From the DEPARTMENT OF CLINICAL NEUROSCIENCE
Karolinska Institutet, Stockholm, Sweden

WHEN ADHD AND SUBSTANCE USE DISORDERS COEXIST

Etiology and Pharmacological Treatment

Charlotte Skoglund

Karolinska Institutet

Stockholm 2015

Published by Karolinska Institutet
Printed by Eprint AB 2015
 ISBN 978-91-7676-074-1

People say: Get sober, use your willpower. I say: Try to use your willpower when you have diarrhea.

Ace Frehley, Rock & Roll Hall of Fame 2014

To: Lena and Kim, two mothers who rock

WHEN ADHD AND SUBSTANCE USE DISORDERS COEXIST

Etiology and Pharmacological Treatment

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Charlotte Skoglund M.D.

Principal Supervisor:
Associate Professor
Henrik Larsson, PhD
Karolinska Institutet
Department of Medical Epidemiology and Biostatistics

Co-supervisor:
Professor
Johan Franck, MD, PhD
Karolinska Institutet
Department of Clinical Neuroscience
Centre for Psychiatric Research and Education

Opponent:
Associate Professor
Timothy Wilens, MD, PhD
Harvard Medical School
Department of Psychiatry

Examination Board:
Professor
Cecilia Magnusson, MD, PhD
Karolinska Institutet
Department of Public Health Sciences

Professor
Jari Tiihonen, MD, PhD
Karolinska Institutet
Department of Clinical Neuroscience
Center for Psychiatry Research and Education

Professor
Fred Nyberg, PhD
Uppsala University
Department of Pharmaceutical Biosciences

ABSTRACT

Individuals with attention-deficit hyperactivity disorder (ADHD) and comorbid substance use disorder (SUD) comprise a significant group of patients displaying various degrees of personal suffering, entailing a substantial economical burden on society and presenting with challenges in treatment. The overlap between the two disorders is well established, but the underlying genetic and environmental mechanisms of their coexistence, are poorly understood. Furthermore, little is known about the effectiveness and safety of stimulant medication when ADHD and SUD coexist.

This thesis aimed to investigate the etiological relationship between ADHD and substance use problems (**Studies I** and **II)** and to explore doses of, and adherence to, pharmacological treatment for ADHD in the presence of SUD (**Studies III** and **IV**).

Quasi-experimental methods (**Study I**) were used to investigate whether smoking during pregnancy (SDP) is causally associated with ADHD in offspring. A family design (**Study II**) was applied to explore whether the overlap between ADHD and SUD arises from shared familial factors or is better explained by harmful effects of ADHD medication. Nationwide population-based cohort designs (**Study III**) were used to explore differences in and development of methylphenidate (MPH) doses in ADHD patients with and without SUD, and the impact of MPH doses on adherence to treatment in individuals with SUD (**Study IV**).

The results show that the increased risk for ADHD in individuals exposed to SDP was attenuated when familial factors were accounted for, suggesting that genetically transmitted factors explain the association. Furthermore, genetic relatedness to an ADHD proband predicts SUD in ADHD-free relatives suggesting that the co-occurrence of ADHD and SUD may be due to common genetic factors shared between the two disorders. The studies focusing on stimulant treatment show that patients with comorbid SUD are prescribed higher MPH doses and have higher adherence to MPH treatment compared to patients with ADHD only. In both groups MPH doses stabilized within two years of treatment. Higher doses of MPH were associated with increased adherence to treatment.

In conclusion, the collective findings from this thesis suggest that ADHD and SUD share common genetic underpinnings, that individuals with comorbid SUD receive higher stimulant doses than individuals with ADHD only, without signs of tolerance, and that stimulant doses predict adherence to pharmacological treatment in individuals with comorbid SUD.

LIST OF SCIENTIFIC PAPERS

I. **Familial Confounding of the Association Between Maternal Smoking During Pregnancy and ADHD in Offspring**
Charlotte Skoglund, Qi Chen, Brian M D′Onofrio, Paul Lichtenstein, Henrik Larsson
Journal of Child Psychology and Psychiatry, Volume 55, Issue 1, pages 61–68, January 2014

II. **Attention-Deficit/Hyperactivity Disorder and Risk for Substance Use Disorders in Relatives**
Charlotte Skoglund, Qi Chen, Johan Franck, Paul Lichtenstein, Henrik Larsson
Biological Psychiatry, Volume 77, Issue 10, pages 880–6, May 2015

III. **Methylphenidate Doses in Attention-Deficit/Hyperactivity Disorder and Comorbid Substance Use Disorders**
Charlotte Skoglund, Lena Brandt, Brian D'Onofrio, Catarina Almqvist, Henrik Larsson, Johan Franck
(Manuscript)

IV. **Predictors of Adherence to Methylphenidate Treatment in Patients with Attention-Deficit/Hyperactivity Disorder and Substance Use Disorder**
Charlotte Skoglund, Lena Brandt, Brian D'Onofrio, Catarina Almqvist, Maija Konstenius, Johan Franck, Henrik Larsson
(Manuscript)

CONTENTS

LIST OF ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
ASPD	Anti Social Personality Disorder
ATX	Atomoxetine
AUD	Alcohol Use Disorder
CD	Conduct Disorder
CDR	Cause of Death Register
CS	Central Stimulant
DA	Drug Abuse
ER	Extended Release
IR	Immediate Release
LISA	Longitudinal Database for Health Insurance and Labor
MBR	Medical Birth Register
MGR	Multi Generation Register
MPA	Medical Products Agency (Läkemedelsverket)
MPH	Methylphenidate
MR	Migration Register
NA	Noradrenaline
NICE	National Institute for Health and Care Excellence
NPR	National Patient Registry
ODD	Oppositional Defiant Disorder
OROS	Osmotic Release Oral System
PDR	Prescribed Drug Register
PIN	Personal Identification Number
SU	Stimulant Use Disorder
SUD	Substance Use Disorder
SDP	Smoking During Pregnancy

1 INTRODUCTION

It is well established that attention-deficit hyperactivity disorder (ADHD) and substance use disorders (SUD) frequently coexist (1, 2). Individuals with ADHD and comorbid SUD are a large group of patients often experiencing great personal sufferings, presenting with significant challenges in treatment and contributing to the economic burden on society (3). Despite the high comorbidity rates between ADHD and SUD (4), the genetic and environmental mechanisms underlying the overlaps are poorly understood. The central stimulant medication methylphenidate (MPH), the first choice for pharmacological treatment of ADHD, is effective and well tolerated in both children and adult with this condition (5, 6). However little is known about the efficacy and safety of MPH medication in individuals with comorbid SUD (7). As a consequence, the present clinical guidelines lack clear and consistent guidance on how this important and vulnerable group of patients should be treated (7-11).

This thesis aims to expand the previous limited understanding in this field by addressing the following questions:

a) How are ADHD and SUD etiologically related?

b) Are stimulant medication prescription patterns different in individuals with ADHD and SUD compared to those with ADHD only?

c) What factors influence adherence to stimulant treatment when ADHD and SUD coexist?

The additional goal of addressing these clinically relevant questions using large scale national population-based registers, is to be able to impact policy making and clinical guidelines that are lacking today. Hopefully, the increased knowledge of common biological underpinnings will also contribute to the societal acceptance of these impairing diagnoses, as medically valid and treatable disorders.

1.1 Attention Deficit Hyperactivity Disorder

"Every humming fly, every shadow, every sound, the memory of old stories will draw him off his task to other imaginations. Even his own imagination, entertains him with a thousand minor subjects." Melchior Adam Weikard 1775

The earliest reference in medical literature of what we today refer to as ADHD, by the German physician, Melchior Adam Weikard, dates back to 1775 (12). Different theories regarding underlying etiological mechanisms and developmental trajectories as well as different treatment strategies for ADHD have been investigated and debated over the years.

The need for systematic classification and statistical information of psychiatric symptoms led to the parallel development of two major diagnostic classification systems during the 1950s; the International Classification of Diseases (ICD) that in the sixth edition included a section on mental disorders and the Diagnostic and Statistical Manual of Mental Disorders (DSM).

1.1.1 Diagnostic Assessment

The ICD classification system is presented in its 10th edition (ICD-10) since 1997, preceded by previous Swedish versions, ICD-7 (1964-1963), ICD-8 (1969-1986) and ICD-9 (1987-1996). The DSM, published by the American Psychiatric Association, is the standard classification of mental disorders used by mental health professionals in the United States. Each DSM diagnostic label is associated with a diagnostic code, derived from the ICD system. The studies included in this thesis were designed and conducted based on ICD diagnoses derived from the DSM-IV definition of ADHD, including three different subtypes; predominantly inattentive type, predominantly hyperactive/impulsive type and ADHD combined type (13). The combined type of ADHD represents a more severe form that bears the greatest resemblance to the ICD-10 diagnosis of hyperkinetic disorder.
According to Swedish national guidelines, issued by The National Board of Health and Welfare (9), a diagnosis of ADHD in adulthood should be made by a specialist psychiatrist after a somatic and psychiatric evaluation including present and childhood history. Cognitive tests and assessments by a psychologist are recommended to chart and grade the specific areas of functional disabilities and impairment. Rating scales are often used as screening tools and supplementary support for the clinical interview.

1.1.2 Prevalence

ADHD is a common neurodevelopmental disorder affecting approximately 5-7% of children (14, 15) and 2.5% of adults (16, 17) worldwide. Public concerns that a shift in societal norms during the last decades may have contributed to the increase in prevalence rates of ADHD diagnoses, and as a consequence increased prescription rates of stimulant medication (18), are not supported by recent scientific literature (19, 20). The variability of prevalence estimates across different countries and time periods can instead be largely explained by specific methodological study characteristics (19, 21).

1.1.3 ADHD Across the Lifespan

Contrary to what was earlier believed, many functional impairments of ADHD persist into adulthood and approximately two thirds of all children with ADHD will continue to be affected throughout life (22). The symptoms and impairment might be differently displayed depending on age and life context. Typically, symptoms associated with hyperactivity and impulsivity diminishes over the years whereas symptoms of inattention tend to be more constant (23). In order to be able to provide age and context appropriate treatment, it is important to acknowledge the trajectory of ADHD symptoms across the lifespan, and to adequately address the common co-diagnoses, including SUD, that occur in adulthood.

In childhood, symptoms often become evident in the home or school environments. Children with ADHD more often experience failure in educational or academic settings (24), and poor or deviant social relationships (25) compared to same-aged children and un-affected siblings. Entering adolescence and early adulthood, the social and academic environment might become more complex and demanding, and the symptoms and impairment of ADHD can manifest into a plethora of adverse psychosocial outcomes. Young adults with ADHD often have a limited social circle (26), and are at increased risk of engaging in criminal activities and dropping out or being expelled from school compared to their peers (27). Importantly, exposure to substances of abuse becomes increasingly more common during the adolescent years (28) and having ADHD further increases the risk of early onset of substance abuse (29). The prevailing nature of ADHD is well established (30) and a majority of individuals with childhood ADHD will continue to experience less self-satisfaction in their personal and professional life (31) and are at increased risk of several adverse outcomes (31-33) including SUD (33) through the transition from adolescence into adulthood.

1.1.4 Etiology

The etiology of ADHD is still largely unknown. It is suggested that multiple genetic and environmental factors contribute to the age inappropriate and impairing symptoms of hyperactivity, impulsivity and inattention in affected individuals (34, 35).

Family and twin studies show that ADHD runs in families, suggestive of a strong genetic predisposition (36) with over 75% of the variance of the disorder explained by genetic factors (37). However molecular genetic studies have failed to reproduce the consistently high estimates of genetic contribution found in observational research (38). Also, some genetic variants have been suggested to have pleiotropic effects across a broad range of diagnostic categories (39, 40), i.e. that the same genetic variants constitute risk factors for several

different disorders. Still, it is not clear to what extent ADHD shares etiological underpinnings with other major psychiatric disorders, including SUD.

In addition to the strong genetic predisposition to ADHD, environmental factors account for an estimated 10% to 40% of the variance in liability to the disorder (35). Findings from imaging and pre-clinical studies have resulted in plausible biological theories indicating how exposure to addictive substances *in utero* may influence brain development (41, 42). Further, epidemiological studies have repeatedly, even after adjustment for measured confounders shown that maternal lifestyle factors are associated with ADHD in offspring (35, 43-46). In particular, maternal smoking during pregnancy (SDP), consistently associated with adverse offspring outcomes such as preterm birth and low birth weight (47), is often cited in the literature as an environmental risk factor for ADHD (48).

1.1.5 ADHD Treatment

It is well established that both non-stimulant (i.e. atomoxetine (ATX)) and central stimulant medication (i.e. MPH, amphetamine and/or dexamphetamine) effectively reduce the core symptoms of ADHD (49). Non-pharmacological treatment, most commonly cognitive behavioral-based interventions is an important component of the multimodal ADHD treatment approach and, according to a growing body of literature, best used as a complement to, not instead of, pharmacological treatment (50).

Non-stimulant treatment

Due to lack of abuse liability, non-stimulant treatment is often considered a safe and attractive treatment alternative when ADHD and SUD coexist (51). In fact, in the National Institute for Health and Care Excellence (NICE) guidelines for ADHD treatment in the presence of SUD or in high-risk individuals such as imprisoned populations, the selective noradrenaline (NA) reuptake inhibitor ATX is recommended as first-line therapy (11). Alpha-adrenergic agonists (clonidine and guanfacine) are approved for treatment of childhood ADHD in the US (but not in Sweden) and are shown to be efficacious in individuals with prominent symptoms of hyperactivity or aggression (52, 53). The evidence for the treatment of ADHD with other antidepressants, such as mixed catecholaminergic agents (e.g. bupropion), serotonin and noradrenaline reuptake inhibitors (e.g. venlafaxine), tricyclics (e.g. despiramine) or monoamine oxidase inhibitors (e.g. pargyline, deprenyl, selegeline), is limited at present (53).

