227]. Molecular genetic studies also support the notion of the AUDIT factors as correlated, but distinct dimensions [39]. We identified participants who used alcohol based on AUDIT item 1. Sum of items 4-10 measuring alcohol dependence symptoms was used as the outcome variable. The internal consistency of alcohol dependence symptoms measure was α=0.67 at age 18, and α=0.70 at age 24. The variables were standardized to ease interpretability.

DUDIT is a parallel instrument to the AUDIT for identification of individuals with drug-related problems [228]. DUDIT consists of 11 items, and has a similar structure as the AUDIT, with items 1-4 measuring frequency and quantity of drug use, and items 5-11 relating to dependence and harm (e.g., craving, loss of control, neglect of other pursuits, continued use despite negative consequences). Validation studies have identified a two-factor structure for the DUDIT, with factors representing 1) drug consumption, and 2) dependence and harmful consequences [229]. We identified participants who used drugs based on DUDIT item 1, and used the sum of items 5-11 as the outcome variable. The internal consistency of the drug dependence symptoms measure was α=0.74 at age 18, and α=0.83 at age 24. The variables were standardized to ease interpretability.

Anxiety and depressive symptoms

Anxiety and depressive symptoms were included as covariates. Both were measured during age 18 assessment. Anxiety was measured with the self-report version of the Screen for Child Anxiety Related Emotional Disorders (SCARED) [230]. The SCARED is a validated [230-232], 38-item symptom checklist including items reflecting common anxiety diagnoses, with items scored on a 3-point scale ranging from 0 (almost never true) to 2 (true most of the time). Internal consistency in the current sample was α=0.93.

Participants provided information on depressive symptoms with the Iowa version of the centre for Epidemiologic Studies Depression Scale (CES-D) [233]. CES-D includes 11 items scored on a 4-point scale ranging from 0 (rarely/none of the time) to 3 (most/all of the time). The scale is validated and has good psychometric properties [234]. In the current study, internal consistency of the scale was α=0.87.

4.2 STUDY DESIGNS AND STATISTICAL METHODS

Table 5 provides an overview of study populations, measures, and methods in each sub-study.

Table 5. *Overview of study methods and materials*

STUDY	PARTICIPANTS	MEASURES	STATISTICAL METHODS
1	1) Population-based sample born in Sweden 1968–1997 (n=2,996,398) 2) Half-siblings, full siblings, dizygotic twins, and monozygotic twins within the population sample	*Exposures*: Lifetime anxiety and depressive disorder diagnoses in the NPR *Outcomes*: Lifetime substance use disorder diagnoses in the NPR or substance-related criminal convictions	Factor analysis Poisson regression Fixed-effects regression Quantitative genetic structural equation modeling
2	1) Population-based sample born in Sweden 1984–2000 (n=1,768,516) 2) CATSS twin study participants born 1992-1998 (n=12,408)	*Exposures:* Population sample: anxiety and depressive disorder diagnoses registered in the NPR before age 13. CATSS: parental report of mood- and anxiety-problems at age 9/12. *Outcomes*: Substance use disorder diagnosis in the NPR or substance-related criminal conviction (registered after age 13)	Cox regression Cox regression stratified within siblings
3	1) Population based-sample born 1932–1997 (n=6,304,188) 2) Half-siblings and full siblings within the population sample 3) CATSS twin study participants who used alcohol or drugs (n=9,230)	*Exposures*: Population sample: lifetime diagnosis of obsessive-compulsive disorder. CATSS: self-reported obsessive-compulsive symptoms at age 18. *Outcomes*: Population sample: substance-related diagnosis in the NPR or substance-related criminal conviction registered after age 15. CATSS: self-reported alcohol and drug dependence symptoms at age 18 and 24.	Linear regression Cox regression Quantitative genetic structural equation modeling

4	1) Patients aged over 15 with at least one dispensed prescription of SSRIs between July 2006 and December 2013, and an ICD-10 diagnosis of anxiety/depressive disorder before the first treatment initiation (n=146,114) 2) Subgroups with and without a comorbid substance use disorder diagnosis	*Exposures*: SSRI medication treatment in the Prescribed drug register *Outcomes*: Diagnoses of acute intoxications and accidental poisonings by alcohol or drugs in the NPR, and substance-related criminal offenses.	Cox regression stratified within individuals

4.2.1 STUDY DESIGNS

4.2.1.1 Family-based designs

In a conventional epidemiological research design, the likelihood of observing an outcome of interest for a group with a hypothesized risk factor (exposure) is compared to those who have not been exposed to the risk factor. The study sample is typically composed of one person per family, i.e., a group of unrelated individuals. Researchers are often interested in finding 'modifiable' risk factors, with the implication that if the exposure is prevented or treated, the likelihood of the outcome will be reduced (thus assuming, at least implicitly, that the association is causal). However, by itself such a between-individual design does not account for the possibility that the association may be confounded by genetic and environmental differences between individuals. In other words, there may be genetic or environmental influences that explain the observed association, instead of the association being causal. This problem can be partly addressed by including measured covariates to adjust for differences between individuals, but in practice, all possible confounders are rarely known, and even if they are, measures for them might not be available leading to unmeasured residual confounding. This is a particularly relevant issue when aiming to adjust for genetic confounding.

An alternative approach is to utilize so-called quasi-experimental designs. Quasi-experiments do not randomly assign individuals to conditions, but use design features to rule out many plausible alternative explanations for an association of interest [115]. Family-based designs are a sub-class within

quasi-experiments. They take advantage of 'natural experiments' based on family relationships. The following sections describe the two family-based research designs used in this dissertation.

Within-family design

The within-family analysis differs from the conventional observational research design by estimating the association between an exposure and outcome stratified *within* pairs or clusters of siblings, instead of estimating the association in a group of unrelated individuals. The within-family design uses information from all families, but the informative clusters are the ones with discordance in the exposure. Discordance is assigned if at least one sibling is exposed while the other siblings are not. In effect, when the risk of outcome is compared between the exposed sibling and their non-affected co-sibling(s), this rules out all genetic and environmental factors which are constant, or shared, within the sibling cluster [235]. The non-affected siblings act as genetically and environmentally (partly) matched 'controls' for their exposed sibling. Thus, the design can be used to account for a wide range of potential confounders without the need to explicitly identify or measure them. The degree to which the within-family analysis accounts for genetic and environmental confounding depends on the degree of sibling relatedness, and whether the siblings shared a rearing environment (Table 6).

Table 6. *Assumed degree of genetic and environmental sharing across siblings in sub-studies of the dissertation*

	Shared genetic factors (%)	Shared environmental factors (%)
Half-siblings	25	100 (reared together) / 0 (reared apart)
Full siblings	50	100
DZ twins	50	100
MZ twins	100	100

If data on siblings with different degrees of relatedness are available, the within-family design allows for testing of competing hypotheses explaining the underlying mechanism for an observed association. An association between an exposure and outcome may be causal, or explained by 1) genetic factors, 2) shared environmental factors assumed to correlate perfectly among all siblings reared together, and 3) non-shared environmental factors which make siblings different from one another. The contribution of genetic and shared environmental factors can be inferred by comparing individual-level estimates (i.e., estimates for the association from a conventional between-individual design) to those obtained from stratified analyses in different sibling types [115, 236]. If within-family estimates are similar to the individual-level estimates, the association is free of familial confounding, and may be causal.

A situation where the association is reduced equally in MZ twins and DZ-twins/full siblings suggests shared environmental variables partly explain the association. In contrast, the association being attenuated more in MZ twins than in other types of siblings suggests the contribution of genetic factors [115].

While the within-family models rule out many possible confounders, they do not account for the non-shared environmental factors that make siblings different from one another. To elaborate, although - for instance - MZ co-twins are genetically identical and share their rearing environment, they are individual persons with unique life experiences. These unique elements cannot be accounted for by the research design, and would have to be measured and included as covariates in the model. Because it is unlikely that all potential non-shared environmental confounders have been measured, the within-family design can rarely be used to establish a causal relationship. Nevertheless, if an association persists within MZ-twins, the finding can be interpreted as *consistent* with a causal hypothesis [237], since a large proportion of confounding has been ruled out.

The within-family design was used in Studies I and II to examine whether the association between anxiety/depression and substance misuse persists once familial factors were accounted for.

4.2.1.2 Quantitative genetic design

Within-family models are useful for ruling out genetic and environmental confounding factors, and can help to establish whether an association of interest is mainly explained by genetic or shared environmental factors. However, they do not provide an estimate for how much of the association is explained by genetic and environmental factors, respectively. Quantitative genetic designs, using twin and/or sibling pairs, can be used to quantify the relative importance of genetic and environmental influences.

Classical twin design

The classical twin design is based on the fact that MZ twins are genetically identical, whereas DZ twins share, on average, 50% of their segregating genes. Assuming that MZ and DZ co-twins share their environments equally, a higher similarity (i.e., a higher within-pair correlation) of MZ co-twins compared to DZ co-twins indicates a genetic contribution to variation in a trait [238]. The underlying logic is that because MZ and DZ twins differ only in the degree of which they share genes, the difference in within-pair similarity must be due to genetic factors [238].

The variance (V) of a given trait (P) can be decomposed into three latent factors by comparing within-pair correlations of MZ and DZ twins: additive genetic (A), shared environmental (C), and non-shared environmental factors (E), which also include measurement error. This is called the ACE-model. An alternative to the ACE-model is the ADE-model, which estimates the

contribution of dominant genetic factors (D, interaction between alleles at the same gene locus), instead shared environmental factors. Since the variance components C and D are mutually confounded, they cannot be simultaneously estimated from only two pieces of information (the MZ and DZ covariance). Generally, if within-MZ correlations are more than twice in magnitude to within-DZ correlations, dominant genetic factors may be contributing to the trait. If MZ correlations are less than twice in magnitude, shared environmental factors are more likely.