Central Stimulant Treatment

Stimulant medications act by increasing brain catecholamine levels (54) and are advocated as first line treatment for ADHD in both children and adults due to robust clinical efficacy (5, 6, 8-11, 49, 55). Discrete increases in blood pressure and heart rate, insomnia, headache, abdominal pain and decreased appetite are relatively common side effects across all age groups (57, 58). However, the recent literature has not found evidence for increased risk of serious adverse events such as future SUD (59), suicidal behavior (60), psychotic episodes (61) or severe cardiovascular incidents (56).

The optimal dose, both in adults and children, can vary considerably across individuals, regardless of baseline characteristics such as sex, age or weight (62). In clinical practice, a titration phase using successively increased doses while simultaneously following ADHD symptoms and possible adverse reactions via clinical assessments and rating scales is used to guide the optimal individual dose regime. Previous studies on MPH treatment in children show a need to increase doses to maintain treatment efficacy during the first year in treatment (63). Thereafter, the doses level off and stabilize. This phenomenon suggesting underlying mechanisms of tolerance to MPH treatment during the first year in treatment has however not been systematically investigated in adults.

MPH is available as both immediate release (IR) and extended release (ER) formulations with different pharmacokinetic properties, differing in time to maximum serum concentration and behavioral effects (64, 65). IR formulations need to be administered twice or thrice a day and can thus entail challenges related to medication management (66). In order to avoid issues such as poor compliance, stigmatization of children having to re-administer medication during school hours and to reduce the abuse liability of MPH, ER formulations of MPH, such as the osmotic release oral system (OROS ®) are often recommended (67).

1.2 Substance Use Disorder

"They ask you about wine and gambling. Say: In them is great sin and yet, some benefit for people. But their sin is greater than their benefit." The Koran 2:219

Humans have used substances with sedative, euphoric or hallucinogenic effects for religious, medical and recreational purposes throughout history (68). Opiates and alcohol are often used as typical models to study addiction since both substances, one illicit and the other one legal, induce the need to increase doses (tolerance), produce adverse physical symptoms when use is discontinued (withdrawal), and can create serious social, legal and professional consequences for the users (adverse psychosocial effects) (69). Some individuals will

progress from sporadic use, to dependence (70) but the environmental and genetic mechanisms behind these trajectories are far from completely understood.

1.2.1 Diagnostic Assessments

According to the ICD-10 and DSM-IV classification system, substance abuse or dependence syndromes are defined as behavioral, cognitive and physiological results of repeated substance use including a strong desire to take the drug, difficulties in controlling the use, persistent use despite harmful consequences, prioritizing drug intake over other activities and obligations, increased tolerance and physical withdrawal symptoms. The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (71) published in 2013, no longer differentiates between substance abuse (i.e. predominantly negative social consequences) and dependence (i.e. predominantly negative physical and psychiatric consequences). Instead, DSM-5 applies a dimensional approach to problematic use of substances of abuse, defining the severity of the condition by a symptom count, requiring two or more symptoms from a list of 11, introducing the collapsed term substance use disorders (SUD). The criterion of substance-related legal problems used to define substance abuse has been removed, and an item related to craving is added. The studies included in this thesis use the ICD diagnoses of SUD based on the DSM-IV definitions of substance abuse and dependence.

1.2.2 Prevalence

Annual reports of the prevalence of alcohol and drug use disorders show a growing problem both in Sweden (72) and globally (70). According to worldwide estimations, almost 5%, i.e. 246 million individuals, aged 15 to 64 used illicit drugs during 2013 (70). The health risks related to illicit drug use increase with the frequency and quantity of use and approximately 10% of the users will experience medical or societal problems. While cannabis is the most frequently used illicit substance worldwide (70), it is opioid dependence that contributes to the highest rates of SUD related morbidity (73). According to WHO, 16% of adults that use alcohol will experience problematic use or dependence sometime during their lifetime. Furthermore, SUD is three times more common among men than women (70).

1.2.3 Etiology

SUD's are chronic, highly genetically influenced disorders (74-76) with alternating relapses and remissions and specific neurobiological alterations (77). The high heritability estimates

shown in family-based research such as adoption (78, 79), and twin studies (80-83) have however not yet been replicated in molecular research (74). In addition, heritability estimates vary considerable between different studies suggesting that both shared and specific environmental factors may contribute to the multifactorial etiology of SUD. Adverse household factors such as abuse and maltreatment during childhood (84, 85), as well as prenatal factors such as *in utero* exposure to both alcohol and cigarette smoking have been associated with an increase risk for SUD and other severe externalizing behaviors (86, 87). Importantly, the role of environmental risk factors does not contradict the genetic approach to addictive disorders. Previous research has shown that a specific gene makeup might increase vulnerability to certain disorders through these factors (88). For example, Cadoret et al. used an adoption study design to show that the presence of alcohol dependence in both biological and adoptive parents increased the risk for alcohol dependence in the adoptive children. However, alcohol dependence in the biological parents only increased the risk of externalizing behaviors in the adoptive child if the child was raised in a dysfunctional adoptive family (89). In line with such a hypothesis, suggesting that gene-environmental interactions needs to be taken into account when assessing the impact of environmental and genetic influences, Cloninger et al., arrived at similar conclusions in their adoption study of almost 900 Swedish men adopted by nonrelatives at an early age (90). Indeed, this study identified two forms of alcoholism that were differently affected by both genetic and environmental factors.
In addition to genetic and environmental risk factors, cultural, religious and societal norms and political ordinances limiting consumption have historically influenced alcohol and drug use consumption (68).

1.2.4 SUD Treatment

Current treatment guidelines often recommend a combination of pharmacotherapy and psychosocial interventions (91). Cognitive behavioral therapy and other techniques based on enhancing individual motivation and reinforcing positive behavioral changes such as motivational interviewing, motivational enhancement therapy, brief intervention and community reinforcement approach have the strongest empirical support for SUD treatment (91, 92).

Pharmacological Treatment

Pharmacological treatment of SUD has gained increased clinical recognition during recent years, focusing specifically on management of withdrawal symptoms, attenuation of craving, reduction of the rewarding effects of substances and prevention of relapse (93). Many of the current approved pharmacological substances for treatment of SUD are either full or partial agonists (e.g. methadone or buprenorphine for opiate dependence) acting as a substitution therapy, or antagonists (e.g. naltrexone for alcohol dependence) that specifically block receptors in the brain and in turn modulate the rewarding effects of the substance of abuse.

1.3 When ADHD and SUD Coexist

There is a robust association between ADHD and SUD. Individuals with ADHD are at increased risk of developing SUD (1) and the prevalence of ADHD among treatment seeking SUD patients is almost 25% compared to estimations of about 2.5% in the general adult population (4, 16, 17). Psychiatric disorders frequently coexist and might mimic symptoms of both adult ADHD (16) and SUD (94, 95), resulting in more severe impairments, worse prognosis (4, 95) and clinical challenges of utilizing pharmacological stimulant treatment in these individuals.

A growing body of evidence from brain imaging research suggests similarities in ADHD and SUD pathophysiology (96). More specifically, dysfunction in dopaminergic transmission in cortical and subcortical pathways is associated with reduction in reward response and inhibitory control, implicated in both disorders (97-99). Indeed, many drugs of abuse, while having different molecular targets, have a common action of increasing dopamine transmission in cortical and subcortical areas of the brain (100). Long-term, chronic drug use results in down regulation of dopamine receptors and decreased dopamine function. These alterations in dopamine transmission might be related to the clinical phenomena of increased craving and loss of control, driving the individuals to compulsive drug intake to avoid the negative effects and symptoms of withdrawal (100). In addition, results from imaging studies show reduced dopamine receptor activity in subcortical brain areas of individuals with ADHD (101). This commonality in action has led to the view that the dopamine system plays a pivotal role in the neurobiology of both ADHD and SUD. This is of particular interest since the first line of pharmacological treatment for ADHD, namely stimulants (9-11, 55), operates by increasing dopamine levels in the same brain regions as those involved in addiction (54, 99).

1.3.1 How are ADHD and SUD Etiologically Related?

Previous research has found a robust association between ADHD and SUD, but the nature of this overlap has remained unclear. There are several alternative explanations for the high coexistence of ADHD and SUD. Firstly, the high degree of symptom overlap between the two disorders, including symptoms occurring in the context of intoxication or withdrawal of SUD, raises the question of whether the co-occurrence of ADHD and SUD in fact only represents a methodological artifact. Secondly, even though a growing body of studies suggests possible protective effects of ADHD medication on future development of SUD (59, 102), there are still lingering concerns surrounding the risk of abuse or addiction related to MPH medication, based primarily on findings from animal and imaging studies (99, 103, 104). Thirdly, in addition to research showing that prenatal exposure to maternal SDP is associated with several adverse pregnancy outcomes (47), studies have also suggested plausible biological mechanisms through which SDP may influence brain development (41, 42). Given the robust association between SDP and ADHD in offspring observed in previous epidemiological studies, even after adjustment for measured confounders (35, 43-46), SDP is often suggested as a causal risk factor for ADHD. Thus, problems associated with SUD and ADHD may overlap across generations via the prenatal period. Importantly however, environmental exposures might also wrongfully be interpreted as causal risk factors when the increased risk actually arises due to familial confounding, such as genetically transmitted factors (105). Fourthly, there is an ongoing debate in the literature as to whether ADHD alone or externalizing disorders such as oppositional defiant disorder (ODD), conduct disorder (CD), and antisocial personality disorder (ASPD) that frequently co-occur with ADHD, mediate the increased risk of SUD (106-112). Either way, ADHD patients with CD tend to show more severe SUD symptoms compared to patients without a childhood history of coexisting ADHD and CD (112) suggesting that ADHD and CD interact synergistically, resulting in particularly severe forms of SUD (109). Fifthly, the overlap between ADHD and SUD may be explained by shared genetic risk factors. This is plausible given that both ADHD (36) and SUD (113) are highly heritable conditions. Previous family and twin studies have, nevertheless, produced inconsistent results regarding the nature of the coexistence of the two disorders (82, 114, 115). That is, some of the previous studies suggest shared genetic risk factors for ADHD and SUD (29, 116, 117), whereas other family-based studies indicate independent transmission of SUD and ADHD, or alternatively, the presence of an etiologically distinct ADHD plus SUD syndrome (118-120). Pleiotropic effects of genetic risk variants have been suggested across a broad range of psychiatric diagnoses (39, 40). This

in turn might indicate that the overlap of ADHD and SUD is unspecific and reflects genetic factors shared by several major psychiatric disorders and increasing the liability for psychiatric disorder in general.

1.3.2 The Effectiveness and Safety of Stimulant Medication when ADHD and SUD Coexist

Are stimulant medication prescription patterns different in individuals with ADHD and SUD compared to those with ADHD only?

As noted earlier, stimulant medication is advocated as first line treatment for ADHD in both children and adults due to its robust clinical efficacy (5, 6, 8-11, 49, 55). On the other hand, we still have limited knowledge regarding several potential concerns, such as stimulant effectiveness, potential development of tolerance to MPH, and liability of non-medical use and abuse of stimulant medication in the comorbid SUD population. Given this substantial gap of knowledge regarding effective and safe treatment of coexisting ADHD and SUD, present clinical guidelines lack clear and consistent guidance on how this important and vulnerable group of patients should be treated (7-11).

Since both adult ADHD (54), and SUD (121) have been linked to a dysregulation of brain dopamine and NA systems, this could hypothetically explain the therapeutic efficacy of catecholaminergic agonists such as stimulant drugs on ADHD. Subsequently, the same medications should theoretically be effective in treating SUD, regardless of impact on ADHD. However, drugs used to treat ADHD have not, in general, proven effective in the presence of comorbid SUD (7) and treatment guidelines for this population are consequently lacking. Nevertheless, the majority of studies on stimulant treatment of coexisting ADHD and SUD are limited by doses adjusted to suit individuals with ADHD only (7).

Previous studies have shown a need for successively increasing MPH doses during the first year of treatment in children (63), but no previous population-based study has explored the extent to which individuals with ADHD and SUD are prescribed higher doses than individuals with ADHD only. Higher doses in the ADHD and SUD group would be expected if individuals with SUD due to neurobiological adaptations resulting from heavy drug use (100), developed tolerance not only to substances of abuse but also to pharmacological compounds such as MPH. Tolerance, a core sign of dependence might, in line with such an hypothesis and supported by results from neuroimaging research (123, 124) lead to attenuated responses to stimulant medication resulting in the need for doses

exceeding those prescribed to drug naïve individuals.

Another reason for expecting differences in doses between individuals with SUD and those with ADHD only, relate to the abuse potential of MPH. Given the risk of non-medical use of stimulants (125), and lack of clinical guidelines, clinicians might fear or suspect that patients feign ADHD symptoms in order to obtain stimulant medication (126). This in turn could influence a physician's decision regarding individual dosing and possibly make him or her reluctant to prescribe adequate doses in patients with coexisting SUD.

Tight societal controls are imposed on production and prescription of MPH for legitimate clinical use in accordance with Schedule II of the Controlled Substance Act in the US (127). In Sweden, MPH is classified among other narcotic medication with abuse potential and license to prescribe is restricted to physicians specialized in psychiatry, pediatric or neurology (128). To minimize the risk of abuse and diversion of stimulant medication, close supervision during initiation and titration phases of treatment periods is often encouraged. Short prescription intervals during the titration phase and before arriving at a stable dose are recommended. The clinical routines, in particular for individuals with comorbid SUD, typically involve evaluating and assessing the patient 1–3 times per week targeting changes in ADHD symptoms, adverse effects, cardiovascular monitoring and collecting of urine samples for laboratory analysis. The urinary analysis allows for detection of substances of abuse, which might or might not violate the treatment agreement and result in temporary treatment discontinuation.

What factors influence adherence to stimulant treatment when ADHD and SUD coexist?

Premature discontinuation of pharmacological treatment is a costly and medically significant problem (129) associated with worse treatment outcome (130-132). Adherence to psychopharmacological treatment in general is low and treatment for ADHD and SUD are no exceptions (133-135). In fact, a recent systematic review and meta-analysis of randomized controlled trials comparing MPH with placebo in adults with ADHD showed no advantage for MPH over placebo in terms of treatment discontinuation (136). One of the more consistent patient-related factors associated with treatment discontinuation in both ADHD and SUD is age. In particular, treatment discontinuation becomes increasingly common during the years of transition from child/adolescent to adult healthcare services (135, 137-139). Hypothetically, individual characteristics such as sex, SUD subtype and psychiatric comorbidity could influence both motivation and ability to adhere to pharmacological treatment. Previous research, however, is inconsistent in regard to what

factors might influence treatment adherence (132, 135, 137-139) and a recent meta-analysis investigating non-adherence to SUD treatment expressed great skepticism towards further exploration of demographic risk factors. Instead the authors highlight the need for potential treatment-related factors such as different treatment programs and treatment processes (135).

2 AIMS

2.1 General Aims

There were two overall aims for this doctorial project:

Firstly, to use genetically informed epidemiological models to explore the etiological overlap between ADHD and SUD.

Secondly, to use naturalistic cohort studies to explore the effectiveness and safety of stimulant medication when ADHD and SUD coexist.

2.2 Study Specific Aims

2.2.1 Study I and II

Studies I and **II** aimed to explore how ADHD and SUD are etiologically related. In **Study I** the impact of familial (i.e. shared environment and genetic factors) confounding of the association between Smoking During Pregnancy (SDP) and ADHD in offspring was investigated. **Study II** explored whether common familial factors (i.e. environmental and genetic factors) were shared between the ADHD and SUD.

2.2.2 Study III

Study III first aimed to describe whether MPH prescription patterns were different in individuals with ADHD and SUD compared to those with ADHD only and whether MPH doses in both populations stabilized or increased after an initial titration interval.

2.2.3 Study IV

Study IV aimed to explore to what extent patient-related factors (i.e. age, sex, SUD subtype and psychiatric comorbidity) or treatment-associated factors (i.e. the prescribing physician's (sub)specialty and MPH dose) influenced adherence to MPH treatment when ADHD and SUD coexist.

3 METHODS

3.1 Data Sources

Described in this section are the different Swedish registers used in the present thesis.

3.1.1 The Personal Identification Number (PIN)

Since 1947 the National Tax Board has assigned a unique, sex-specific, ten-digit personal identification number to all individuals resident in Sweden (birth or immigrated) (140). The ten digits represents, in order, the year, month and day of birth followed by a four-digit control number. The Swedish PIN covers the entire Swedish health care system and enables linkages between different population and medical registers. To ensure anonymity PIN's were replaced by random index numbers by the authorities before delivery to the researchers.

3.1.2 The National Patient Register (NPR)

The NPR, held by The National Board of Health and Welfare since 1964, provides data on hospital discharge diagnosis according to the International Classification of Disorders (ICD-codes). The register has complete coverage on psychiatric in-patient care since 1987 and registers outpatient public and private care since 2001. All Swedish county councils provide annual updates, however primary care is not yet covered in the NPR. Prior external register validations have shown 85-90% diagnose specific validity and low rates of dropout and missing data (141).

3.1.3 The Swedish Prescribed Drug Register (PDR)

The PDR, held by the National Board of Health and Welfare, provides almost complete coverage (0.3% missing data) on drug identity (Anatomical Therapeutic Chemical (ATC-codes)) of all dispensed prescriptions to the entire population in Sweden since July 2005 (142).

3.1.4 The Medical Birth Register (MBR)

The MBR is held by the Swedish National Board of Health and Welfare and provides information on all pregnancies (around 95,000 annually), deliveries and newborn infants in Sweden since 1973. Smoking during pregnancy (SDP) has been recorded since 1983 at the registration to antenatal care (in pregnancy week 8-12) (143, 144).

3.1.5 The Multi-Generation Register (MGR)

The MGR is held by Statistics Sweden and contains information on over 13 million individuals by linking every individual born in Sweden since 1932 (the index person) to corresponding biological and adoptive parents (145). The register coverage is over 95% regarding parental status of index individuals born from 1932 onwards and alive on January 1, 1961. For index individuals born outside of Sweden but immigrated before the age of 18 the register coverage is comparable to Swedish-born individuals (145).

3.1.6 The Cause of Death Register (CDR)

The CDR is held by the Swedish National Board of Health and Welfare and provides information on all deceased Swedish citizens since 1958 and is considered to have almost complete coverage from 1961. The data contains date of death and ICD codes on main and contributory causes of death. In about 1-2% of the individuals in the CDR data on cause of death was missing (146).

3.1.7 Database for Health Insurance and Labor Market (LISA)

The LISA register is held by Statistics Sweden and contains annually updated information on education, employment and income of individuals over 16 years of age in each Swedish household since 1990. The database integrates existing data from the labor market, educational and social sectors and is updated each year with a new annual register (147).

3.1.8 The Migration Register (MR)

The MR is part of the Total Population Register (TPR) founded by Statistics Sweden in1968 and includes information on dates of all registered migrations into or out of Sweden since 1969.

3.1.9 The Stockholm Child and Adolescent Psychiatric Care Register (Pastill)

The Pastill Register covers information on psychiatric diagnoses based on both ICD-10 and DSM-IV codes for all children and adolescents living in Stockholm County since 2001.

3.2 Operationalization of Exposure and Outcome

3.2.1 ADHD diagnosis

ADHD was defined as an in- or outpatient diagnosis of Hyperkinetic Disorder (HKD) (F90 in ICD-10) between January 2001 and December 2009 from the NPR, and/or a diagnosis of HKD (F90 in ICD-10) or ADHD (DSM-IV:314) from Pastill (**Study I**), or a diagnosis of HKD (ICD-9: 314; ICD-10: F90) in the NPR (**Study II**). In addition, an individual was categorized as an ADHD case if he or she had received at least one prescription of a stimulant or non-stimulant medication for ADHD (ATC-code for methylphenidate (N06BA04); atomoxetin (N06BA09); amphetamine (N06BA01); dexamphetamine (N06BA02)) at any time between July 2005 and December 2009, identified from the PDR.

3.2.2 SUD Diagnosis

Information on SUD was acquired using both ICD-codes from the NPR and ATC-codes from the PDR (for drugs used exclusively in the treatment of SUD). Alcohol use disorder was defined using ICD-codes from the NPR (ICD-8: 291 and 303, ICD-9: 291, 303 and 305A and ICD-10: F10.0-F10.9). The alcohol use disorder index from the PDR was based on ATC-codes for prescriptions of drugs used in the treatment of alcoholism (N07BB03 (acamprosate), N07BB04 (naltrexone) and N07BB01 (disulfiram)). Psychoactive drug abuse was measured by ICD-codes from the NPR (ICD-8: 304, ICD-9: 292, 304 and 305X and ICD-10: F11.0-F16.9) and ATC-codes from the PDR (N02AE01 (buprenorphine), N07BC51 (buprenorphine+naltrexone) and N07BC02 (methadone)).

3.2.3 Operationalization of MPH Doses and Treatment Periods

Individual daily MPH doses were estimated by means of the text variable in the PDR. Each prescription contains a text variable stating the quantity of medication prescribed and individualized instructions on how the drug is to be consumed. A treatment period was defined as the number of days the prescription would last according to the text variable on the prescription, plus 25% of that time, to avoid individual minor irregularities in dispensing patterns. During subsequent periods or those without any new prescription, the patient was assumed to be off treatment.

3.3 Observational Study Designs

Described in the section below are the different study designs used in the current thesis. An observational study draws inferences about a possible effect of an exposure, where the assignment of exposure status is beyond the control of the investigator. This is in contrast to randomized controlled trials (RCTs), where each subject is randomly assigned to an exposed group or a control group. A major challenge in observational research is to design the study and draw inferences that are acceptably free from influences by confounding or biases. However, observational studies have several advantages over experimental research including the possibility to study large samples representative of the general population over long periods of time at an affordable cost.

Observational research might seem ideal to establish associations between exposures and outcomes. Nevertheless, an association or a correlation, however strong and convincing, does not equal causality. To make a judgment as to whether an exposure is causal or not several alternative explanations, such as chance, bias or confounding, must be considered, evaluated and eliminated.

3.3.1 Cohort Studies

All the studies included in this thesis are cohort studies where a defined group of individuals (i.e. a cohort) are followed over a specific time period. The incidence of a specific outcome is then described in relation to a certain exposure status at the end of follow-up. Register-based cohort studies use prospectively collected information (i.e. assess exposure status before any information of the outcome is known) and thus become less sensitive to bias than other observational studies.

3.3.2 Quasi-Experimental Study Designs

RCTs are, in clinical research, often considered to be the gold standard for making causal inference. However, as in the case of being exposed to SDP, randomization to exposure is not always ethical or feasible. For example, in **Study I** a quasi-experimental approach was used to examine individuals exposed to an experimental (sibling exposed to SDP) or control condition (sibling unexposed to SDP) determined by nature or other factors outside the control of the investigators. Family-based, quasi-experimental studies, as in **Study II**, make use of the fact that the individuals with different genetic relatedness and family relationships might differ in both environmental exposure and genetic risk (148).

Within siblings and cousins design

As shown in **Study I**, quasi-experimental research can address many of the serious limitation of traditional observational research by estimating the impact of residual familial confounding from unmeasured genetic factors. A confounder is a variable associated with both the exposure and the outcome, creating an association that can wrongfully be mistaken to be causal. For example, familial confounding can arise in the association between SDP and offspring ADHD since mothers provide both *in utero* exposure to tobacco and part of the genetic makeup transmitted to the child. The comparisons of differently exposed full-siblings within nuclear families allow for control of unmeasured factors that make siblings similar. Similarly, the comparisons of differently exposed full-cousins (offspring of adult full-siblings) within extended families control for unmeasured factors that make cousins similar (148). If an environmental risk, such as SDP in **Study I**, is causally associated with an outcome (e.g. ADHD) the increased risk should be robust to the sibling and cousin design. However, if the association is confounded by familial factors (e.g. genetics) the association should attenuate along with genetic relatedness, when the sibling and cousin design is applied.

Family design

Within the family design, individuals with different levels of genetic relatedness and environmental exposure are compared using the underlying assumption that full-siblings and parent-offspring share environment and approximately 50% of their co-segregating genome. In line with these assumptions maternal and paternal half-siblings share approximately 25% of their genes. Since children, at least historically, tend to continue to live predominantly with their mothers following parental separation maternal half-sibling are more similar regarding shared environmental exposure than paternal half-siblings (148, 155). Furthermore, family studies can utilize the fact that individuals within the extended family, such as cousins, share approximately 12.5%, and different levels of exposure to environmental factors. **Study II**, explores the risk of developing SUD among individuals with different genetic relatedness to an ADHD proband compared to relatives to matched non-ADHD control subjects.

3.4 Study Designs and Subjects

3.4.1 Study I

Subjects

All individuals born in Sweden between 1992 and 2000 were identified from the MBR. Individuals with serious congenital malformations, multiple births, still born before or during delivery, dead or emigrated before 3 years of age or before 2001, for whom data on mother's identification number was missing or who had received an ADHD diagnosis before 3 years of age and with missing values on SDP were excluded. The study population of 768 227 individuals covering 365 442 full siblings nested within 172 701 families and 155 852 cousins nested within 52 183 families, were followed up from the age of 3 until diagnosis of ADHD, death, emigration, or December 31, 2009, whichever occurred first.

Exposure

The MBR provided information on SDP through self-reported prospective information at the registration to antenatal care (in pregnancy week 8-12) (149). SDP was measured on a three-point scale (No SDP = 0, moderate SDP = 1-9, or high SDP = ≥10 cigarettes per day).

Outcome

ADHD was defined as an ICD-diagnosis (ICD-10: F90) in the NPR and/or an ICD and DSM-IV diagnosis (ICD-10: F90, DSM-IV: 314) in Pastill and/or a prescription with an ATC-code for stimulant or non-stimulant ADHD medication (MPH (N06BA04); atomoxetine (N06BA09); amphetamine (N06BA01); dexamphetamine (N06BA02) in the PDR.

Covariates

Based on previous research (150, 151), measured covariates included sex, birth year (1992-1994, 1995-1997, and 1998-2000), mother's parity (1st, 2nd, 3rd, or ≥4th), maternal age at childbirth (≤19, 20-24, 25-29, 30-34, or ≥ 35 years), cohabitation with offspring's father (yes or no), highest level of maternal education (≤9 years, 10-12 years or graduate education) and mother's country of birth (Sweden, other Scandinavian countries or others). Since low birth weight might be an intermediate factor of the association between SDP and ADHD, the analyses were not adjusted for that measure. Pre-pregnancy BMI is considered partly adjusted for by maternal education level and could potentially be an intermediate factor, thus it is not included as a covariate in the model.

Study design

Population based cohort study. Within sibling and cousin design (see 3.3.2).

Statistical analyses

Cox proportional survival analysis, (crude and adjusted for measured covariates) estimated the magnitude of the associations between SDP and offspring ADHD at the population level. A stratified Cox regression model was used to adjust for the occurrence of dependent data (sibling and cousins) by assigning each set of siblings or cousins a separate stratum. The models calculated hazard ratios for time to ADHD diagnosis. Robust standard errors adjusted the 95% confidence intervals for the presence of familial clustering in the analyses at the population level.

Sensitivity analyses

The potential modifying effect of birth order (i.e. carry-over effect), bias from outcome misclassification in a birth year restricted sibling cohort and generalizability of the sibling sample to the entire cohort was tested.