Under the assumption of no interaction and no covariance between A, D, C, and E, the total variance of a phenotype (P) can be expressed as

$$V_{(P)} = A + D + C + E$$

The classical twin design can also be used to examine the contribution of genetic and environmental factors to the association between two or more traits. In a bivariate ACE-model, the covariance between two traits is partitioned into the A, C, and E components, for which genetic and environmental correlations can be calculated. A genetic correlation is the degree to which genetic factors of trait 1 co-vary with genetic factors of trait 2. For example, a genetic correlation of 1 would imply that genetic factors for the two traits overlap entirely. A non-shared environmental correlation between two traits is compatible with a causal relationship, but it does not confirm causality, as the correlation also reflects individual-specific environmental confounding [237].

In Studies I and III, the classical twin design was used to estimate the contribution of genetic and environmental factors to the association between anxiety/depressive disorders with substance misuse, and OCD symptoms with alcohol dependence symptoms, respectively.

Quantitative genetic design extended to other sibling types

The classical twin design can be extended to other types of siblings. Similarly to the twin design, the sibling quantitative genetic design uses information from the degree of genetic and environmental sharing across different types of siblings to estimate variance components A, C, and E.

An advantage of the sibling design is, for instance, that it addresses a common critique concerning twin designs of twins not being representative of the general population. Further, the larger number of ordinary siblings (compared to twins) in the population allows for studying rare disorders, which is often difficult with twin samples due to lack of statistical power [239, 240].

In a design that utilizes full siblings and maternal half-siblings, the assumption is that both sibling types share environments with their co-siblings equally. In Sweden, children most often live with their mothers, e.g., after parental divorce [79, 241]. Therefore, it is plausible to assume that maternal half-siblings of similar age would share a rearing environment. To

ensure that the shared environments assumption holds in both full and half-siblings, we only included sibling pairs with a maximum of five-year age difference. The assumed genetic sharing is 50% for full siblings and 25% for half-siblings. Taken together, this information allows for estimating variance components A, C, and E, based on within-pair correlations.

In Study III, we estimated the contribution of genetic and environmental influences to the association between OCD and substance misuse with a sample of full siblings and maternal-half siblings.

4.2.1.3 Within-individual design

A within-individual design is a longitudinal study design which estimates an exposure-outcome association using each individual as his/her own 'control' [242]. The design requires that the exposure varies over time, since the risk of outcome is compared during time-periods when the individual was exposed vs. in periods when not exposed. A major advantage of the within-individual design is that it eliminates confounding by all factors which remain constant over time for the individual (e.g., genetic factors and baseline characteristics).

In pharmacoepidemiological studies, the within individual-design also addresses the issue of confounding by indication. Confounding by indication means bias in the treatment-intended outcome relationship due to the clinical reasons for the treatment [243]. For instance, if an exposure of interest is SSRI medication, comparing the risk of some outcome in individuals who are on SSRI medication to those who are not, is likely to be confounded by anxiety or depression, which are the main indications for SSRIs. In the within-individual design, all participants must be on SSRIs at some point during the follow-up, which eliminates time-invariant indication bias.

The within-individual study design does not account for time-varying confounds (e.g., the effect of other drugs or psychosocial treatment, life-events, or worsening of symptoms during follow-up). However, time-varying factors can be adjusted for by including them as covariates, if measures are available.

The within individual design was used in Study IV to investigate the association of SSRI medication with acute substance misuse outcomes.

4.2.2 STATISTICAL METHODS

4.2.2.1 Regression models

Study I

Between-individual regression models

In Study I, we estimated lifetime associations of anxiety and depressive disorders with substance misuse. A lifetime association in this context means diagnoses/criminal convictions registered any time during the follow-up between January 1997 and December 2013. The ordering of the exposure and outcome was not restricted (anxiety/depression diagnosis could precede substance misuse or vice versa). The exposure and outcome variables were dichotomous. We used Poisson regression to obtain risk ratios (RRs). Poisson regression is a generalized linear model form of regression analysis used to model count data, but it can also be used for binary outcome variables [244, 245]. RR is a measure for the strength of the association, and is defined as the relative risk of the outcome in the exposed group compared to the non-exposed. RR can be expressed as

$$RR = \frac{IE/IE + IN}{CE/CE + CN}$$

where,

IE = No. of individuals with substance misuse among those with anxiety/depression diagnosis

IN = No. of individuals without substance misuse among those with anxiety/depression diagnosis

CE = No. of individuals with substance misuse among those without anxiety/depression diagnosis

CN = No. of individuals without substance misuse among those without anxiety/depression diagnosis

In the first regression model, we adjusted for sex and birth year. The second model was further adjusted for parental education, family socioeconomic status, parental history of psychopathology, and parental immigration status. The non-independence of observations due to familial clustering was accounted for by using a cluster-robust sandwich estimator for standard errors. We also estimated the associations separately for men and women.

Within-family regression models

RRs for the association between anxiety/depressive disorders and substance misuse were estimated in clusters of half-siblings, full siblings/DZ twins, and MZ twins with fixed-effects (conditional) Poisson regression models [242]. In the fixed-effects regression model, each family cluster is assigned a dummy indicator variable, which is included in the regression equation. This procedure creates an individual intercept for each family, and the regression equation can be expressed as

$$Y_{ij} = \beta X_{ij} + \alpha_i + \varepsilon_{ij}$$

where,

Y_{ij} = predicted outcome (substance misuse) for person $_j$ in family $_i$

βX_{ij} = regression coefficient for the exposure (anxiety/depressive disorder) X_{ij}

α_i = dummy-variable for family

ε_{ij} = error term

Thus, fixed-effects regression provides an estimate for whether the difference in the exposure within siblings is associated with the outcome. Models for full siblings and half-siblings were adjusted for sex and birth year.

Study II

Between-individual regression models

In Study II, we estimated the association of childhood anxiety/depression with substance misuse in two samples. In the population sample, the exposure was a diagnosis of anxiety or depressive disorder registered before age 13, and in the CATSS sample the exposure was parent-reported mood and anxiety problems at age 9/12. In both data, the outcome was a register-based diagnosis of substance use disorder, or a substance-related criminal conviction, registered after age 13.

We used Cox proportional hazards regression to model the associations. Cox regression is used to analyze time-to-event data, and it models the hazard rate, $h(t)$ of an outcome at time t, as a function of the baseline hazard and specified covariates:

$$h(t) = h_0\,(t) \exp(\,\beta_1 x_{i1} + \beta_2 x_{i2} + \cdots + \,\beta_n x_{in})$$

Cox regression produces a Hazard Ratio (HR) for each covariate, which is an estimate of the relative hazard of the outcome on one level of the covariate, compared to the reference level (e.g., the relative risk of the event occurring in the exposed group compared to the unexposed). Unlike a standard regression model which includes a constant, Cox regression does not make assumptions about the shape of the baseline hazard nor is it explicitly estimated. The model assumes that each covariate has a multiplicative effect in the hazards function that is constant over time (i.e., the proportional hazards assumption). Model assumptions were examined graphically.

The participants of both CATSS and the population-based sample were followed up from their 13th birthday until the date of first substance misuse event, emigration, death, or December 31, 2013, whichever occurred first. We used age as the underlying time-scale, and accounted for the non-independence of observations in families by using a cluster-robust sandwich estimator for standard errors. We also present separate coefficients for men and women.

All models were adjusted for birth year and sex. In the first step, associations were adjusted for covariates only. To account for psychiatric comorbidity, the second models further adjusted for externalizing psychopathology (diagnoses of ADHD and conduct disorders registered before age 13; parental rated symptoms of ADHD, ODD, and conduct problems at age 9/12).

Within-family regression models

We conducted within-family analyses using stratified Cox regression models within twin pairs in the CATSS sample and within clusters of full siblings in the population sample. In the context of Cox regression, each family is entered as a separate stratum, which allows for a separate baseline hazards for every family cluster. Thus, the model estimates whether the difference in the exposure within siblings is associated with 'survival time' in regards to the outcome (with a similar logic as described in Study I methods).

Within-family models were adjusted for covariates, and estimated first without and then with adjustment for externalizing psychopathology.

Study III

Between-individual regression models

In the population sample, we estimated the association between OCD (diagnosis registered any time in 1997-2013) and substance misuse outcomes, including alcohol-related disorders, drug-related disorders, substance use-related criminal convictions, and substance use-related deaths (all registered after age 15).

Associations were estimated with Cox proportional hazards regression models (see previous section), with age as the underlying time-scale. Participants were followed-up from January 1, 1997 or their 15th birthday, whichever occurred last, until the date of first substance misuse event, emigration, death, or December 31, 2013, whichever occurred first. All models were adjusted for sex and birth year. We also present estimates separately for men and women.

First, we estimated the associations adjusted for sex and birth year. Second, we excluded all individuals with a diagnosis of anxiety or depressive disorder to examine whether the association of OCD with substance misuse was independent of these comorbidities.

In the CATSS sample, we estimated concurrent and longitudinal associations between self-reported OCD symptoms and alcohol and drug dependence symptoms.

First, we investigated whether OCD symptoms were associated with substance dependence symptoms concurrently and longitudinally among participants who used alcohol or drugs. Second, models were estimated with adjustment for age 18 anxiety and depressive symptoms. Third, association between OCD symptoms and age 24 dependence symptoms was estimated

with adjustment for age 18 dependence symptoms. Models were estimated with linear regression. We used cluster-robust sandwich estimator for standard errors in all analyses, and adjusted the models for sex and birth year.

Study IV

Within-individual regression models

In Study IV, we estimated the association between SSRI treatment and substance misuse with stratified Cox proportional-hazards regression models, where each individual enters as a separate stratum, and the rate of substance misuse outcomes is compared during periods on- versus off-treatment [246]. Stratification produces a separate baseline hazard for each individual, and estimates whether the difference in exposure status within the individual is associated with the likelihood of outcome occurrence. Both the exposure and outcome were recurring: participants could switch from on- to off-treatment multiple times during the follow-up, but also experience the outcome more than once. Time-at-risk was reset to zero after each outcome event.