3.4.2 Study II

Subjects

In total 62 015 unique ADHD cases were identified, 47 794 patients with an ADHD diagnosis were identified from the NPR (ICD-9: 314; ICD-10: F90) and 46 186 ADHD patients treated with stimulant or non-stimulant medication for ADHD (methylphenidate (N06BA04); atomoxetine (N06BA09); amphetamine (N06BA01); dexamphetamine (N06BA02)) at any time between July 2005 and December 2009 were identified from the PDR. Patients aged 3-65 years at the time of the first ADHD diagnosis (or first prescription of stimulant or non-stimulant medication for ADHD) were included.

For each case, ten unaffected control subjects were randomly selected. Matching the control subjects on sex, birth year, and residential factors ensured equal follow-up time. According to well-established procedures for nested case-control designs (152, 153), controls were alive and living in Sweden and had not been diagnosed with ADHD at the time of the first ADHD diagnosis of the proband.

Exposure

Genetic relatedness to ADHD proband or matched control subject in the MGR and the TPR. ADHD defined as an ICD-diagnosis in the NPR and/or a prescription with an ATC-code for ADHD medication in the PDR (See 3.2.1).

Outcome

SUD defined as an ICD-diagnosis in the NPR and/or purchase of any drug with an ATC-code used in the treatment of SUD in the PDR (See 3.2.2).

Covariates

Sex, age, education level, psychiatric comorbidity (schizophrenia, bipolar disorder, major depression, conduct disorder).

Study design

Population-based matched cohort study. Family design (See 3.3.3).

Statistical analyses

The statistical analyses were performed using a nested case-control design. Conditional logistic regression models adjusted for the fact that associations within the same families were not statistically independent of one another. The logistic regression model fitting potential confounding factors allowed unequal follow-up time thus minimizing bias introduced when individuals in the population registries enter the study at different time points (i.e. left truncation).

Confidence intervals were obtained with a robust sandwich estimator function to adjust for non-independence.

Sensitivity Analyses

The sensitivity analyses first explored to what extent familial factors for ADHD and SUD were shared with other major psychiatric disorders by analyzing subsamples of individuals without a diagnosis of schizophrenia and bipolar disorder, depression or conduct disorder (CD). Secondly, the sensitivity analyses explored whether the familial association was driven by the fact that many families contributed with more than one case-relative pair. This was done by selecting and analyzing a sample with only one case-relative pair per family. Thirdly the validity of the ADHD diagnosis was studied by analyzing a sample of individuals identified as ADHD cases in both the NPR and the PDR. And finally, age differences adjusted for education level between different degrees of relatives to cases and controls was explored to establish whether this influenced our results.

3.4.3 Study III

Subjects

A total of 14 314 individuals, aged 18-59, with an initial prescription of MPH (ATC-code for MPH N06BA04), between January 1, 2006, and December 31, 2009 were identified in the PDR. Among them, 4870 individuals with a diagnosis of SUD in the NPR or the PDR were included in the main analysis.

Exposure

ICD-diagnosis of SUD in the NPR and/or purchase of any drug with an ATC-code used in the treatment of SUD in the PDR (See 3.2.2).

Outcome

Differences in mean MPH doses between patients with and without SUD. MPH doses were stratified into 0-72 mg and >72 mg based on recommendations issued by the British Association for Psychopharmacology (recommended maximum dose 100 mg) (10), the American Food and Drug Administration (recommended maximum dose 72 mg) (127), and the National Institute for Health & Clinical Excellence NICE guidelines (recommended maximum dose 60 mg) (11). Also, OROS MPH, the most commonly prescribed MPH formulation in Sweden, are only commercially available in multiples of 18 mg. The prescribed dose was calculated with annual point estimates every 100 days. The follow-up period allowed for times during which medication was discontinued or resumed. Individuals were considered to be in active treatment if a prescription was refilled within the number of days that the prescription would last according to the text variable on the prescription, plus an additional 25% of this time sequence to account for irregularities in dispensing patterns.

Covariates

Given the potentially confounding effects of age, sex, SUD subtype, calendar year of the initial prescription and comorbid psychiatric diagnoses these covariates were simultaneously fitted into the adjusted model.

Study design

Population-based cohort study.

Statistical analyses

Logistic regression models calculated ORs for dichotomized MPH dose (≤72, >72 mg/day) day 365 and 730 after first MPH prescription. Time trends in mean doses in patients with and without SUD were tested with linear regression and described in a graph depicting a point estimate of the mean dosage every 100 days.

Sensitivity analysis

A subsample of the population with doses over 72 mg/day (N=659) was analyzed to test whether individuals with MPH doses over 72 mg/day actually picked up doses corresponding to those prescribed by the physician. Doses in the PDR on days 300 and 400 were compared with the total accumulated dose filled by the pharmacy between days 200 and 400 to explore whether the amount of prescribed medication corresponded to the amount of medication actually dispensed at the pharmacy.

3.4.4 Study IV

Subjects

An eligible sample of 4870 individuals with SUD diagnosis in the NPR or the PDR aged 18-59 years at the first prescription prescribed MPH between January 1, 2006, and December 31, 2009 was identified from the register linkages. After excluding individuals with inadequate follow-up time, treatment discontinuation before day 100, and lack of dose information, 2659 individuals with a known prescribed MPH dose at day 100 were included in the main analyses.

Exposure

Patient-related factors were identified based on previous research (135, 138) and measured baseline characteristics included sex, age (18-26, 27-39 and 40-59 years of age), SUD subtype (alcohol, stimulant or combined) according ICD-8, ICD-9 and ICD-10, and ICD-8, ICD-9 and ICD-10 diagnoses for comorbid psychiatric disorders (i.e. schizophrenia, mood disorders or anxiety disorders, eating disorders, personality disorders and conduct disorder) were identified from the NPR. Treatment-related factors such as the prescribing physician's (sub)specialty (i.e. psychiatry, addiction medicine or other) and MPH doses stratified into six different dose categories (≤ 36mg, ≥37mg - ≤54mg, ≥55mg - ≤72mg, ≥73mg - ≤90mg, ≥91mg - ≤108mg and ≥109mg) were obtained from the PDR.

Outcome

Days in active MPH treatment until first discontinuation. Individuals were considered to be in active treatment if a prescription was refilled within the number of days that the prescription would last according to the text variable on the prescription (plus an additional 25% of this time sequence to account for irregularities in dispensing patterns), or within 30 days after the last prescription was issued.

Covariates

Sex, age, SUD subtype, comorbid psychiatric disorders, and the prescribing physician's (sub)specialty.

Study design

Population based cohort study.

Statistical analyses

A Cox regression model, adjusted for individual baseline characteristics, was used to estimate time to first treatment discontinuation in relation to six categories of MPH doses. Logistic regression models were used in the sensitivity analyses to explore whether base line characteristics such as sex, age, SUD subtype, comorbid psychiatric disorders, and the prescribing physician's (sub)specialty (addiction medicine, general psychiatry or other) differed between the subsample of individuals who discontinued MPH treatment before the initial titration phase of 100 days was completed (early discontinuation) and individuals with ongoing MPH treatment day 100. In addition, ongoing MPH treatment at day 100 was modeled in a logistic regression model using sex and age as predictors.

Sensitivity analyses

The sensitivity analyses explored whether baseline characteristics such as sex, age, SUD subtype, comorbid psychiatric disorders, and the prescribing physician's (sub)specialty differed between individuals who discontinued MPH treatment before the initial titration phase of 100 days was completed and individuals with ongoing MPH treatment day 100. In addition, a possible modifying effect of the above mentioned background factors and a time dependent incline in prescribed MPH doses was explored by analyzing subsamples of individuals prescribed MPH treatment during different years. Given that the risks of relapse into alcohol or drug use might be more pronounced during the first time of abstinence, a separate analysis was made to explore if the dose at day 200 was an equally strong predictor of treatment adherence as the dose at day 100.

4 RESULTS

4.1 Study I

Two different quasi-experimental designs (i.e. cousin and sibling comparisons) were used to explore the mechanisms through which maternal smoking during pregnancy (SDP) influence ADHD. Table 1 show that offspring exposed to maternal SDP were at increased risk for ADHD ($HR_{ModerateSDP}$ 1.89; $HR_{HighSDP}$ 2.50). The dose-dependent association decreased marginally after adjustment for measured covariates but remained statistically significant ($HR_{ModerateSDP}$ 1.62; $HR_{HighSDP}$ 2.04). The associations were further attenuated in the cousin comparisons; that is, after adjustment for all unmeasured factors that are constant within extended families ($HR_{ModerateSDP}$ 1.45; $HR_{HighSDP}$ 1.69). In the sibling comparisons, the associations observed at the population level were completely attenuated and no longer statistically significant, indicating that unmeasured familial factors that are constant within nuclear families explain the associations ($HR_{ModerateSDP}$ 0.88; $HR_{HighSDP}$ 0.84).

Table 1 Relative risks of ADHD among offspring exposed to SDP

	HR (95%CI)			
Exposure	Crude[a]	Adjusted[b]	Cousins[c]	Full sibling[d]
No SDP	Reference	Reference	Reference	Reference
Moderate SDP (1-9 cigarettes per day)	1.89 (1.83-1.97)	1.62 (1.56-1.69)	1.45 (1.24-1.68)	0.88 (0.73-1.06)
High SDP (≥10 cigarettes per day)	2.50 (2.40-2.61)	2.04 (1.95-2.13)	1.69 (1.40-2.04)	0.84 (0.65-1.06)

[a] N = 768 227, [b] N = 720 853 Adjusted for offspring sex, birth year, mother's parity, maternal age, cohabitation status, maternal highest education, and mother's country of birth. [c]N = 155 852 Adjusted for offspring sex, birth year, mother's parity, maternal age, cohabitation status. [d] N = 365 442 Adjusted for offspring sex, birth year, mother's parity, maternal age, cohabitation status.

Sensitivity analyses

Stratified analyses at the population level showed that the results were robust to the fact that second-born offspring were more often exposed to maternal SDP than first-born offspring. In addition, the results from the restricted sibling sample were similar to that observed when the entire sibling sample was analyzed, indicating limited impact from bias due to misclassification. The results in the sibling sample were very similar to those in the entire cohort, suggesting adequate external validity.

4.2 Study II

Probands with ADHD were more likely to have been diagnosed with SUD, drug abuse and alcohol use disorder compared to age, sex and residency matched non-ADHD controls (OR_{SUD} 10.8 95 % CI; 10.5-11.1, OR_{Drug} 19.2, 95% CI; 18.5-19.8, OR_{Alc} 8.3, 95% CI; 8.0-8.5).

The risk for SUD increases considerably along with increased genetic relatedness to an ADHD proband. Table 2 shows the numbers and percentages of SUD, drug abuse and alcohol use disorder for first and second degree relatives to ADHD probands or controls. First-degree relatives of ADHD probands were at elevated risk for SUD (OR_{SUD1st} 2.2 and 1.8) compared to relatives of controls. The corresponding risk in second-degree relatives was substantially lower and similar for maternal and paternal half-siblings (OR_{SUD2nd} 1.4 and 1.4). The results were robust to adjustments for bipolar disorder and schizophrenia (OR_{SUD1st} 2.2 and 1.7; OR_{SUD2nd} 1.4 and 1.4), and depression and conduct disorder (OR_{SUD1st} 2.2 and 1.7; OR_{SUD2nd} 1.4 and 1.3).

Table 2 Risk for SUD in relatives to ADHD probands compared to relatives to controls

	SUD in relatives		
	ADHD N (%)	**Control N (%)**	**OR[a] (95 % CI)**
1° relatives			
Parent	7555 (8.9)	31 748 (4.2)	2.2 (2.2-2.3)
Full sibling	1805 (3.5)	9564 (2.0)	1.8 (1.7-1.9)
2° relatives			
Maternal half sibling	1098 (5.2)	6291 (3.9)	1.4 (1.3-1.5)
Paternal half sibling	1170 (5.1)	7068 (3.9)	1.4 (1.3-1.4)

[a] after exclusion of probands and controls with SUD and relatives to probands or controls with ADHD
SUD=Substance Use Disorder

Sensitivity analyses

The sensitivity analyses found no significant confounding effect from the fact that 40 300 families contributed with more than one case-relative pair. The analyses of individuals identified as ADHD cases in both the NPR and the PDR showed good validity of the ADHD diagnosis. Adjustments for age among relatives to probands and controls and differences in parental education level showed no potentially confounding effect of age and socioeconomic factors.

4.3 Study III

A sample of 14 314 adults (including 4870 individuals with SUD) with a prescription of MPH between January 1, 2006, and December 31, 2009 was included in the main analysis. The mean follow-up period was approximately 550 days in both populations and allowed for times during which medication was discontinued or resumed and 93% of the targeted population was monitored from date of first prescription to December 31, 2009. Psychiatric comorbidity including personality disorders and conduct disorder was more prevalent among individuals with comorbid SUD than among individuals with ADHD only.

One year after start of follow-up, at day 365, 37.1% of individuals with comorbid SUD were prescribed MPH doses exceeding 72 mg compared to 20.6% of those with ADHD only (chi-square $p<0.0001$). Approximately two years into the treatment, day 730, 44.4% of individuals with comorbid SUD were prescribed MPH doses exceeding 72 mg, compared to 22.8% of individuals with ADHD only (chi-square $p<0.0001$). Among individuals with SUD, 7.3% had doses exceeding 180 mg/day at day 730, compared to 1.2% of those with ADHD only (chi-square $p<0.0001$). Two years after start of follow-up (i.e. day 730), 48% of the individuals with ADHD and SUD and 42% of those with ADHD only (chi-square $p<0.0001$) were still actively picking up their prescriptions. The proportion of patients who had been prescribed ER formulations was high, both in patients with SUD (86%) and in patients with ADHD only (82%) (chi-square $p=0.01$).