To account for potential time-varying effects of treatment duration, we further divided the on- and off-treatment periods in relation to initiation of SSRI treatment (Figure 2). Off-treatment periods consisted of periods of more than 30 days before treatment start and 0-30 days before treatment start. On-treatment periods consisted of 1-30 days, 31-120 days, and over 120 days after treatment initiation. We used the period more than 30 days before treatment start as the reference category. Study participants were followed-up until December 31st 2013, emigration, or death, whichever occurred first. Time periods in prison or in inpatient care were excluded.

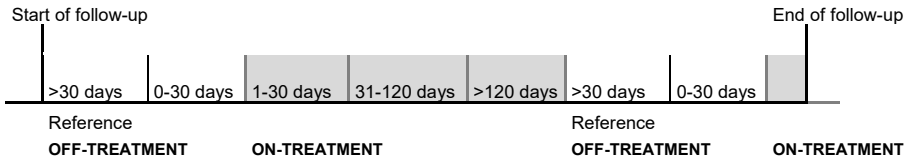


Figure 2 Division of treatment periods in relation to treatment initiation. Reproduced with permission from the copyright holder (Wiley).

We also estimated the associations of SSRI treatment and acute substance misuse outcomes in participants with and without a diagnosis of comorbid SUD (registered during the follow-up; acute intoxications were excluded from the definition of SUD, since they were included in the outcome). We estimated the models separately for alcohol use disorder and drug use disorders.

All models included age and concurrent use of non-SSRI antidepressants, benzodiazepines, and other psychotropic medications as time-varying covariates.

4.2.2.2 Factor analysis

In Study I, we used exploratory factor analysis to reduce the large number of diagnoses into a smaller set of underlying dimensions [247]. Factor analysis uses item-level correlations (e.g., correlations between different diagnoses) to produce statistical factors representing latent (i.e., underlying, not directly measured) variables. By using variables representing a latent factor structure, we aimed to maximize statistical power for within-sibling analyses, and to reduce multiple testing by using fewer exposure and outcome variables.

We used information from previous studies on the factor structure of psychopathology to determine the number of factors to extract. In addition, a parallel analysis was performed to empirically evaluate the number of potential underlying factors [248]. In the parallel analysis, random correlation matrices were simulated and factor analyzed, after which the resulting eigenvalues were compared to the eigenvalues of the observed data. Number of potential factors was determined based on the point of inflection, the eigenvalue greater than one rule, and examination of the curves in the scree plots for large drops in the actual data.

As previous studies suggest a non-orthogonal factor structure, we used maximum likelihood extraction with oblimin rotation in the factor analyses. Further, we used the root mean square error of approximation (RMSEA), standardized root mean square residuals (SRMR), and the Tucker-Lewis Index (TLI) to compare the fit of different factor solutions. Analyses were performed with 'psych' package within R [249].

In the main regression analyses of Study I, we did not use the obtained factor solution directly (i.e., utilize factor scores) but instead used dichotomous variables as proxies for the factors. Having any of the disorders loading on a given factor was coded as 1 and having no diagnoses within the factor was coded as 0.

4.2.2.3 Quantitative genetic structural equation models

Structural equation modeling was used in Studies I and III to estimate the contribution of genetic and environmental factors to the association between anxiety and depressive disorders or OCD and substance misuse. Structural equation modeling is a statistical method used to model covariance matrices. Similarly to factor analysis, structural equation modeling is used to model latent variables underlying the observed data. The relationship between latent variables are typically expressed via regression or path coefficients.

In quantitative genetic structural equation modeling, the latent variables of interest are the A, C, and E variance components (described in section 5.2.1.2). In this dissertation, a bivariate model was fitted in both Studies I and III using Cholesky decomposition and the direct-symmetric parameterization,

respectively. In the bivariate model, the latent factors A, C and E are estimated for both traits (e.g., OCD and substance misuse) individually, but also the extent to which they contribute to the covariance of the two traits [250].

Figure 3 shows a graphical representation of the twin/sibling bivariate structural equation model. As per conventions of structural equation modeling, latent factors are represented as circles and the measured traits as rectangular boxes. Numbers in the latent factor names indicate which trait it represents, e.g. A1 is the latent factor A for trait 1 (OCD), whereas A2 is the latent factor A for trait 2 (substance misuse), and so on. The double-headed arrows represent the assumed correlations across siblings. Assumed correlation between A-components of MZ pairs is 1, 0.5 in DZ twins/full siblings, and 0.25 in half-siblings. For all sibling types, C-components were assumed to correlate perfectly. Latent E factors are uncorrelated across sibling pairs.

One-headed arrows from latent factors to measured variables indicate path-coefficients that quantify the genetic or environmental variance unique to each trait (e.g., the arrow from A1 to OCD), or the genetic or environmental variance which is shared between both traits (e.g., the arrow from A1 to substance misuse – the genetic covariance between traits). Genetic and environmental correlation across traits can be calculated based on the path-coefficients. For instance, genetic correlation r_g is the genetic covariance between the traits divided by the square root of the product of the genetic variances of each trait [250].

Different models were compared using the Likelihood ratio test and the Akaike information criterion (AIC), where a lower Log likelihood ratio and AIC values indicate a superior fit.

When the measured variables were dichotomous, modeling was conducted using a liability-threshold model, where the categories (diagnosis present vs. not present) were assumed to reflect an imprecise measurement of an underlying normal distribution of liability [251]. In Study III, we also allowed for different thresholds for full and half-siblings, as substance misuse was more prevalent among half-siblings. All models were adjusted for birth year and sex. Modeling was performed with OpenMx statistical package (version 2.18.1) within R [252].

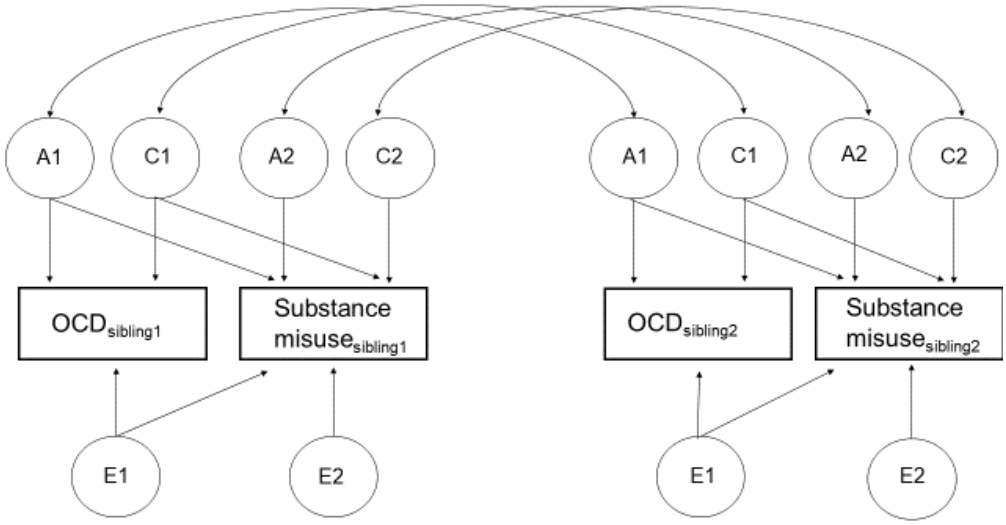


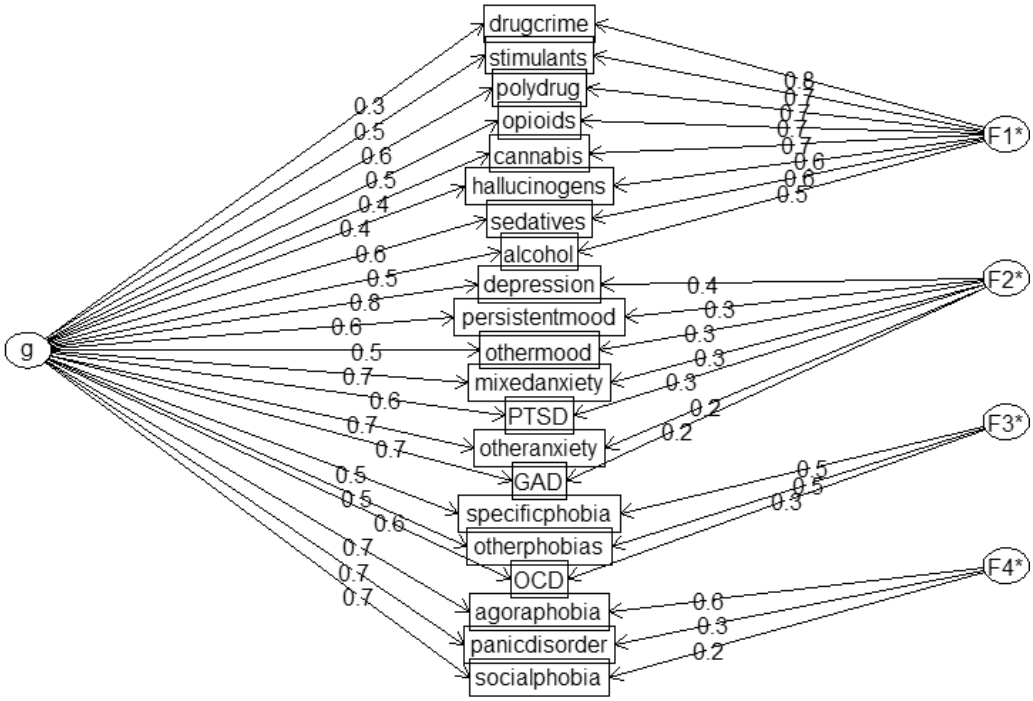
Figure 3 **Bivariate structural equation model of OCD and substance misuse**. Assumed sibling correlations for A-components: MZ twins 1.0, full siblings/DZ twins 0.5, maternal half-siblings 0.25; Assumed sibling correlations for C-components are 1.0 for all sibling types.