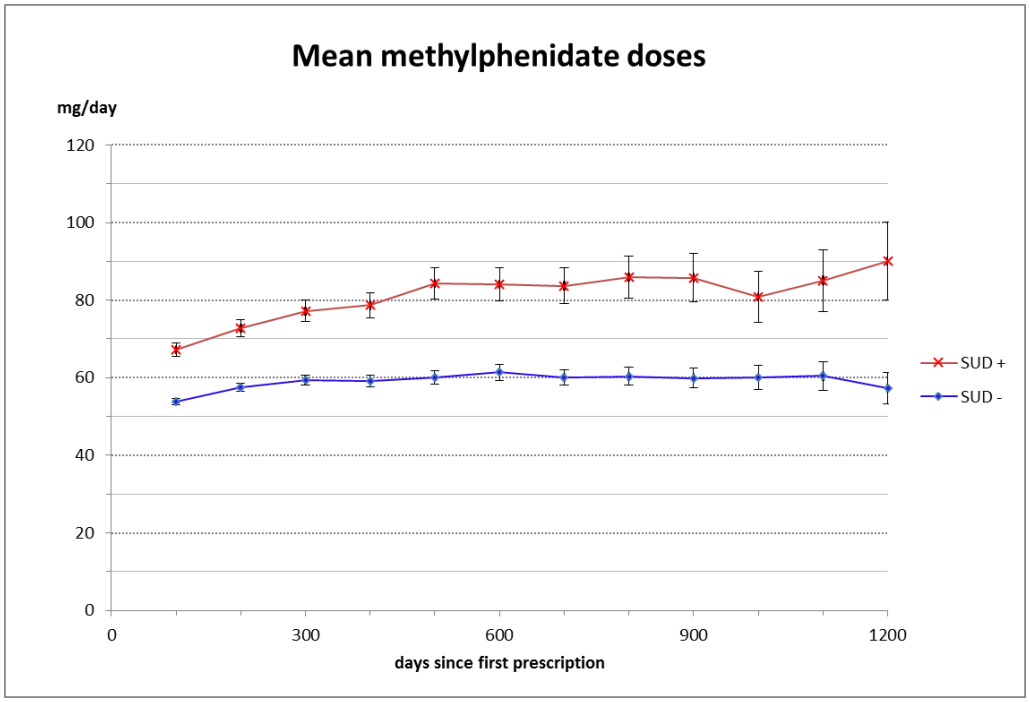
Table 3 shows ORs for MPH doses exceeding 72 mg/day in individuals with comorbid SUD and ADHD only. Individuals with SUD were at increased risk of exceeding a daily dose of 72 mg ($OR_{SUDday365}$ 2.12 and $OR_{SUDday730}$ 2.65). A diagnosis of drug abuse (DA), a combined diagnosis of both DA and alcohol use disorder (AUD) and a diagnosis of stimulant use disorder (SU) significantly increased the risk of exceeding a dose of 72 mg/day ($OR_{DAday365}$ 2.53, $OR_{DAday730}$ 3.09, $OR_{DA+AUDday365}$ 2.53 and $OR_{DA+AUDday730}$ 2.97, $OR_{SUday365}$ 3.08, $OR_{SUday730}$ 3.63). The corresponding risk associated with a diagnosis of AUD only was lower ($OR_{AUDday365}$ 1.49 and $OR_{AUDday730}$ 2.01), indicating that SUD subtype and/or severity is correlated to MPH dose.

Table 3 Logistic regression model of MPH doses exceeding 72 mg/day

	Day 365			**Day 730**		
		Dose >72 mg/day			Dose >72 mg/day	
		Unadjusted	Adjusted[b]		Unadjusted	Adjusted[b]
	N (%)	OR (95% C.I.)	OR (95% C.I.)	N (%)	OR (95% C.I.)	OR (95% C.I.)
Total	4010 (26)			1826 (31)		
SUD						
No	2610 (21)	ref=1	ref=1	1169 (23)	ref=1	ref=1
Yes	1400 (37)	2.28 (1.98-2.64)	2.12 (1.81-2.47)	657 (44)	2.72 (2.21-3.34)	2.65 (2.13-3.30)
SUD Subtype[a]						
AUD	473 (29)	1.56 (1.25-1.94)	1.49 (1.19-1.87)	208 (37)	2.00 (1.46-2.73)	2.01 (1.46-2.78)
DA	453 (41)	2.69 (2.18-3.32)	2.53 (2.03-3.15)	227 (48)	3.14 (2.34-4.21)	3.09 (2.28-4.20)
AUD+DA	474 (42)	2.77 (2.25-3.40)	2.53 (2.03-3.16)	222 (48)	3.10 (2.31-4.17)	2.97 (2.16-4.09)
SU	500 (47)	3.48 (2.85-4.25)	3.08 (2.49-3.81)	256 (53)	3.79 (2.86-5.02)	3.63 (2.69-4.91)

SUD=Substance Use Disorder, AUD=Alcohol Use Disorder, DA=Drug Abuse, SU=Stimulant Use Disorder (F14 Amphetamine Use Disorder and F15 Cocaine Use Disorder)
[a]Diagnosis of /Medication for [b]Adjusted for sex, age, year of initial prescription and psychiatric comorbidity

Figure 1 Mean MPH doses over time in individuals with SUD compared to individuals with ADHD only



SUD+=Individuals with comorbid Substance use disorder who have been prescribed methylphenidate,
SUD-=Individuals with ADHD only who have been prescribed methylphenidate

Figure 1 shows a small but significant increase in mean doses (1.1 mg/100 days) between days 100 and 600 in individuals with ADHD only. The increase of mean doses in individuals with comorbid SUD was greater (3.2 /100 days) (p-value for interaction 0.001). In contrast, no statistically significant trend in mean doses was observed between days 700 and 1200 (p=0.30 in the entire population; p=0.21 in individuals with comorbid SUD and p=0.15 in individuals with ADHD only).

S*ensitivity analysis*

The sensitivity analysis showed that 90 % (95 % CI 87.5 to 92.1) of individuals who were prescribed a daily dose of over 72 mg on days 300 and 400 picked up corresponding daily doses of over 72 mg at the pharmacy between days 200 and 400.

4.4 Study IV

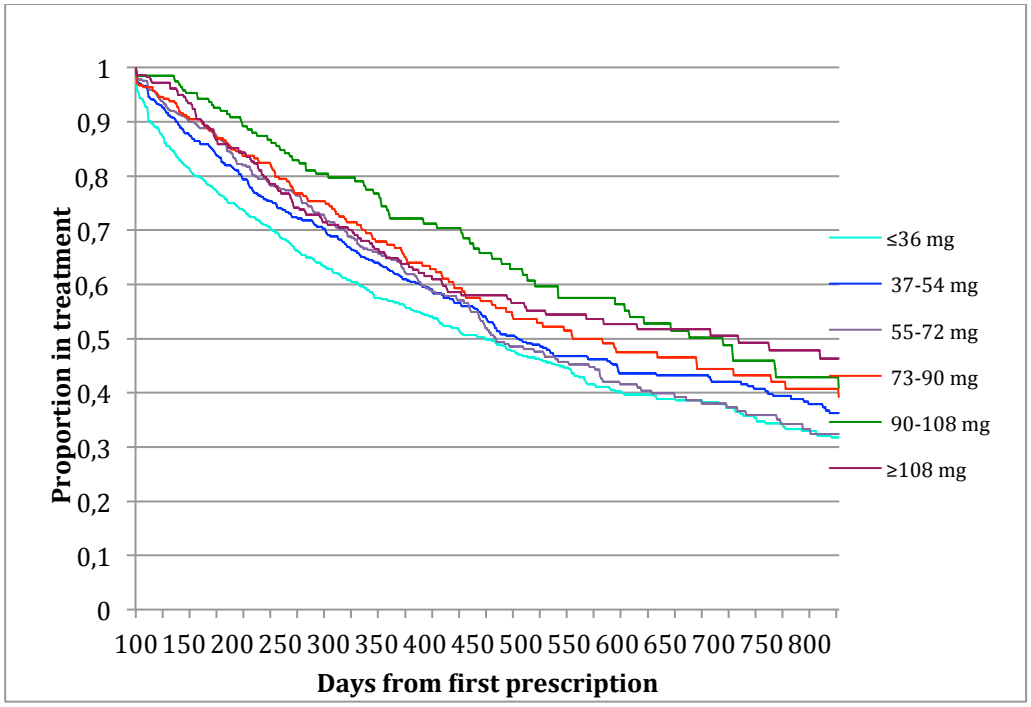
The adjusted proportional hazard ratios for MPH treatment discontinuation day 101 to 830 are shown in Table 4. Hazard ratios for treatment discontinuation decrease in conjunction with increasing MPH dose up until doses exceeding 72 mg ($HR_{\leq 36\ mg}$ 1.71 (1.33-2.20); $HR_{37\text{-}54mg}$ 1.43 (1.10-1.85); $HR_{55\text{-}72mg}$ 1.37 (1.05-1.80); $HR_{73\text{-}90mg}$ 1.19 (0.89-1.60); $HR_{\geq 108mg}$ 1.12 (0.83-1.51). The results for doses exceeding 72 mg were non-significant compared to the reference selected but remained significant compared to other dose categories. A significant trend (linear trend, $p<0.0001$) towards decreased risk for treatment discontinuation in conjunction with increased MPH doses is shown across all dose categories. The point estimates for doses over 108 mg exceed the estimates for the reference category (90-108mg), possibly due to low sample size. Neither a diagnosis of alcohol use disorder alone nor individuals with a SUD diagnosis of several drugs in combination were associated with an increased risk for treatment discontinuation, whereas individuals with a diagnosis of stimulant use disorder were at an 25% increased risk for treatment discontinuation (HR_{SU} 1.26 (1.06-1.49)). Figure 2 shows a Kaplan Meier survival graph depicting crude treatment discontinuation rates among individuals with different MPH doses.

Table 4 Hazard ratios for MPH treatment discontinuation day 101-830

	N[a]	HR[b] (95% CI)
Prescribed Dose Day 100		
≤36 mg	789	1.71 (1.33-2.20)
37-54 mg	653	1.43 (1.10-1.85)
55-72 mg	447	1.37 (1.05-1.80)
73-90 mg	280	1.19 (0.89-1.60)
90-108 mg	202	ref=1
≥108 mg	288	1.12 (0.83-1.51)

Proportional hazard regression
MPH=Methylphenidate. [a]numbers of individuals with ongoing MPH prescriptions day 100.
[b]HRs are adjusted for sex, age, SUD subtype, prescribing physician's (sub)speciality and psychiatric comorbidity.

Figure 2 Crude MPH discontinuation rates day 101-830



Sensitivity analyses

Males, young individuals and patients receiving their prescriptions from a physician specialized in addiction medicine were more likely to experience early treatment discontinuation (i.e. before day 100) (OR_{Male} 1.19 95% CI 1.03-1.38; $OR_{Age18-26}$ 1.20 95 % CI 1.01-1.42; OR_{Addict} 1.28 95% CI 1.01-1.62). Coexisting psychiatric comorbidity or SUD diagnosis however did not significantly influence the risk of early treatment discontinuation. The dose dependent pattern for treatment discontinuation remained when women were analyzed separately and within different SUD subtypes. No time-dependent incline in treatment discontinuation among individuals prescribed MPH treatment year 2006-2007 and 2008-2009 was found (test for linear trend in adjusted model $p<0.0001$, for both groups), and MPH dose at day 200 was an equally strong predictor of treatment discontinuation as dose at day 100 (test for linear trend in crude model $p=0.02$ and in adjusted model $p=0.04$).

5 CONCLUSIONS AND DISCUSSION

Despite the substantial co-occurrence of ADHD and SUD, we have limited knowledge of possible common etiological factors and the safety and effectiveness of pharmacological treatment. Contradictive research findings, lack of treatment guidelines and the controversial issue of both the origin and treatment of ADHD and SUD put potentially vulnerable patients at risk, not only due to increased societal stigmatization, but also because effective treatment might be withheld. This thesis aims to expand the knowledge of common risk factors for ADHD and SUD and to explore the effectiveness and safety of stimulant treatment when ADHD and SUD coexist.

5.1 How are ADHD and SUD Etiologically Related?

By making use of quasi-experimental family designs, **Studies I** and **II** were able to test and rule out several different potential explanations for the high overlap between ADHD and SUD, arriving at the conclusion that common genetic mechanisms underlie the association.

Firstly, **Study I** shows the importance of taking unmeasured familial confounding into account before making causal claims in observational research. The previously well-established increased risk of ADHD in children whose mothers smoked during pregnancy, in the literature often interpreted as a causal relationship, was totally attenuated when genetically transmitted factors, shared between different family members were taken into account. The results suggest that familial factors rather than prenatal environmental mechanisms explain the association.

Secondly, the results in **Study II** show that pure ADHD (i.e. individuals with ADHD but not SUD) predicts pure SUD in relatives (i.e. individuals with SUD but not ADHD) ruling out both the possibility of methodological artifacts and harmful effects of ADHD treatment as feasible explanations for the prevalent overlap of ADHD and SUD.

Thirdly, CD is one of the most robust risk factors for SUD (109, 110, 154) and previous research indicates that CD drives the association between ADHD and SUD. In other words, several studies indicate that the association between ADHD no longer remains after adjustment for CD (109-112). However, if and when CD is taken into account, such studies are often limited by difficulties in generalizing from childhood to adult populations. **Study II** addresses these alternative explanations and limitations by a) including patients aged 3-65 years at the time of the first ADHD diagnosis and b) performing sensitivity analyses in a subsample excluding all individuals with CD and major depression as well as relatives of

cases and controls with ADHD diagnoses and cases and controls with SUD diagnoses, showing that pure ADHD in fact predicts pure SUD in relatives even in the absence of CD and other common psychiatric comorbidities. These results can be used as further support for ADHD as an independent risk factor for SUD.

Fourthly, in addition to comparing individuals sharing different levels of genetic makeup, **Study II** also attempts to explore the influence of shared environmental influences on the co-occurrence of ADHD and SUD. Based on the assumption that maternal half-siblings are more similar with regard to shared environmental exposures than paternal half-siblings since children continue to live predominantly with their mothers following parental separation (155), significant differences between different kinds of half siblings would indicate that environmental factors were of importance. Given similarities in risk estimates across maternal and paternal half-siblings, the results further support underlying genetic rather than shared environmental factors.

Fifthly, after establishing common genetic underpinnings for ADHD and SUD, **Study II** further explored the possibility that pleiotropic effects of genetic risk variants across a broad range of diagnostic categories result in a general liability to psychiatric disorder. The results show that the familial aggregation pattern remained similar after excluding individuals with a diagnosis of bipolar disorder and schizophrenia, suggesting that at least part of the genetic overlap is specific for ADHD and SUD.

Previous sibling comparison studies have been limited by the underdiagnosis of ADHD cases (156-158) and potential recall bias and misclassification due to the fact that mothers reported on both their own smoking habits and their children's behavior (156). **Study I** addressed these two critical limitations by a) capturing more than twice as many ADHD cases thus allowing for more precise estimates, and b) using information on SDP obtained from the MBR and ADHD diagnoses based on clinical diagnosis or medical prescriptions by physicians. In addition, cousin comparisons were performed to overcome concerns of external validity expressed by researchers who have explicitly hypothesized that women who vary in their smoking status across pregnancies are not comparable to all smoking women (159).

5.2 Are Stimulant Medication Prescription Patterns Different in Individuals with ADHD and SUD Compared to Those with ADHD Only?

Previous research suggests that stimulant ADHD treatment during childhood and adolescence might reduce the risk for future SUD (59, 102). Nonetheless, the most recent

meta-analysis by Cunill et al. shows a paucity of evidence for stimulant treatment efficacy on both ADHD and SUD related outcomes when ADHD and SUD coexist (7). **Study III** shows that patients with comorbid SUD, two years into stimulant treatment, were prescribed approximately 40% higher MPH doses than individuals with ADHD only. Doses in both groups stabilized during the first two years of treatment. Individuals with ADHD and SUD not only had higher stimulant doses but also higher adherence to pharmacological treatment than individuals with ADHD only, across the entire follow-up.

There might be different explanations to why individuals with ADHD and comorbid SUD are prescribed higher stimulant doses compared to those without SUD. On the one hand, the dose differences between the two groups may indicate that patients with SUD need higher MPH doses to achieve optimal ADHD symptom control. Individuals with comorbid SUD might, due to long term drug abuse, have developed a tolerance to central stimulants. An increase in tolerance is likely to result in a need for higher doses and prolonged titration periods. This would be consistent with two recent randomized controlled trials (160, 161) showing significant improvements in both ADHD symptoms and SUD outcomes using higher stimulant doses than earlier studies. If accurate, this may explain why previous research, limited by MPH doses recommended in current guidelines (mean doses of 62.2 mg/day) (7), has found little evidence for any beneficial effects of MPH on SUD-related outcomes. In line with this hypothesis, **Study III** show that a diagnosis of drug abuse, a combined diagnosis of both drug abuse and alcohol use disorder and a diagnosis of stimulant use disorder significantly increased the risk of exceeding a dose of 72 mg/day, indicating that SUD severity and/or subtype also may be correlated to MPH dose. On the other hand, MPH is a schedule II classed medication (127), and can be used for non-medical purposes, possibly indicating a more alarming interpretation of the higher doses among individuals with SUD. However, the vast majority of individuals with comorbid SUD were prescribed MPH ER formulations, associated with low abuse liability. Consistent with these result there are research suggesting that rates of abuse and diversion of MPH may be lower than expected compared to e.g. opiates or sedatives despite its reinforcing effects (162).

The efficacy of agonist maintenance therapy available for opioid addiction has been extensively studied (163), whereas substitution treatment for stimulant use disorders has been less investigated and research targeting the direct effect of stimulant medication on SUD pathophysiology is as yet inconclusive (164-168). Adequate treatment, more specifically adequate dosage, may increase motivation to stay in treatment and prevent

relapses to illegal drug use.

The tendency towards increasing doses during the first two years of treatment, more pronounced in individuals with comorbid SUD, may reflect a reluctance to prescribe adequate doses due to lack of clinical guidelines. The dose-response relationship of MPH on ADHD symptoms is well established (62). Less is known about inter-individual serum concentration variability in relation to ADHD symptom control (169), and clinicians are left to arbitrarily titrate the medication based on the patient's subjective response. Given the lack of objective assessment procedures, biomarkers or clear treatment guidelines, clinicians might, due to fear of misuse, abuse or diversion (125, 170) be reluctant to increase doses to optimal levels for individuals with ADHD and SUD.

Adherence to treatment is one of the most consistent factors associated with a favorable addiction treatment outcome. The findings that individuals with comorbid SUD, at any given time point during the follow-up had higher adherence to treatment than those with ADHD only therefore becomes important. Three years following the initial prescription of MPH, 45% of patients with ADHD and SUD, compared to 37% of individuals with ADHD only, were still actively picking up their prescriptions. There might be several explanations for this, and the use of adequate MPH dosage may be one factor that affects motivation to stay in treatment and prevent relapses to illegal drug use.

5.3 What Factors Influence Adherence to Stimulant Medication when ADHD and SUD Coexist?

As discussed previously, adherence to treatment is associated with a favorable addiction treatment outcome (135) and sometimes used as a proxy for successful treatment outcome (e.g., reduction or cession of drug intake) (171, 172). Treatment discontinuation is a costly and medically significant problem (129) associated with worse course of both somatic and psychiatric disorders (130-132). Previous research is inconsistent regarding factors that might influence treatment adherence. Patient age, and in particular the years of transition from child and adolescent to adult healthcare services, has consistently been a strong predictor for treatment discontinuation for both ADHD and SUD (135, 137-139). Consistent with studies investigating treatment discontinuation in individuals with ADHD only, a large meta-analysis exploring adherence to addiction treatment in individuals with SUD suggests that even though young age is an important demographic factor for treatment discontinuation, other patient-related factors might be of limited importance (135). As such, the authors suggest that future research should focus primarily on treatment-associated factors (135). **Study IV**

explore if patient related factors such as sex, age, SUD subtype or psychiatric comorbidity and treatment related factors such as the prescribing physicians (sub)specialty, or MPH dose are associated with adherence to pharmacological treatment.

Surprisingly, and contrary to the current perception that comorbid ADHD and SUD display particularly severe symptoms and impairments (173-176), **Study III** found that individuals with comorbid SUD consistently had greater adherence to pharmacological treatment compared to patients with ADHD only. Furthermore, **Study IV**, more specifically showed that higher stimulant doses were associated with higher adherence to treatment, supporting the hypothesis that inadequate stimulant doses might at least be part of the explanation for the lack effectiveness of stimulant treatment in comorbid SUD (7).

Consistent with previous research (138, 139, 177), **Study IV** found that male sex and young age increased the risk of early ADHD treatment discontinuation (i.e. before day 100). Since several studies show that the discontinuation patterns within these age groups far exceed the estimated rate of ADHD persistence (137-139) it might be of particular importance for policy makers and healthcare professionals to focus resources on young adults before and after the discharge from pediatric services. Young age continued to be discretely associated with increased risk for treatment discontinuation after day 100, whereas most measured patient-related factors such as SUD subtype and psychiatric comorbidity seemed to be less important predictors of both long and short-term adherence to treatment. Importantly however, individuals with a diagnosis of stimulant use disorders, when analyzed separately and in contrast to individuals with both alcohol use disorder and abuse of several drugs in combination, showed an increased risk of treatment discontinuation. One explanation to as why individuals with a diagnosis of amphetamine and/or cocaine use disorder distinguish themselves from other SUD subtypes might be associated with the unstable living conditions common among active amphetamine users (178). Socializing with substance using peers, low rates of permanent employment and high prevalence of criminal activities are all factors known to negatively impact treatment outcome and adherence (178). A more biologically oriented theory, supported by imaging studies showing that individuals with stimulant use disorder present extremely week dopamine responses to MPH exposure (123, 124), suggest that similarities in pharmacokinetic properties of illicit stimulants of abuse and MPH, might lead to a more severe form of tolerance to stimulant compounds.

Treatment with MPH, being a schedule II classed drug (127) is often surrounded by tight and rigorous clinical control systems (9, 128), in particular in the presence of SUD. Self-reported or toxicologically verified relapses violate the treatment agreement and should,

according to current guidelines, result in discontinuation of pharmacological treatment until SUD remission (9, 128). Adherence to treatment is one of the most consistent factors associated with a favorable addiction treatment outcome (135) and the increased adherence to MPH treatment in individuals with SUD might, at least in the current Swedish setting, also represent a proxy for alcohol and drug abstinence. These hypotheses however need to be replicated by future research with the ability to control for diversion of collected prescriptions and confounding by indication.

5.4 Limitations and Methodological Considerations

The studies included in this thesis rely on several assumptions made regarding ADHD, SUD and stimulant medication. All the studies must also be viewed in light of the limitations associated with observational research in general and each specific study design in particular. The assumptions underlying the methods used in **Studies I** and **II** rely on the well-established theory of meiosis, the type of cell division that produces eggs and sperm and randomly distributes alleles from parents to each of their offspring. Accordingly, first-degree relatives (i.e. full siblings and parents) share approximately 50% of their co-segregating genes and are thereby more genetically similar than second-degree relatives (half-siblings) who only share approximately 25% of their co-segregating genes. In addition parents and full siblings are assumed to share 100% of their environmental exposures, whereas maternal half-siblings are more similar with regard to shared environmental exposures than paternal half-siblings since children continue to live predominantly with their mothers following parental separation (155). Finally, cousins, being offspring of full-siblings, share approximately 12.5% of their cosegregating genes.

The ascertainment of ADHD cases in **Studies I** and **II** was predominantly based on ICD-10 diagnosis of hyperkinetic disorder and prescribed medication unique for the treatment of ADHD. The ICD-10 definition of ADHD is stricter compared with that in DSM-IV, and national guidelines for medication of ADHD, issued by the Swedish National Board of health and Welfare in 2002, state that medication should be reserved for cases where other supportive interventions have failed, indicating that the proxies used for ADHD most likely underestimate the incidence of ADHD and identify the more severe ADHD cases. Given that these strategies probably could not avoid producing false negatives, bias due to false positives is more unlikely. Also, this potential bias would, in the case of **Study I**, affect the estimates on the population level and the sibling and cousin samples in the same direction, diluting the risk estimates, driving all associations towards the null. In addition, **Study I** captures more

than twice as many ADHD cases compared to previous sibling comparison studies (157, 158) allowing for more precise estimates than previous research.

Studies exploring exposures or outcomes of SUD and SDP might be limited by the fact that these diagnoses can be considered stigmatizing and consequently under diagnosed, resulting in bias due to misclassification. In addition, the risk or chance of getting a diagnosis might be dependent on cultural norms, legal aspects regarding different drugs of abuse and local differences in accessibility to SUD treatment. The probability of an individual being misclassified as not having SUD can be considered substantial, thus severely limiting the use for register-based research on SUD related outcomes. However, there are ways to get around some of these limitations by making use of proxy variables for SUD related outcomes. **Studies II-IV** used prescriptions for medications that are almost exclusively used in the treatment of SUD as a proxy for a SUD diagnosis as a complement to the ICD diagnosis in the NPR. Of course, these strategies can never fully compensate for incomplete register coverage of SUD, but individuals actually diagnosed with SUD probably represent a more severe subsample of the diagnoses and the diagnostic specificity can be considered high.

SDP was assessed at the first visit to antenatal care and applied as a proxy for the entire pregnancy. As in all observational studies, it is difficult to fully rule out residual confounding due to a lack of intact information or misclassification of the exposure. The magnitude of this potential bias was considered limited however, since previous studies exploring SDP and low birth weight show equally strong associations (47, 179).

ADHD probands and their relatives might be more exposed to healthcare interventions resulting in an obvious risk of detection bias of both ADHD and SUD. Also, given the significant time trend in the diagnosis of ADHD (138), the observed association for parents in **Study II** could be overestimated due to under-diagnosis of ADHD in older people and could thus explain the higher risk of SUD in parents compared to siblings of ADHD probands. The age differences between full and maternal half-siblings could lead to differences in the level of the shared environment exposures. Adjustments for parental education however, used as a proxy for socioeconomic environment, indicated that potential confounding from differences in shared environmental factors across sibling types might be of limited importance.

Selection bias can arise when the probability of being selected to a specific group is associated with either the exposure or the outcome. In **Study I** younger siblings of ADHD cases might be at increased risk of being diagnosed with ADHD compared to a child in a family without prior experience of the disorder. In **Study II**, individuals with ADHD might

be at increased risk of being diagnosed with SUD as a consequence of general knowledge of the frequent coexistence of both disorders. However, the results were robust to sensitivity analysis specifically addressing these potential limitations.

Although sibling comparison is not confounded by factors shared by siblings, the estimates might theoretically be more sensitive to bias due to non-shared confounders than the unpaired estimates (159). Given that only discordant sibling pairs are informative and random measurement error is not shared by siblings, the within-sibling design might favor selection of this bias and consequently increase the attenuation of the observed association between SDP and ADHD in offspring.