5 RESULTS

5.1 LIFETIME ASSOCIATION OF SUBSTANCE MISUSE WITH ANXIETY AND DEPRESSIVE DISORDERS (STUDY I)

Factor analysis

We computed a tetrachoric correlation matrix[3] between all study variables, which was used to fit models with one to four underlying factors (as suggested by previous studies and the parallel analysis). A four-factor model provided the best fit to the data. Because the between-factor correlations and within-factor loadings were high, a bi-factor structure was also tested, in which all items loaded on a general factor in addition to the four specific factors. The model fit and structure of item loadings were virtually identical in both four-factor models. Figure 4 shows the factor structure and loadings of the bi-factor model with four specific factors.



[3] Correlation matrix available in the Online Supplement (Figure S2) of the original article. https://doi.org/10.1017/S0033291719001788

Figure 4 **Bi-factor solution with standardized factor loadings**. **Reproduced with permission from the copyright holder (Cambridge University Press).** OCD = Obsessive-compulsive disorder; Persistent mood = Persistent mood disorders; Other mood = Mixed/Other mood-related disorders & Mood disorder, not otherwise specified; GAD = Generalized anxiety disorder; PTSD = Post-traumatic stress disorder; Mixed anxiety = Mixed anxiety and depression; Other anxiety = Anxiety disorder, not otherwise specified & Other anxiety disorders; Stimulants = Cocaine use disorder & stimulant use disorder; Hallucinogens = Inhalant use disorder & hallucinogen use disorder; Polydrug = Other psychoactive substance-related disorders (poly drug use); Drugcrime = Substance-use related criminal convictions.

The four underlying factors included: 1) a factor representing SUDs and substance-related crimes (substance misuse), and three anxiety/depression factors representing 2) depressive disorders and nonspecific, generalized anxiety; 3) specific phobias and OCD; and 4) panic disorder, agoraphobia and social phobia, respectively.

Depression (standardized factor loading: 0.8), generalized anxiety disorder (0.7), and mixed (0.7) and non-specified (0.7) anxiety disorders had the strongest factor loadings with the general psychopathology factor. Within the specific substance misuse factor, criminal offenses (0.8), stimulant use disorder (0.7), and opioid use disorder (0.7) had high factor loadings. Most of the anxiety and depressive disorders loading on the other specific factors had weak to moderate (0.2-0.5) factor loadings (since most of the variance was explained by the general factor).

Based on this factor solution, we created the main study variables which were used as proxies for the factors in the subsequent analyses. For instance, if a participant had any of the disorders loading on factor 1, a dichotomous variable 'substance misuse' was coded as 1. If the participant had none of the disorders loading on factor 1, the substance misuse variable was coded as 0, and so forth.

Lifetime association of anxiety and depressive disorders with substance misuse

Table 7 shows the results from between-individual and within-family regression analyses estimating the association of different anxiety/depressive disorder diagnosis groups with substance misuse.

The between-individual models showed an increased risk of substance misuse in those with all types of anxiety/depressive disorders, compared to individuals without these disorders. Based on the non-overlapping CIs, the highest relative risk for substance misuse was among individuals with generalized anxiety/depression, where the risk was over 5-fold compared to non-affected individuals. Adjusting for measured covariates had little effect on the estimates.

Table 7. *Risk ratios (95% CIs) of anxiety/depression dimensions with substance misuse*

	Generalized anxiety/ depression	Panic disorder/social phobia	Specific phobias/OCD
Between-individual models			
Model 1	5.14 (5.10–5.19)	4.32 (4.26–4.39)	2.81 (2.73–2.88)
Model 2	4.45 (4.41–4.49)	3.60 (3.55–3.66)	2.51 (2.44–2.58)
Men	3.69 (3.65–3.73)	3.11 (3.06–3.17)	2.05 (1.97–2.12)
Women	6.05 (5.96–6.15)	4.34 (4.24–4.44)	3.13 (3.01–3.25)
Within-family models			
Half-siblings	3.33 (3.22–3.44)	2.48 (2.35–2.61)	2.05 (1.87–2.25)
Full siblings & DZ twins	3.43 (3.37–3.50)	2.61 (2.53–2.69)	2.15 (2.04–2.26)
MZ twins	1.90 (1.39–2.61)	1.79 (1.04–3.08)	3.25 (1.22–8.66)

Note: Model 1 adjusted for sex and birth year; Model 2 adjusted for sex, birth year, socioeconomic covariates, and parental psychopathology; Within-family and sex-stratified models adjusted for sex, birth year, socioeconomic covariates, and parental psychopathology if there was variability in the covariate. DZ = Dizygotic; MZ = Monozygotic; Full and half-siblings include both same-sex and opposite-sex siblings.

Separate models for men and women revealed a higher relative risk of substance misuse among women with anxiety/depressive disorders as compared to men, and the difference was consistent for all types of anxiety/depressive disorders. In terms of absolute risks, 35.4% of men, and 19.2% of women with generalized anxiety/depression had comorbid substance misuse. In panic disorder and agora/social phobia, 36.1% of men, and 21.2% of women had substance misuse. Altogether 21.6% of men, and 15.6% of women with specific phobias/OCD had comorbid substance misuse.

The associations between anxiety/depressive disorders and substance misuse attenuated notably in the within-family regression analyses, when compared to the between-individual estimates. However, the increased risk of substance misuse persisted even within MZ twin pairs.

The contribution of genetic and environmental factors

The associations between substance misuse and the three anxiety/depression dimensions were best explained by additive genetic (A) and non-shared environmental (E) influences, with no evidence for the contribution of shared-environmental (C) factors.

Genetic factors explained 76% of the covariance between generalized anxiety/depression and substance misuse, and the remaining 24% was explained by non-shared environmental factors. Genetic and non-shared environmental correlations were 0.60 (95% CI 0.50–0.69) and 0.30 (95% CI 0.16–0.44), respectively.

Genetic (77%) and non-shared environmental factors (23%) best explained the association between panic disorder and agora/social phobia and substance misuse, with genetic and non-shared environmental correlations of 0.47 (95% CI 0.28–0.66) and 0.23 (95% CI –0.03 to 0.47).

Finally, the covariance between specific phobias/OCD and substance misuse was explained by genetic (53%) and non-shared environmental influences (47%), with genetic and non-shared environmental correlations being 0.24 (95% CI 0.00–0.47) and 0.29 (95% CI –0.03 to 0.60), respectively.

5.2 INTERNALIZING PSYCHOPATHOLOGY IN CHILDHOOD AND SUBSEQUENT SUBSTANCE MISUSE (STUDY II)

In Study II, we estimated the association between childhood anxiety and depression with subsequent substance misuse.

Table 8 shows the association of parent-reported anxiety and mood problems at age 9/12 and subsequent register-based substance misuse in the CATSS cohort.

Table 8. *Hazard ratios (95% CIs) for the association of childhood anxiety and mood problems with substance misuse in the CATSS sample*

	Anxiety problems	Mood problems
Total sample		
Between-individual		
Model 1	1.12 (0.51–2.25)	**2.28** (1.69–3.08)
Model 2	0.48 (0.22–1.06)	1.26 (0.87–1.85)
Within-family		
Model 1	0.80 (0.21-2.98)	**2.67** (1.24-5.74)
Model 2	0.44 (0.11–1.82)	2.16 (0.93–5.00)
Men		
Between-individual		
Model 1	1.58 (0.75-3.32)	**1.96** (1.34–2.90)
Model 2	0.60 (0.25-1.42)	0.99 (0.61–1.60)
Women		
Between-individual		
Model 1	0.37 (0.05-2.67)	**2.97** (1.82–4.84)
Model 2	0.22 (0.03-1.57)	**1.86** (1.11–3.11)

Note: Bolded coefficients indicate the 95% CI does not include 1. Model 1=Adjusted for sex and birth year; Model 2=Adjusted for sex, birth year, and symptoms of ADHD, ODD, and conduct disorder

Mood problems, but not anxiety, were associated with an elevated risk of substance misuse when adjusted for sex and birth year only. However, the association attenuated and the estimate became imprecise (i.e., with wide CIs) when externalizing symptoms were adjusted for. When the models were estimated separately for men and women, the association attenuated close to 1 in men, but remained clearly elevated in women.

Mood problems, but not anxiety, were associated with an increased risk of substance misuse when estimated within sibling pairs, although the CI did include 1 after adjustment for externalizing psychopathology.

Table 9 shows the results from the population-based sample, where we estimated the association of anxiety and depressive disorders registered before age 13 and subsequent substance misuse.

Both anxiety and depressive disorders were associated with an elevated risk of substance misuse, but the associations attenuated almost entirely once externalizing disorders were adjusted for. However, childhood-specific anxiety disorders (e.g., separation anxiety), were associated with a decreased risk after adjustment for externalizing disorders. Similarly to the CATSS data, the risk of substance misuse remained elevated even after externalizing adjustment in women, but not in men. Anxiety and depressive disorders were associated with a decreased risk of substance misuse in men, when externalizing disorder were accounted for.

In the within-sibling models, the estimates became imprecise, with wide CIs, although childhood depressive disorders remained clearly associated with an elevated risk substance misuse. The association attenuated (and the CI included 1) once externalizing disorders had been adjusted for.