In addition, clinicians might be reluctant to prescribe stimulant medications to patients with co-occurring ADHD and SUD due to lack of clear clinical guidelines and concerns about medication abuse or diversion. This begs the question of whether the registry-identified patients with ADHD and SUD who were prescribed stimulant medications comprise a representative sample, raising concerns about potential selection bias. Specifically, in the case of a general clinical reluctance to prescribe stimulants to dually-diagnosed patients, the individuals identified in **Studies III** and **IV** could theoretically possess characteristics making clinicians more comfortable prescribing stimulants to them. By identifying study participants based on dispensed MPH prescriptions, the studies' design inherits potential limitations to generalizability of the results. That is, the design does not exclude the possibility that subgroups of patients with coexisting ADHD and SUD may have sought treatment but were not prescribed stimulant medication due to specific characteristics of their co-occurring SUD.

Confounding by indication can be a serious threat to observational pharmacoepidemiological studies since the probability of receiving a certain medical treatment can be associated with individual prognostic factors for which this particular drug is used. Even for individuals affected by the same disorder, the severity of the disorder might influence treatment indication, duration and dose. In **Studies III** and **IV** register-based data unfortunately did not allow for control of ADHD or SUD symptom severity making it hard to fully exclude the possibility that different displays of these disorders influenced treatment decisions such as dosage. However, since Swedish ADHD treatment recommendations dictate that pharmacological treatment is reserved for more severe ADHD cases (9), it seems reasonable to assume that individuals included in the studies are among the more severely affected ADHD patients. A remaining question is also whether SUD severity per se affects the possibility of being prescribed a certain MPH dose. Attempts made to control for this possibility indicated that doses were unaffected by SUD subtype and the prescribing

physicians (sub) specialty, suggesting limited influence of bias due to SUD symptom severity.

Data on dispensed prescriptions obtained from the PDR used in **Studies III** and **IV** cannot guarantee that the quantity of medication prescribed and received equals the amount of medication actually consumed. Only a strict experimental protocol would allow control for this but clinical trials do not allow for the large sample sizes and long follow-up periods used in **Studies III** and **IV**. Consequently, the observed finding of higher MPH doses in individuals with ADHD and comorbid SUD needs to be considered in light of the possible diversion of medication. However, although non-medical use and diversion of stimulants may be more prevalent in certain populations (170), and despite that diversion of prescription opioids has been recently studied (180), the diversion of stimulants has not yet been systematically investigated in a Swedish context.

Treatment with MPH, a schedule II classed medication is controlled (127), and treatment guidelines often recommend abstinence from abused substances prior to and during such pharmacological treatment (9, 11, 91). As a consequence, individuals with ADHD and comorbid SUD might be more closely monitored than individuals with ADHD only. Hence, individuals with SUD might, in order to prevent abuse and medication diversion, be subject to different or more intense psychosocial interventions and/or monitoring, which in turn could explain the proportionally higher adherence to treatment among patients with SUD shown in **Study III**.

5.5 General Conclusions

This thesis had two overall aims: a) to explore the etiological overlap between ADHD and SUD and b) to explore effectiveness and safety of stimulant medication when ADHD and SUD coexist. The results from the four studies included in this thesis expand current knowledge in several ways. Firstly, **Studies I** and **II** show that common genetic underpinnings largely explain the well-established overlap of ADHD and SUD. This will have several important implications for clinicians, researchers and policymakers. Familial history of ADHD needs to be taken into account when assessing risk for future SUD since it is not only the individuals themselves, but also their relatives who are at risk for SUD. Consequently, with further understanding of the etiological overlap between the two disorders, clinicians might be able to target individuals at high risk for SUD at an early stage. The findings of common genetic underpinnings for ADHD and SUD may help researchers to tailor molecular studies to increase the chances of identifying genetic risk variants shared

across ADHD and SUD. This, in turn would generate a better understanding of the pathophysiological mechanisms that are common to ADHD and SUD. Even though there is mounting evidence that SDP is harmful in many ways, it is essential for policymakers to focus on true causal risk factors for ADHD. The results from the current thesis suggest that SDP is most probably not one of them.

Secondly, **Study III** show that individuals with comorbid SUD were prescribed approximately 40% higher stimulant doses that those with ADHD only. Moreover, stimulant doses stabilized over time in both groups, with no signs of tolerance. Individuals with comorbid SUD rather surprisingly had higher adherence to pharmacological treatment than individuals with ADHD only. Furthermore, **Study IV** showed that higher MPH doses predict long-term treatment adherence in individuals with comorbid SUD. The studies, despite being of a naturalistic and descriptive nature, provide important information increasing knowledge of effectiveness and safety of stimulant treatment in individuals with ADHD who also have SUD. The lack of objective assessment procedures, biomarkers or clear treatment guidelines gives clinicians little guidance in managing ADHD in the presence of SUD. The concerns around the safety of stimulant treatment might make clinicians reluctant to increase doses to optimal levels for individuals with ADHD and SUD or result in the withholding of essential and effective pharmacological treatment in affected individuals.

Finally, individuals with ADHD and SUD not only experience great personal suffering and functional impairment but are also exposed to a variety of misunderstandings and misinterpretations regarding their ADHD symptoms and SUD disorders. Hopefully the findings from this thesis can help to increase societal acceptance for ADHD and SUD as valid medical diagnoses, reduce the personal and psychosocial stigmatization associated with both disorders, and ensure that these individuals receive effective treatment.

6 FUTURE IMPLICATIONS

6.1 Show Me The Genes!

Molecular genetic studies have so far failed to reproduce the consistently high estimates of genetic contribution to several psychiatric disorders, including ADHD (38) found in observational research. Based on the findings from this thesis indicating shared genetic underpinnings for ADHD and SUD, future molecular genetic studies may identify genetic risk variants that are shared across ADHD and SUD in order to generate a better understanding of the pathophysiological mechanisms that are common to the two disorders and to thereby individualize and optimize future psychosocial and pharmacological treatment.

6.2 The Devil Is In The Details

A major problem in the clinical management of ADHD and SUD appears when we fail to recognize the heterogeneity of these disorders. The importance for future studies to stratify participants by more refined SUD and ADHD assessments was highlighted by Covey et al showing that smoking cessation responses to MPH, depend both on ADHD subtype and severity of nicotine dependence (181). The current classification systems (i.e. DSM-IV and ICD-10) are categorical, assigning individuals to a discrete clinical entity (case yes/no). However, genetically informed research (182) as well as the most recent diagnostic instruments (71) support a more continues approach where ADHD and SUD symptoms are best viewed along a continuous spectrum towards increased disorder severity. Increased focus on ADHD and SUD endophenotypes (refined neural or behavioral entities more proximal to the etiology of the original phenotype (183)) might be an important complement to DSM or ICD definitions. This approach might also increase the chances of identifying genetic variants involved in disease etiology, improve the understanding of the complex clinical picture, the liability for certain comorbidities and individual variations in response to pharmacological treatment (183, 184). Current research has as yet failed to identify any distinct behavioral or neurocognitive endophenotypes of ADHD and SUD, but this approach remains very useful in managing and tailoring individual treatment programs in a clinical setting.

6.3 Medical Treatment Or Just Drugs For People with Addiction?

The rationale behind maintenance therapy (e.g. methadone for opioid dependence) is to prevent relapse into active illicit drug use by providing orally administered compounds,

with mechanism of action similar to but with lower addictive potential, than the drug of abuse (168, 185). An important question that deserves further investigation is whether MPH primarily targets ADHD symptoms or modulates the pathophysiology of SUD directly, or both. Based on efficacy of agonist maintenance therapy available for opioid (163, 186) and nicotine addiction (187), several researchers have hypothesized that medically prescribed psychostimulants such as MPH might reduce withdrawal and craving, as well as the reinforcing effects of amphetamine or methamphetamine (160, 164-167, 188, 189). However, the direct effect of stimulant medication on SUD pathophysiology is as yet inconclusive (185). The results from **Studies III** and **IV** indicate that adequate treatment, or more specifically adequate dosage, might increase motivation to stay in treatment. Future research should use more detailed information on ADHD and SUD and outcome proxies for relapses to illegal drug use or diversion of stimulant medication to further explore the potential for MPH treatment of SUD.

6.4 Can I Trust You?

Despite several epidemiological studies suggesting possible protective effects of ADHD medication on future development of SUD (59, 102), there are still some lingering concerns about harmful effects of stimulant treatment stemming primarily from findings of animal and imaging studies (99, 103, 104).

In addition, MPH can be used for non-medical purposes, by healthy students without ADHD to stay awake (190), by athletes to enhance performance (191) and for recreational purposes to gain high or increased sociability (192). The studies included in this thesis cannot rule out the possibility that the prescribed medication was used in another way than was the intention of the prescribing physician.

IR formulations of MPH designated for oral use that are administered intravenously affect brain areas involved in the reward system, resulting in reinforcing experiences almost identical to those of cocaine (99, 103, 104). This risk could make clinicians fear or suspect that patients may feign ADHD symptoms in order to obtain stimulant medication (126). Consequently the extent and nature of non-medical use, abuse and diversion, becomes an important area for future research. It is crucial to explore specific factors associated with abuse and diversion of stimulants to be able to target and protect vulnerable individuals. This, in turn, will ensure that adequate treatment interventions are aimed at individuals who need and benefit from them, increasing the security and validity of stimulant medication when ADHD and SUD coexist.

7 SVENSKSPRÅKIG SAMMANFATTNING

Trots att det är välkänt att personer med ADHD har en ökad risk för att drabbas av skadligt bruk eller beroende av alkohol eller droger (Substance Use Disorder, SUD), vet vi förhållandevis lite om hur olika ärftliga och miljömässiga faktorer bidrar till denna riskökning. Centralstimulerande medicin, till exempel methylfenidat (MPH), rekommenderas som säker och effektiv behandling vid ADHD, men vi har relativt lite kunskap kring effekt och säkerhet av sådan behandling hos personer som även har SUD. Det finns idag få konsekventa riktlinjer för hur dessa ofta utsatta patienter bäst ska behandlas.

I **Studie I** och **II** undersöker vi olika förklaringar till den höga samsjukligheten mellan ADHD och SUD. Den första frågan vi ställer är om rökning under graviditet (Smoking During Pregnancy, SDP) orsakar ADHD eller om det starka sambandet man sett i tidigare studier istället kan förklaras av att ärftliga faktorer kan påverka både risken för att röka under graviditeten och risken för ADHD. **Studie I** visar att risken för ADHD inte kvarstår när man jämför syskon vars mödrar rökt under den ena graviditeten men inte den andra. Vi tolkar resultaten som att genetiska faktorer snarare än själva rökningen skapar den riskökning man ser när obesläktade individer jämförs. I **Studie II** som är en familjestudie, undersöker vi flera olika förklaringar till den ökade risken för SUD hos personer med ADHD. Genom att jämföra risken för SUD hos släktingar till personer med, respektive utan ADHD kan man undersöka om den höga samsjukligheten förklaras bäst av en överlappande symtombild, skadliga effekter av ADHD medicinering eller delade genetiska och miljömässiga faktorer. Det visade sig att risken för SUD är högre ju närmare släkt man är med en person som har ADHD. Detta stämmer bäst överens med en gemensam genetisk förklaringsmodell.

I **Studie III** och **IV** jämför vi förskrivningsmönstret av MPH hos personer med och utan SUD. Vi undersöker hur MPH doserna utvecklas över tid och om man kan se några tecken på successivt ökande doser i någon av grupperna. **Studie III** visar först och främst att patienter med SUD förskrivs högre doser, men även att de fortsätter att hämta ut sina recept under en längre tid än patienter utan SUD. I **Studie IV** tittar vi närmare på hur olika patient- och behandlingsrelaterade faktorer påverkar hur länge personer med SUD stannar kvar i MPH behandling.

Att vara drabbad av både ADHD och SUD kan leda till många olika typer av problem, ofta kopplat till ett stort lidande både för de drabbade och deras anhöriga. Personer med både ADHD och SUD kan ha svårt att finna sig tillrätta inom hälso- och sjukvården och de psykosociala konsekvenserna av denna samsjuklighet kostar samhället stora summor pengar.

Med den här avhandlingen vill vi öka förståelsen och acceptansen för ADHD och SUD som valida och behandlingsbara tillstånd. Vi hoppas att ökade kunskaper om de bakomliggande orsakerna till ADHD och SUD ska leda till att samhällets resurser används där de kan göra mest nytta. Förhoppningsvis kan även resultaten i denna avhandling bidra med en pusselbit till den långsamt växande kunskapen kring behandling av personer med samtidig ADHD och SUD.

8 ACKNOWLEDGEMENTS

First and foremost, thanks to all the amazing, intelligent, intense and passionate kids, adolescents and adults I meet daily in my clinical practice. I am so grateful for being invited into your lives and that you share your strengths and struggles with me. I learn so much from every one of you, every day and nothing of this would matter, if it weren't for you.

Henrik Larsson, my main supervisor. For support and guidance over these years. Your dedication to science and your professionalism has made my journey into research stimulating and educative. You have guided me with patience and accuracy and you possess many extremely valuable supervisory characteristics. You always reply on time with such informed and productive suggestions, and your vast knowledge in the field of pharmacoepidemiology has been absolutely crucial for the progression and quality of this thesis. I have particularly come to appreciate how much time and effort you have invested in my excessive and voluminous scientific writing. Most importantly though, and extremely annoying for an impulsive, hyperactive person like me, I feel safe that you would never let me get away with anything less then doing my absolute best.

Johan Franck, my co-supervisor and Head of Stockholm Center for Dependency Disorders. It has been a privilege to tap into your endless knowledge and expertise. Your great name in the field of psychiatry has opened many doors and rendered me many invaluable connections for the future. By being truly dedicated to improving the lives of our patients, you encourage and enable the research-oriented clinical environment that made this doctoral thesis possible to begin with.

Tom Palmstierna, my mentor. Thank you for providing all the support and guidance a lost doctoral student needs. You combine true compassion for patients and excellent clinical expertise along with brilliant science and you have been my No 1 role model since I first set foot in Stockholm Center for Dependency Disorders almost 20 years ago.