Table 9. *Hazard ratios (95% CIs) for the association of childhood anxiety and depressive disorders with substance misuse in the population sample*

	Childhood-specific anxiety disorders	**Anxiety disorders**	**Depression**
Total sample			
Between-individual			
Model 1	1.36 (0.87–2.13)	**1.52** (1.35–1.73)	**2.75** (2.36–3.20)
Model 2	**0.56** (0.36–0.89)	0.99 (0.88–1.12)	0.98 (0.85–1.15)
Within-family			
Model 1	3.34 (0.68–16.47)	1.21 (0.86–1.68)	**2.17** (1.37–3.45)
Model 2	2.75 (0.54–13.97)	0.91 (0.64–1.29)	1.52 (0.93–2.51)
Men			
Between-individual			
Model 1	1.27 (0.72-2.23)	**1.34** (1.12–1.59)	**2.35** (1.93–2.87)
Model 2	**0.51** (0.29-0.90)	**0.80** (0.67–0.96)	**0.77** (0.63–0.94)
Women			
Between individual			
Model 1	1.55 (0.74-3.26)	**1.77** (1.49–2.11)	**3.65** (2.86–4.64)
Model 2	0.69 (0.33-1.45)	**1.29** (1.08–1.54)	**1.67** (1.33–2.16)

Note: Bolded coefficients indicate the 95% CI does not include 1. Model 1=Adjusted for sex and birth year; Model 2=Adjusted for sex, birth year, and ICD diagnoses of ADHD and conduct disorders

5.3 ASSOCIATION OF OBSESSIVE-COMPULSIVE DISORDER WITH SUBSTANCE MISUSE AND DEPENDENCE (STUDY III)

In Study III, we investigated the association between OCD and substance misuse-related outcomes in a population sample and in CATSS.

Table 10 shows the association of OCD with substance misuse outcomes in the population sample. OCD was associated with a substantially elevated risk of all types of substance misuse outcomes (Table 10). The risk of sedative- and other drug-related disorders was particularly elevated, with over a 9-fold and 6-fold increased risk, respectively, when compared to individuals without OCD. Women had a higher relative risk of opioid, stimulant, and other drug-related disorders, and substance-related criminal offenses than men, but the absolute risks for most outcomes were either similar in men and women, or lower in women.

Next, we estimated the associations of OCD with substance misuse outcomes when all individuals with anxiety and depressive disorders had been excluded (Table 11). A large majority (70%) of those with OCD had comorbid anxiety or depressive disorder. All associations attenuated, but remained clearly elevated – with the exception of substance-related criminal convictions.

In the CATSS sample, OCD symptoms at age 18 were associated with an increased risk of both alcohol and drug dependence symptoms in participants who reported using alcohol or drugs (Table 12). In people who used alcohol, a 1 standard deviations (SD) increase in OCD symptoms was associated with a 0.2-SD increase in concurrent alcohol dependence symptoms. Similarly, among those who reported using drugs, a 1-SD increase in OCD symptoms was associated with a 0.2-SD increase in concurrent drug dependence symptoms. Similar associations were observed in longitudinal analyses. The associations persisted, both concurrently and longitudinally, even after adjustment for anxiety and depressive symptoms. Further, OCD symptoms remained significantly associated with alcohol dependence symptoms at age 24 when age 18 alcohol dependence symptoms were accounted for. This model was not estimated for drug dependence symptoms due to insufficient sample size.

Table 10. *The absolute and relative risk of substance-related disorders, deaths, and criminal offenses among individuals with OCD, compared with unaffected*

	Individuals, no. (%)		
Outcome	**Individuals with OCD (n=27,342)**	**Unaffected general population (n=6,276,846)**	**HR (95% CI) adjusted for sex and birth year**
Any substance misuse outcome	5,444 (19.9)	359,393 (5.7)	3.84 (3.74-3.95)
Men	2,571 (21.9)	247,188 (7.7)	3.10 (2.98-3.23)
Women	2,873 (18.4)	112,205 (3.4)	4.75 (4.58-4.93)
Alcohol-related disorders	2,720 (10.0)	163,591 (2.6)	5.10 (4.91-5.30)
Men	1,449 (12.4)	112,223 (3.5)	4.78 (4.54-5.04)
Women	1,271 (8.1)	51,368 (1.7)	5.23 (4.94-5.53)
Acute alcohol intoxications	1,577 (5.8)	90,351(1.4)	3.40 (3.24-3.58)
Men	716 (6.1)	54,203 (1.7)	3.24 (3.01-3.49)
Women	861 (5.5)	36,148 (1.2)	3.43 (3.20-3.67)
Any drug-related disorders	3,279 (12.0)	100,165 (1.6)	6.78 (6.55-7.02)
Men	1,434 (12.2)	57,595 (1.8)	6.03 (5.72-6.36)
Women	1,845 (11.8)	42,570 (1.4)	7.60 (7.25-7.96)
Opioid-related disorders	618 (2.3)	21,810 (0.4)	5.93 (5.47-6.43)
Men	280 (2.4)	12,986 (0.4)	5.24 (4.65-5.90)
Women	338 (2.2)	8,824 (0.3)	6.77 (6.07-7.55)
Cannabis-related disorders	448 (1.6)	17,410 (0.3)	4.34 (3.95-4.77)
Men	300 (2.6)	13,396 (0.4)	4.26 (3.80-4.78)
Women	148 (1.0)	4,014 (0.1)	4.48 (3.80-5.29)
Sedative-related disorders	1,942 (7.1)	44,013 (0.7)	9.66 (9.22-10.11)
Men	734 (6.3)	20,411 (0.6)	9.51 (8.84-10.25)
Women	1,208 (7.7)	23,602 (0.8)	9.80 (9.24-10.39)
Stimulant-related disorders	495 (1.8)	18,999 (0.3)	5.04 (4.61-5.51)
Men	244 (2.1)	12,929 (0.4)	4.33 (3.82-4.92)
Women	251 (1.6)	6,070 (0.2)	5.84 (5.14-6.64)
Other drug-related disorders	1,620 (5.9)	49,547 (0.8)	6.33 (6.03-6.66)
Men	801 (6.8)	32,002 (1.0)	5.71 (5.32-6.12)
Women	819 (5.2)	17,545 (0.6)	7.12 (6.64-7.65)
Substance-related convictions	697 (2.6)	122,703 (2.0)	1.43 (1.33-1.55)
Men	511 (4.4)	106,848 (3.3)	1.27 (1.16-1.38)
Women	186 (1.2)	15,855 (0.5)	2.30 (1.99-2.66)
Substance-related deaths	161 (0.6)	27,479 (0.4)	2.53 (2.17-2.96)
Men	105 (0.9)	21,317 (0.7)	2.27 (1.87-2.75)
Women	56 (0.4)	6,165 (0.2)	3.28 (2.52-4.27)

Table 11. *Association of OCD with substance misuse outcomes after excluding individuals with anxiety and depressive disorders*

	HR (95% CI) adjusted for sex and birth year	
Outcome	**No exclusion**	**Excluding anxiety and depressive disorders**
Any substance misuse outcome	3.84 (3.74-3.95)	2.23 (2.08-2.40)
Alcohol-related disorders	5.10 (4.91-5.30)	3.58 (3.24-3.96)
Acute alcohol intoxications	3.40 (3.24-3.58)	2.03 (1.78-2.31)
Any drug-related disorders	6.78 (6.55-7.02)	4.35 (3.89-4.86)
Opioid-related disorders	5.93 (5.47-6.43)	3.05 (2.27-4.10)
Cannabis-related disorders	4.34 (3.95-4.77)	3.19 (2.51-4.07)
Sedative-related disorders	9.66 (9.22-10.11)	6.63 (5.56-7.89)
Stimulant-related disorders	5.04 (4.61-5.51)	3.06 (2.31-4.07)
Other drug-related disorders	6.33 (6.03-6.66)	4.37 (3.74-5.12)
Substance-related convictions	1.43 (1.33-1.55)	0.96 (0.81-1.13)
Substance-related deaths	2.53 (2.17-2.96)	1.74 (1.21-2.51)

Table 12. *Association of OCD symptoms at age 18 with substance dependence symptoms in participants who use alcohol/drugs*

	Exposure: OCD symptoms age 18		
	β (95% CI) adjusted for sex and birth year	**β (95% CI) adjusted for sex, birth year, age 18 anxiety & depression**	**β (95% CI) adjusted for sex, birth year, age 18 dependence symptoms**
Age 18			
Alcohol dependence symptoms			
In individuals using alcohol	0.19 (0.16-0.21)	0.11 (0.09-0.14)	
Drug dependence symptoms			
In individuals using drugs	0.19 (0.11-0.27)	0.12 (0.04-0.20)	
Age 24			
Alcohol dependence symptoms			
In individuals using alcohol	0.10 (0.06-0.14)	0.05 (0.00-0.10)	0.05 (0.01-0.09)
Drug dependence symptoms			
In individuals using drugs	0.15 (0.04-0.26)	0.11 (0.00-0.23)	NA

The contribution of genetic and environmental factors

In the population sample, the phenotypic (tetrachoric) correlation between OCD and substance misuse (a dichotomous composite variable indicating the presence of any substance-related disorder/criminal offense/death) was 0.27. The best-fitting model for full and maternal half-siblings included additive genetic (A) and non-shared environmental (E) components for both OCD and substance misuse. Additive genetic factors explained 56% of the covariance between OCD and substance misuse, and non-shared environmental factors explained 44%. The estimated genetic correlation between traits was 0.28 (95% CI: 0.24-0.32), and the non-shared environmental correlation was 0.27 (95% CI: 0.22-0.32).

In the CATSS sample, the phenotypic correlation between traits was 0.19. The best-fitting model for monozygotic and dizygotic twins included A and E components for both OCD symptoms and alcohol dependence symptoms. Additive genetic factors explained 68% of the covariance, and non-shared environmental influences explained the remaining proportion (32%). The estimated genetic correlation was 0.31 (95% CI: 0.23-0.40), and the non-shared environmental correlation was 0.10 (95% CI: 0.05-0.16).

5.4 ASSOCIATION OF SSRI MEDICATION WITH ACUTE SUBSTANCE MISUSE OUTCOMES (STUDY IV)

In Study IV, we investigated the association of SSRI medication with acute substance misuse outcomes (accidental poisonings, acute intoxications, and substance use-related offenses) in patients with anxiety and depressive disorders.

Rate of substance misuse events one year before and after first treatment initiation

First, as a descriptive analysis, we examined dynamic changes in substance misuse in relation to SSRI treatment initiation by calculating the absolute rate of events (per 1000 person-years) monthly for 12 months before and after the first SSRI treatment initiation. Individuals were censored at switching from on- to off-treatment, emigration, death, or at 12 months after the first treatment initiation, whichever occurred first.

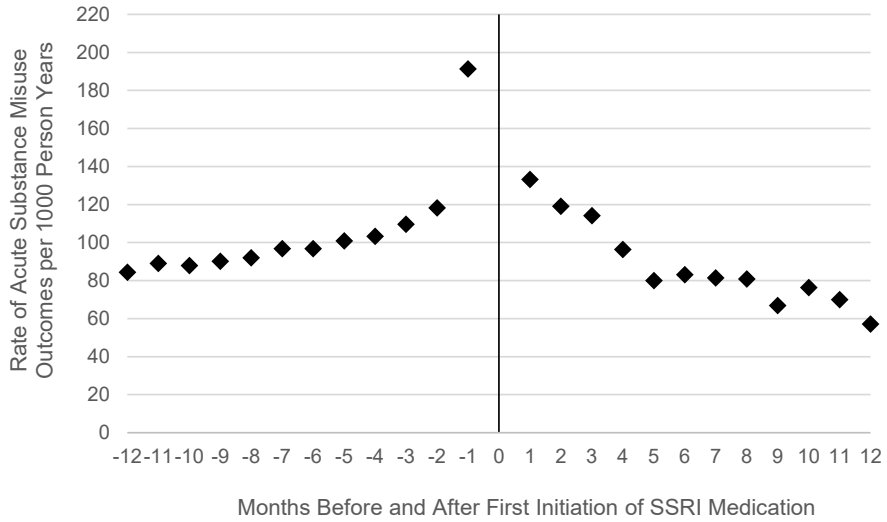


Figure 5 Rate of acute substance misuse outcomes 12 months before and after first initiation of SSRI medication. Reproduced with permission from the copyright holder (Wiley).

As shown in Figure 5, the absolute rate of acute substance misuse outcomes increased steadily during 12 months preceding the first SSRI treatment period, with a markedly sharp increase, from 79 to 146 events per 1000 person years, during one month before the treatment start. Substance misuse started to

decrease after treatment initiation, reaching a lower rate by 12 months than the rate at baseline.

Within-individual analysis

Table 13 shows results from the within-individual analysis. Within-individual models showed a 70% increased risk of acute substance misuse outcomes during the month preceding SSRI treatment, compared to the reference period over 1 month before treatment start. The on-treatment estimates were consistently lower than the 1 month pre-treatment estimate, but still elevated when compared to the reference period. The within-individual estimates did not attenuate as much as did the absolute rates due to the former being the average relative risk of substance misuse *within-individuals who experienced at least one event,* whereas the latter describes the number of overall events in the entire cohort, i.e., these estimates describe substance misuse on different levels of analysis.

Table 13. *Within-individual association of SSRI treatment with acute substance misuse outcomes in patients with a diagnosis of anxiety or depressive disorder*

	Days Before Treatment Initiation		Days After Treatment Initiation		
	>30 Days	0-30 Days	1-30 Days	31-120 Days	>120 Days
Rate[a]	99.02	153.30	113.64	98.24	61.45
HR (95% CI)[b]	ref.	1.70 (1.62-1.78)	1.29 (1.23-1.37)	1.30 (1.24-1.35)	1.24 (1.18-1.30)

[a] Rate of acute substance misuse outcomes per 1000 person years.

[b] Adjusted for time-varying covariates: age, use of non-SSRI antidepressants, benzodiazepines, and other psychotropic medications.

ref.=reference period

The risk of substance misuse was elevated during the 1-month period before treatment start in individuals with a diagnosis of comorbid alcohol use disorder and drug use disorders, but also in patients who did not have a substance use disorder diagnosis (Table 14). The 1-month pre-treatment risk was more elevated in people with a comorbid alcohol use disorder than in those with drug use disorders. The associations attenuated after SSRI treatment initiation in people with alcohol use disorders, but based on overlapping CIs, the risk for substance misuse remained similar to the 1-month pre-treatment period in people with drug use disorders.

Table 14. *Within-individual association of SSRI treatment with acute substance misuse outcomes in patients with and without comorbid substance use disorder diagnosis*

	Days Before Treatment Initiation		Days After Treatment Initiation		
Diagnoses	**>30 Days**	**0-30 Days**	**1-30 Days**	**31-120 Days**	**>120 Days**
Anxiety/Depression without SUD (n=128,016)					
Rate[a]	36.89	72.74	51.19	43.95	28.01
HR (95% CI)[b]	ref.	2.04 (1.87-2.23)	1.41 (1.28-1.56)	1.41 (1.31-1.52)	1.24 (1.15-1.34)
Anxiety/Depression with Alcohol Use Disorder (n=11,978)					
Rate[a]	441.07	721.89	476.31	442.11	311.85
HR (95% CI)[b]	ref.	1.71 (1.60-1.84)	1.23 (1.13-1.33)	1.26 (1.19-1.34)	1.25 (1.16-1.34)
Anxiety/Depression with Drug Use Disorder (n=9,314)					
Rate[a]	671.37	785.73	753.07	668.62	489.41
HR (95% CI)[b]	ref.	1.28 (1.19-1.37)	1.18 (1.09-1.27)	1.18 (1.12-1.25)	1.26 (1.18-1.35)

a Rate of acute substance misuse outcomes per 1000 person years.

b Adjusted for time-varying covariates: age, use of non-SSRI antidepressants, benzodiazepines, and other psychotropic medications.

SUD=any substance use disorder

ref.=reference period

6 DISCUSSION

The aim of this dissertation was to examine the association of depression, anxiety, and OCD with substance misuse using data from the Swedish population registers and from a longitudinal twin cohort study. The four sub-studies utilized genetically informative and quasi-experimental designs to test competing hypotheses for the underlying mechanisms, namely, whether the associations were best explained by shared genetic/environmental factors or whether there was evidence for the associations being independent of underlying genetic and shared environmental influences, which could be interpreted as compatible with a causal effect.

6.1 PATTERNS OF COMORBIDITY ACROSS DEVELOPMENT

Sub-studies of this dissertation demonstrate that depression, anxiety, and OCD are associated with a substantially elevated risk of substance misuse, during the lifetime as well as during the developmental period from childhood to early adulthood.

Depression
The association of depression with SUDs had been well established in previous survey studies [116-126], which we further confirmed using register-based data showing a 2 to 5-fold increased risk of substance misuse in people with depression compared to unaffected individuals. Previous studies have often overlooked comorbidity across the internalizing and externalizing spectrum, which can confound the association between depression and substance misuse. In Study II, we found that the association between childhood depression and subsequent substance misuse remained elevated in women even after adjusting for childhood ADHD and conduct disorder, which are strong predictors of substance use problems [23, 89, 90]. Furthermore, in Studies I and II, estimates for the association with substance misuse were consistently higher for depressive disorders than for anxiety disorders, in line with some of the earlier findings [120, 132]. Since these patterns emerged during the lifetime, as well as longitudinally from childhood to late adolescence, depression appears to be an important correlate of substance misuse.

Anxiety disorders
Anxiety disorders have a complicated relationship with substance misuse. Some anxiety disorders such as generalized anxiety disorder (GAD) seem to occur together with depression more frequently than do other anxiety

disorders. In the p-factor literature, GAD is often included in the lower-order 'distress' factor with depression, whereas other anxiety disorders cluster together under the 'fears' factor [78]. In Study I, this 'distress' factor had the strongest lifetime association with substance misuse. However, it is possible that the association was mainly driven by other disorders within the factor, such as depression, and the not due to the contribution of GAD. Moreover, we replicated some notable findings from previous survey-based studies: panic disorder and social anxiety disorder were strongly associated with substance misuse [117, 120], whereas specific phobias/OCD were associated with the lowest risk of substance misuse out of the disorder factors [116, 117, 120], although the risk was still clearly elevated. Some of the associations may have been explained by psychiatric comorbidity. In psychiatric specialist services, having more than one diagnosis is very common, and the estimates presented in Study I do not represent associations with substance misuse that are independent of any other psychiatric disorders. To elaborate, although there was an association between, for instance, specific phobias and substance misuse, it is possible that patients with specific phobias had other comorbidities which may explain the observed association.

In Study II, we found that childhood anxiety disorders were associated with an elevated risk of subsequent substance misuse, but the association depended on the measurement and type of anxiety disorder. Clinical diagnoses were associated with a significantly increased risk of substance misuse, and the association remained elevated in women even after accounting for childhood ADHD and conduct disorders. On the other hand, there was no clear evidence that parent-reported anxiety symptoms or 'childhood-specific' anxiety disorders (i.e., separation anxiety, childhood social anxiety) were associated with substance misuse. It should be noted, that the estimates for the non-significant associations were imprecise, and the exact magnitude of the association was thus unclear – in other words even though the CIs were wide and associations were statistically non-significant, we cannot rule out that the association exists, but can merely conclude that our data were not sufficient, because of measurement error or otherwise, to detect it [253]. Another interesting finding in Study II was that once externalizing disorders had been accounted for, anxiety disorders were associated with a *decreased* risk of substance misuse in men. This suggests that there is notable shared variance between anxiety and externalizing disorders, which is mainly responsible for driving the association between anxiety and substance misuse. The independent effect of anxiety disorders on substance misuse may in fact be protective, at least in men. In these analyses, however, it is important to consider that the maximum age at the end of follow-up was 21 or 29 years. Previous studies suggest earlier-onset SUDs to have distinct characteristics as compared to adult-onset SUDs [254], which may have affected the observed associations.

Obsessive-compulsive disorder

OCD was associated with a substantially increased risk of all types of substance misuse outcomes in the population-based sample, corroborating previous findings from epidemiological surveys [116, 173-177]. Particularly elevated associations were observed for some specific drug-related disorders such as sedative use disorder, with over a 9-fold increased risk compared to unaffected population controls. This finding requires further investigation. It is possible that people with OCD are initially prescribed sedatives by their physician, eventually leading to misuse, or alternatively, that sedatives are acquired elsewhere for 'self-medication' purposes. Comorbidity with internalizing spectrum disorders was pervasive, as approximately 70% of people with OCD also had a diagnosis of anxiety or depressive disorder. One of the important findings in Study III was that the elevated risk of substance misuse outcomes persisted, with the exception of criminal offenses, even after individuals with anxiety or depressive disorders were excluded, which suggests that the link between OCD and substance misuse was independent and not driven by internalizing comorbidity. Interestingly, OCD had a relatively weak association with criminal offenses. The association might be due to surveillance bias, whereby clinical diagnoses are more easily detected because of the pre-existing contact with the health-care system. Alternatively, some people with OCD may lack traits such as high impulsivity [255], which is associated with an increased risk of criminal offending.

We found support for the notion that once people with OCD start using substances, they are at an increased risk of developing addiction. For both alcohol and drugs, higher OCD symptoms were associated with increased dependence symptoms, in line with the smaller scale laboratory-based study which was among the first to suggest that OC-traits may be related to cocaine use escalating into dependence [169]. Importantly, these associations were observed both concurrently and longitudinally, and were not explained by anxiety and depressive symptoms.

Sex-differences

A consistent finding across sub-studies was the higher relative risk of substance misuse in women with internalizing disorders compared to men. The higher effect sizes likely reflect the lower overall prevalence of substance use problems in women, where even a modest absolute increase in individuals with substance misuse can produce a large relative risk estimate. In register-based data, sex-differences might also be produced by differences between men and women in treatment seeking, as well as in diagnostic accuracy. Nevertheless, it is possible that internalizing psychopathology increases vulnerability for substance use problems especially in women [120, 154].

In Study II, we investigated this question further, and found a pattern suggesting sex-specific developmental pathways to substance misuse. The developmental pathways framework includes the concept of equifinality, which denotes that a common outcome such as SUD can develop over time

from different starting points [256]. When externalizing disorders were accounted for, anxiety and depressive disorders were still associated with an elevated risk of substance misuse in women. In men, comorbid externalizing psychopathology appeared to be the main driver for the association, and in fact, the independent association of internalizing disorders showed a decreased risk of substance misuse. The sex-specific pathways to substance misuse are in line with a previous smaller scale study from the US [140]. Taken together, these findings suggest that the internalizing pathway to substance misuse may be more prominent in women than in men.

6.2 THE ROLE OF GENETIC FACTORS

Our findings show that genetic factors have a major role in explaining the association of depression, anxiety, and OCD with substance misuse, with genetic influences accounting for at least 50% of the covariance across the board. Further, there was significant overlap between the genetic factors influencing internalizing disorders and the genetic factors influencing substance misuse. The relatively large genetic correlation between depressive disorders and substance misuse found in Study I is in line with previous quantitative and molecular genetic studies [133-143]. Further, anxiety disorders such as panic disorder also have substantial genetic overlap with substance misuse, which corroborates findings from an earlier Norwegian twin cohort study using interview-based assessments [159].

In Study III we found evidence supporting shared genetic factors in OCD and substance misuse. Approximately 56-68% of the covariance was explained by genetic factors, and genetic factors of the two traits showed moderate overlap with correlations ranging from 0.28 to 0.31. The validity of the results was increased by the use of study designs with different modeling assumptions, the classical twin design and the sibling design, which revealed relatively similar results. Further, the findings were consistent when using self-reported, continuous measures and clinical diagnoses. Interestingly, the estimates were similar in both data despite the different contexts in which the traits were measured, suggesting that the relative contribution of genetic factors is rather stable. There are only a few previous family-based studies on the topic. A handful of familial co-aggregation studies showed mixed findings [178, 183, 187], but their study designs were not adequate for separating genetic influences from shared environmental influences. A molecular genetic study using GWAS summary statistics indicated a negative genetic correlation between OCD and SUDs [188], but validity of the reported associations was limited because of the low number of OCD cases in the original GWAS [257]. Our well-powered samples with robust, complementary research designs strongly suggest a shared genetic component for OCD and substance misuse.

The positive genetic correlation between OCD and substance misuse is consistent with the hypothesis of a shared genetic predisposition, e.g.

compulsivity or an overreliance on the habit-learning system [167]. Nevertheless, a genetic correlation in itself is not sufficient to confirm the hypothesis. First, the correlation might reflect some other genetically influenced trait instead of the hypothesized compulsivity endophenotype. Second, while a genetic correlation is often interpreted as evidence for a shared genetic etiology, i.e. horizontal pleiotropy, it may also arise due to genetic influences of one trait increasing the risk of the other trait indirectly (vertical pleiotropy, or phenotypic mediation) [258]. For instance, a genetic correlation between OCD and substance misuse may arise because genetic predisposition for OCD increases the risk of substance misuse via self-medication, without there being any shared genetic variants directly affecting the two phenotypes. GWA studies on OCD are merely starting to gain momentum: the number of affected cases remains relatively low, resulting in insufficient statistical power to detect associated genetic variants with very small effect sizes (which are the norm in psychiatric genetics). Once the number of OCD cases in GWA studies catches up with other psychiatric disorders, molecular genetic methods, such as genetic colocalization, can be used to interrogate whether the genetic correlation between OCD and substance misuse reflects vertical or horizontal genetic pleiotropy [259].

6.3 DO INTERNALIZING DISORDERS CAUSE SUBSTANCE MISUSE?

To evaluate whether there is evidence to support the hypothesis that anxiety, depression, and OCD causally increase the risk of substance misuse, revisiting some of the requirements for causal inference in observational studies is in order. First, there should be an association between the exposure and outcome. The sub-studies of this dissertation clearly demonstrate a positive association between all of the exposures and substance misuse. Second, the exposure should precede the outcome in time. The longitudinal results from Studies II and III show that anxiety and depressive disorders as well as OCD predict subsequent substance use problems. Third, the associations should not be explained by measured or unmeasured confounders.

For depression, the association with substance misuse appears to be independent of externalizing psychopathology in women. Moreover, we found at least a 2-fold increased risk of substance misuse in within-sibling (Study II) and within-MZ twin (Study I) analyses. This finding means that the sibling who had depression was twice as likely to have substance misuse compared to their unaffected sibling. As sibling comparison rules out many unmeasured confounders, the association of depression and substance misuse seems robust. However, while the within-family estimate remained elevated, the association became statistically non-significant after adjustment for externalizing disorders in Study II. Further, Study I examined lifetime

associations and did not consider the order of onset in depression and substance misuse.

The association of anxiety disorders with substance misuse was less robust to various adjustment methods. In Study II, once externalizing disorders were adjusted for, only clinical diagnoses of non-childhood specific anxiety disorders remained associated with substance misuse in women. The estimate for the association became imprecise and non-significant in the within-family analyses. In Study I, panic disorder/social anxiety disorder remained associated with an elevated risk of substance misuse even within MZ-twins, but the order of onset remained unclear because of the study design.

The potential causal link between anxiety/depression and substance misuse was also supported by the results of Study IV, where the rate of intoxications, overdoses, and substance-related criminal offenses steadily increased during a 12-month period preceding the first SSRI treatment initiation, possibly reflecting the emergence or worsening of substance use problems concurrently with anxiety/depression. Once SSRI treatment was initiated, rate of substance misuse events started to decrease. Findings were similar in within-individual analyses, which showed a consistently lower risk of substance misuse on-treatment, compared to the particularly high risk period 1 month before treatment start. Assuming SSRIs medication reduced anxiety and depression but did not directly influence substance misuse, the results suggest that anxiety/depression may increase the risk of substance misuse via self-medication. While the risk of substance misuse was attenuated on-treatment, SSRI medication did not fully resolve the elevated risk of substance use problems. This may be due to non-response to SSRIs in some individuals [260], or alternatively, due to SSRIs not necessarily increasing sustained abstinence even if the quantity of substance use is reduced [200].

For OCD, the results of Study III indicate that the association with substance misuse was not explained by the primary psychiatric comorbidities, anxiety and depressive disorders. Moreover, the significant non-shared environmental correlations across the two traits can be interpreted as consistent with the causal hypothesis [237]. A limitation of Study III in the context of causal inference was that we did not have access to measures of OCD symptoms at an age preceding the typical onset of substance use, as we did for anxiety and depression. Thus, we cannot exclude the possibility of reverse association. Nevertheless, there is little to no empirical evidence of 'substance induced' OCD in the scientific literature.

As discussed in the Introduction, a single study, particularly when using observational data, is unlikely to be able to demonstrate causality. Therefore, the findings of this dissertation should be considered in concert with previous literature. If similar findings are noted in several studies using different types of quasi-experimental designs, this increases confidence that the effect may indeed reflect a causal association. The evidence for a causal association between depression and substance misuse is relatively strong. In addition to the results of this dissertation, several prospective twin cohort studies show

that the association between depression and substance use problems is not explained by shared familial factors, and may reflect a direct effect [144-146]. A recent Mendelian randomization study, which relies on entirely different set of assumption from twin studies, also found evidence of a causal effect of major depression on alcohol dependence [146]. The findings of Study I together with a Norwegian twin study [159] imply that anxiety disorders, particularly social anxiety disorder, may directly increase the risk of substance misuse, but in the absence of studies with quasi-experimental designs other than the twin design, the conclusion remains tentative. To our knowledge, Study III was the first to test the hypothesis of a direct effect of OCD on substance misuse – therefore the finding remains preliminary and need to be replicated with different quasi-experimental designs and in other datasets.

In conclusion, findings of this dissertation provide evidence consistent with a hypothesis of depression, anxiety, and OCD causally increasing the risk of substance misuse. When interpreted in the context of previous literature, depression is the only exposure with robust support. It should be noted, that although quasi-experimental studies are useful for disproving a causal hypothesis, they cannot be used to explicitly confirm causality. This issue is discussed further in the limitations-section.

6.4 CLINICAL IMPLICATIONS

The results of this dissertation offer some implications for prevention of substance misuse, and for the treatment of patients with internalizing disorders and SUDs. First, the detection and treatment of childhood psychopathology is a potentially relevant starting point for preventing substance misuse. Childhood depression and mood-related problems in particular were robust correlates of subsequent substance misuse. Early intervention may prevent the onset of substance use problems, although our studies cannot support this conclusion for certain. Nevertheless, providing timely, evidence-based treatment for children and adolescents with depression is crucial because the disorder can cause disruptions for important developmental tasks, such as education and social relationships [261].

Asking about substance use when treating patients with internalizing disorders should be a routine part of clinical practice, even if the patient presents with OCD, which some clinicians might consider indicating a low-risk for substance use problems [179]. It is also important to keep monitoring for signs of emerging substance use problems, since internalizing disorders may increase the risk of new onset substance misuse, even if there were no problems present during the initial assessment. Moreover, the results of Study IV suggest that while the risk of acute intoxications, poisonings, and substance-related criminal offenses was attenuated on-treatment when compared to the high-risk period 1 month before treatment start, the risk did remain elevated even after treatment initiation. Patients with a history of

intoxications and overdoses should be offered enhanced support which targets substance use problems specifically, because SSRI treatment might not be sufficient to reduce the risk of adverse outcomes in some patients.

Our findings lend support to previous RCTs showing SSRIs to be effective in reducing substance misuse in patients with comorbid depression and alcohol use disorder [202, 203]. SSRI treatment seemed beneficial also in patients who did not have a SUD diagnosis. The effectiveness of SSRIs in those with comorbid drug use disorders was less clear: associations did not attenuate on-treatment in a similar fashion as was observed in other patient groups. Prior RCTs also show no evidence for SSRIs in reducing substance use in drug use disorders [204]. However, the associations were difficult to interpret as the effect sizes did show some attenuation, but the CIs for the off- and on-treatment periods were overlapping. Patients with comorbid drug use disorders had the highest baseline rate of substance misuse, possibly because they use "riskier" substances, i.e., substances with a higher likelihood of leading to hospitalizations and contacts with the police, more frequently and in higher doses than others. Because of the high rate of substance misuse events off-treatment, a large decrease in the absolute number of events on-treatment would be required to produce a notable attenuation in the *relative* risk estimate. Therefore, it is possible that SSRIs do work in reducing drug use, but the magnitude of the effect in reducing these acute outcomes may depend on the baseline severity of the SUD and the frequency of use of high-risk substances.

If a shared causal endophenotype between OCD and SUDs exists, it may have important implications for treatment of SUDs. If compulsivity is a key concept for explaining why substance use escalates into dependence, and how problematic substance use patterns are maintained, similar treatment approaches that are effective in treating OCD might also work for SUDs. Many patients with OCD have a good treatment response to a form behavioral therapy called exposure and response prevention (ERP), which involves graded exposure to compulsion-provoking stimuli/situations and prevention of the associated compulsions [262]. Most SUD treatments, in contrast, advocate for total avoidance of drug cues (i.e., avoiding situations that may lead to temptation to use substances). This approach is often not feasible in the long-term. It is very difficult to lead a normal life while avoiding all possible situations that may serve as triggers for relapse. There have been attempts to translate ERP to substance use treatment in the past, with disappointing results [263]. However, updated treatment protocols based on animal research are promising [264], suggesting that abandoning ERP may have been premature. Nevertheless, there is a need for more robust evidence in humans that a link between obsessive-compulsive traits and SUDs exists before moving on to larger scale clinical trials.

6.5 LIMITATIONS

Coverage and validity of register-based data

The primary strength of the register data is that is allows for utilizing large, population-based samples with prospective and uniformed data collection which minimizes the risk of selection, recall, and report biases. On the other hand, the NPR can only capture treatment-seeking individuals who required treatment from the psychiatric specialist services. The majority of common mental health disorders are treated in primary care [265], which is not covered by the NPR. Further, the NPR does not cover private clinics, social services, prison services, or non-governmental agencies, which also provide mental health and substance abuse treatment in Sweden [266]. This leads to overrepresentation of more severe psychopathology in our data, as well as diagnostic misclassifications. Similarly, the crime registers do not cover all committed crimes since a large number of crimes remain unrecorded by the police and the criminal justice system [268]. Some people never seek treatment nor have any contact with the police, and cannot be captured with register data.

When interpreting the associations based on register data, it is important to keep in mind the potential surveillance bias, whereby substance use disorder is more likely to be detected in those who already have a contact with health care services, which can inflate effect sizes. To partially address this issue, we also included substance use-related criminal offenses in our definition of substance misuse. Since the criminal justice system is independent of health care, common method bias is reduced. Moreover, people with comorbidities are more likely to end up being treated in psychiatric specialist services, which can likewise inflate the associations between disorders. While rates of comorbidity are typically higher in register-based data as compared to survey samples, some studies suggest that the underlying etiological factors (e.g. genetic factors) are likely to be largely generalizable across mode of assessment [267].

Another issue concerns the timing of diagnoses. The date of the first registered diagnosis does not correspond well with disorder onset, since there can be large gaps in time between the period psychopathology first emerges and when the individual seeks treatment. The analyses of the population sample of Study II in particular should be interpreted with this caveat, because it is likely that many individuals were misclassified as not having childhood anxiety/depression because they received a diagnosis later in life.

The validity of diagnoses in the NPR is generally good [219], and the validity of OCD diagnoses is excellent [269]. However, the ICD codes for SUDs and anxiety/depressive disorders are yet to be formally validated. Studies examining the validity of psychiatric diagnoses in other Nordic patient registers have found adequate agreement between registered SUD diagnoses and diagnoses based on structured interviews by external examiners [270]. Validity of diagnoses is an important issue to consider when interpreting

within-family estimates, because diagnostic misclassification may introduce bias which appears as evidence for genetic confounding in within-family analyses [115].

Finally, in Study IV it is possible that the dispensed medications were not consumed, and therefore all estimates should be regarded as intention-to-treat, which may produce attenuated effect sizes [271]. Because the treatment periods were estimated based on the 90-day rule and median lengths between prescriptions, there is likely imprecision regarding the periods when individuals were exposed to SSRI medication. As we did not have access to the diagnosis the SSRI was indicated for, the sample is clinically heterogeneous, and the anxiety or depressive disorder diagnosis before first treatment initiation does not necessarily capture the specific disorder SSRI was prescribed for.

Coverage and validity of the CATSS data

The CATSS is an exceptionally large twin cohort study, with assessments spanning from childhood into adulthood which allows for investigating psychopathology from a developmental perspective. Similarly to all voluntary survey-based studies, those who participate are a selected group. Families with low socioeconomic status and children with the most severe psychopathology are unlikely to be well covered by the CATSS. The use of both register data and the CATSS in the present dissertation offered complementary perspectives to the studied phenomena, since both types of data have their distinct strengths and weaknesses in terms of measurement and selection biases. The CATSS data offered more valid estimates for the longitudinal associations, since the timing of the exposures and outcomes did not rely on the date the individual first sought treatment. Moreover, with the use of CATSS, we had access to data on individuals with less severe psychopathology, who are less likely to be present in the NPR. Since findings based on register data and the CATSS were generally in agreement, this increases confidence in the validity of our results.

Study drop-out is common in cohort studies, and this was also the case in the CATSS sample. Individuals experiencing mental health problems are more likely to drop out, which may have led to attenuation in the longitudinal associations in Study III. Yet, selective dropout does not necessarily lead to invalid statistical inferences [272]. Further, since we restricted the CATSS cohort to participants who used alcohol or drugs, this may have resulted in selection of individuals with higher levels of psychopathology, and inflated the concurrent associations. The decision to include only people who used alcohol or drugs was made based on how to best address the research question (i.e., were OCD symptoms associated with substance use progressing into dependence). It remains unclear how OCD is related to transitions between different stages of substance use (e.g. from initiation to use and dependence) which future studies are encouraged to investigate.

Finally, although the factor structure and neuropsychiatric sub-scales of A-TAC are well validated [222, 223], psychometric properties of the mood and

anxiety problem scales have not been examined. The mood problems scale includes a variety of symptoms and problematic behaviors and may not capture primarily depression. Parents are also more accurate at identifying externalizing than internalizing symptoms in their children, which may produce bias [273]. The validity of the BOCS-scale may have been reduced with the exclusion of three items that did not describe the core OCD phenotype.

Causal inference

Despite the increased validity of quasi-experimental research designs compared to the conventional observational study design, they cannot be used to explicitly demonstrate causality. In the case of the within-family design and the twin design, a significant association within MZ-twins or a non-shared environmental correlation merely shows that the association between the exposure and outcome was not explained by genetic and environmental factors co-twins share. The twins are individuals with unique life experiences, and one or several of these unique elements may explain the observed association. For instance, experiencing trauma is associated with both internalizing disorders and SUDs [274], and the study design does not rule out the effect of variables that make twins dissimilar. Further, the decreased risk of substance misuse events when on-SSRI treatment compared to the 1-month pre-treatment period does not confirm a causal effect. Instead, there may be unmeasured, time-varying factors that are not accounted by the study design, such as instructions from a clinician to abstain from using alcohol and other substances during SSRI medication, which explain the change in the risk of substance misuse, rather than SSRI treatment itself. There were many clinical factors we were unable to account for, such as psychosocial treatment and clinical visits, which were likely to confound our estimates. Therefore, our results did not capture treatment effect specific to SSRIs, but reflected the combined effect of SSRI and receiving treatment in general.

6.6 CONCLUSIONS

Depression, anxiety, and OCD are important correlates of substance misuse across development. There was evidence to suggest these disorders might increase the vulnerability for substance misuse particularly in women. Genetic factors play a major role in explaining comorbidity, but the associations were not entirely explained by familial confounding. This pattern of results suggests that the relationship between internalizing disorders and substance misuse partially reflects shared etiology, in line with theories such as the p-factor model, but the findings were also consistent with (partially) direct effects between the disorders as proposed by the self-medication hypothesis. Thus, it appears that the comorbidity of internalizing disorders and substance misuse arises via several, not mutually exclusive mechanisms.

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