Lena Brandt, a.k.a Sadistikern, my statistical wizard. It has been a pleasure doing business with you. Thank you for making me believe in myself, for never getting tired of my stupid questions and for all our important discussions on poodles and potatoes.

Nitya Jayaram Lindström, It would take another book to fully describe what a dedicated, intelligent, loyal and compassionate scientist you are. You are an equally qualified boss, mentor, supervisor, colleague and friend. The most precious gift from this doctoral project is our friendship.

Joar Guterstam, co-PhD student, colleague and a true inspiration in research. Thank you for being one of the most intelligent, humble, generous and honest persons I have come across in this business.

Pia Steensland, **Maija Konstenius**, **Anders Hammarberg, Lotfi Khemiri**, **Christoffer Brynte, Kristine Feltman, Ida Fredriksson** and **Camilla Hellspong** for selflessly investing time and effort in your fellow group members' projects and careers. I don't always understand the details of your research projects, but I always enjoy trying.

Brian Donofrio, Catarina Almqvist, Paul Lichtenstein, Maija Konstenius and **Qi Chen**, my co-authors, for inspiring and valuable feedback.

Ingrid Davstad and **Karin Ekdahl** for investing both time and effort in helping me start up this doctoral thesis.

Qi Chen, a statistical wonder-kid and fellow MD, wherever you are in the world, regardless of time differences, you always respond with respect to my uninformed questions.

Agnes Ohlsson Gotby, Anci Fredman, Andrea Johansson Capusan, Andreas Jangmo, Carolyn Cesta, Emma Frans, Gustaf Brander, Isabell Brinkell, Jie Song, Laura Ghirardi, Martin Cederlöf, Mina Rydell, Ralf Kujala-Halkola, Shuyang Yao, Tong Gong and Ylva Ginsberg for stimulating discussions, important feedback and for sharing your profound knowledge in epidemiological research with a simple clinician like me.

Clara Gumpert for sound advice on the topic of combining clinical work and research.

Helena von Schewen and **Torbjörn Högberg** for providing a challenging and stimulating clinical environment at Maria Ungdom & **Anette Rosén** for endless administrative support (my worst game). **Mathias Sjöberg**, co-pilot since med-school. Thank you for being so cool and stable and regularly picking up the pieces of me.

Fatima Tajik, Peter Inkö, Johanna Bengtsson, Madeleine Sköld, Johanna Pousette, Hans-Martin Engström, Eva Clasing, Ida Tomner and **Emil Jäder**, the crew at Livsstilsmottagningen & Maria Ungdom Vasa, where truly meaningful work is done. For putting up with my stress, anxiety and research-related mood swings all these years.

Kjell and **Torsten** at IT-support for patiently solving all sorts of (real and imagined) technically related emergencies and crises.

Madhuri, what have I done to deserve a friend like you? With love, drama, laughter and intellectual challenge you enrich my life and broaden my perspectives. You never let me get away with bullshit or self-deception. You are a truly beautiful human being. **Magnus**, thank you for generously inviting us into your life and for enriching our dinners with your strong (and occasionally adequate) opinions.

Fuffen and Lojsan, for generously sharing everyday efforts of life through the good and challenging times without any aspiration of making cosmetic adjustments. You tell it like it is and that's what family is for!

Tue, a.k.a the Artist. You are a truly gifted soul. Thank you for the beautiful picture. Your energy and confidence in life is contagious and I cherish all our precious memories.

Nicke and Jonas, my loyal, loving brothers. Thank you for all your dedicated support during this process and for always providing for the kids and me. A special thanks to my amazing sister-in-law **Sophie**, you are such an important part of our family. I am so thankful for having all of you, including precious **Olivia** and **Ludvig**, close by in my life.

Kim, my intelligent, strong and compassionate mother-in-law. All women should have the privilege of a female role model like you. Thanks to you I can enjoy an inspiring job without ever having to compromise the children's wellbeing. You provide a safe, warm and stable home for all of us. Thank you for raising such an empathic, tolerant and loving son. There are not enough words to express my gratitude…

Mom, for always being there. For your loyalty, generosity and for always keeping your door open. **Dad**, for being my idol and my constant source of inspiration. For genetically transferring some strange energy that, looking at you, will never run out. For always believing in me and giving me the courage to try new things.

Per, you are the love of my life. Without you I would be lost. You are the most generous, loving, considerate, intelligent and funny person I know. We are a great team, you and I.

Nike, Hanna, Klara, Filip & **Alexander**, my beautiful children. The true meaning of my life. I am so proud of you all I could explode. The way you care for each other makes me confident that you will make smart choices throughout life. You have shown me such respect and compassion these last months. I feel truly rich.

REFERENCES

1. Charach A, Yeung E, Climans T, Lillie E. Childhood attention-deficit/hyperactivity disorder and future substance use disorders: comparative meta-analyses. Journal of the American Academy of Child and Adolescent Psychiatry. 2011;50(1):9-21.

2. Wilens TE. A sobering fact: ADHD leads to substance abuse. Journal of the American Academy of Child and Adolescent Psychiatry. 2011;50(1):6-8.

3. van Emmerik-van Oortmerssen K, van de Glind G, Koeter MW, Allsop S, Auriacombe M, Barta C, et al. Psychiatric comorbidity in treatment-seeking substance use disorder patients with and without attention deficit hyperactivity disorder: results of the IASP study. Addiction. 2014;109(2):262-72.

4. van Emmerik-van Oortmerssen K, van de Glind G, van den Brink W, Smit F, Crunelle CL, Swets M, et al. Prevalence of attention-deficit hyperactivity disorder in substance use disorder patients: a meta-analysis and meta-regression analysis. Drug and alcohol dependence. 2012;122(1-2):11-9.

5. Faraone SV, Glatt SJ. A comparison of the efficacy of medications for adult attention-deficit/hyperactivity disorder using meta-analysis of effect sizes. The Journal of clinical psychiatry. 2010;71(6):754-63.

6. Faraone SV, Buitelaar J. Comparing the efficacy of stimulants for ADHD in children and adolescents using meta-analysis. European child & adolescent psychiatry. 2010;19(4):353-64.

7. Cunill R, Castells X, Tobias A, Capella D. Pharmacological treatment of attention deficit hyperactivity disorder with co-morbid drug dependence. Journal of psychopharmacology. 2014.

8. Canadian ADHD Resource Alliance. http://www.caddra.ca/practice-guidelines/download. Accessed 2015-10-30.

9. National Board for Health and Welfare. Läkemedelsbehandling av adhd hos barn och vuxna – Stöd för beslut om behandling http://www.socialstyrelsen.se/riktlinjer/beslutsstodforbehandling/lakemedelsbehandlingavadhd. Accessed 2015-10-30.

10. Bolea-Alamanac B, Nutt DJ, Adamou M, Asherson P, Bazire S, Coghill D, et al. Evidence-based guidelines for the pharmacological management of attention deficit hyperactivity disorder: update on recommendations from the British Association for Psychopharmacology. Journal of psychopharmacology. 2014;28(3):179-203.

11. National Institute of Health and Care Excellence, NICE. Attention deficit hyperactivity disorder: Diagnosis and management of ADHD in children, young people and adults. http://www.nice.org.uk/guidance/cg72
Accessed 2015-10-30.

12. Barkley RA, Peters H. The earliest reference to ADHD in the medical literature? Melchior Adam Weikard's description in 1775 of "attention deficit" (Mangel der Aufmerksamkeit, Attentio Volubilis). Journal of attention disorders. 2012;16(8):623-30.

13. DSM-IV A. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th edition. Washington (DC): American Psychiatric Association; 1994.

14. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. The American journal of psychiatry. 2007;164(6):942-8.

15. Polanczyk GV, Willcutt EG, Salum GA, Kieling C, Rohde LA. ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. International journal of epidemiology. 2014.

16. Kessler RC, Adler L, Barkley R, Biederman J, Conners CK, Demler O, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. The American journal of psychiatry. 2006;163(4):716-23.

17. Simon V, Czobor P, Balint S, Meszaros A, Bitter I. Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. The British journal of psychiatry : the journal of mental science. 2009;194(3):204-11.

18. Centre for Disease Control and Prevention. Increasing Prevalence of Parent-Reported Attention-Deficin/Hyperactivity Disorder Among Children http://www.cdc.gov/ncbddd/adhd/ Accessed 2015-10-30.

19. Polanczyk GV, Willcutt EG, Salum GA, Kieling C, Rohde LA. ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. International journal of epidemiology. 2014;43(2):434-42.

20. Sciutto MJ, Eisenberg M. Evaluating the evidence for and against the overdiagnosis of ADHD. Journal of attention disorders. 2007;11(2):106-13.

21. Willcutt EG. The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review. Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics. 2012;9(3):490-9.

22. Biederman J, Faraone SV. Attention-deficit hyperactivity disorder. Lancet. 2005;366(9481):237-48.

23. Larsson H, Lichtenstein P, Larsson JO. Genetic contributions to the development of ADHD subtypes from childhood to adolescence. Journal of the American Academy of Child and Adolescent Psychiatry. 2006;45(8):973-81.

24. Loe IM, Feldman HM. Academic and educational outcomes of children with ADHD. Journal of pediatric psychology. 2007;32(6):643-54.

25. DuPaul GJ, McGoey KE, Eckert TL, VanBrakle J. Preschool children with attention-deficit/hyperactivity disorder: impairments in behavioral, social, and school functioning. Journal of the American Academy of Child and Adolescent Psychiatry. 2001;40(5):508-15.

26. Glass K, Flory K, Hankin BL. Symptoms of ADHD and close friendships in adolescence. Journal of attention disorders. 2012;16(5):406-17.

27. Barkley RA, Fischer M, Smallish L, Fletcher K. Young adult outcome of hyperactive children: adaptive functioning in major life activities. Journal of the American Academy of Child and Adolescent Psychiatry. 2006;45(2):192-202.

28. Bauman A, Phongsavan P. Epidemiology of substance use in adolescence: prevalence, trends and policy implications. Drug and alcohol dependence. 1999;55(3):187-207.

29. Chang Z, Lichtenstein P, Larsson H. The effects of childhood ADHD symptoms on early-onset substance use: a Swedish twin study. Journal of abnormal child psychology. 2012;40(3):425-35.

30. Faraone SV, Biederman J, Mick E. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. Psychological medicine. 2006;36(2):159-65.

31. Biederman J, Faraone SV, Spencer TJ, Mick E, Monuteaux MC, Aleardi M. Functional impairments in adults with self-reports of diagnosed ADHD: A controlled study of 1001 adults in the community. The Journal of clinical psychiatry. 2006;67(4):524-40.

32. Cox DJ, Cox BS, Cox J. Self-reported incidences of moving vehicle collisions and citations among drivers with ADHD: a cross-sectional survey across the lifespan. The American journal of psychiatry. 2011;168(3):329-30.

33. Arias AJ, Gelernter J, Chan G, Weiss RD, Brady KT, Farrer L, et al. Correlates of co-occurring ADHD in drug-dependent subjects: prevalence and features of substance dependence and psychiatric disorders. Addictive behaviors. 2008;33(9):1199-207.

34. Martin J, Hamshere ML, Stergiakouli E, O'Donovan MC, Thapar A. Genetic Risk for Attention-Deficit/Hyperactivity Disorder Contributes to Neurodevelopmental Traits in the General Population. Biological psychiatry. 2014.

35. Banerjee TD, Middleton F, Faraone SV. Environmental risk factors for attention-deficit hyperactivity disorder. Acta paediatrica. 2007;96(9):1269-74.

36. Larsson H, Asherson P, Chang Z, Ljung T, Friedrichs B, Larsson JO, et al. Genetic and environmental influences on adult attention deficit hyperactivity disorder symptoms: a large Swedish population-based study of twins. Psychological medicine. 2013;43(1):197-207.

37. Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA, et al. Molecular genetics of attention-deficit/hyperactivity disorder. Biological psychiatry. 2005;57(11):1313-23.

38. Neale BM, Medland SE, Ripke S, Asherson P, Franke B, Lesch KP, et al. Meta-analysis of genome-wide association studies of attention-deficit/hyperactivity disorder. Journal of the American Academy of Child and Adolescent Psychiatry. 2010;49(9):884-97.

39. Cross-Disorder Group of the Psychiatric Genomics C. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. Lancet. 2013;381(9875):1371-9.

40. Larsson H, Ryden E, Boman M, Langstrom N, Lichtenstein P, Landen M. Risk of bipolar disorder and schizophrenia in relatives of people with attention-deficit hyperactivity disorder. The British journal of psychiatry : the journal of mental science. 2013;203(2):103-6.

41. Dwyer JB, McQuown SC, Leslie FM. The dynamic effects of nicotine on the developing brain. Pharmacology & therapeutics. 2009;122(2):125-39.

42. Slotkin TA, Tate CA, Cousins MM, Seidler FJ. Prenatal nicotine exposure alters the responses to subsequent nicotine administration and withdrawal in adolescence: Serotonin receptors and cell signaling. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2006;31(11):2462-75.

43. Langley K, Rice F, van den Bree MB, Thapar A. Maternal smoking during pregnancy as an environmental risk factor for attention deficit hyperactivity disorder behaviour. A review. Minerva pediatrica. 2005;57(6):359-71.

44. Linnet KM, Dalsgaard S, Obel C, Wisborg K, Henriksen TB, Rodriguez A, et al. Maternal lifestyle factors in pregnancy risk of attention deficit hyperactivity disorder and associated behaviors: review of the current evidence. The American journal of psychiatry. 2003;160(6):1028-40.

45. Motlagh MG, Katsovich L, Thompson N, Lin H, Kim YS, Scahill L, et al. Severe psychosocial stress and heavy cigarette smoking during pregnancy: an examination of the pre- and perinatal risk factors associated with ADHD and Tourette syndrome. European child & adolescent psychiatry. 2010;19(10):755-64.

46. Rodriguez A, Bohlin G. Are maternal smoking and stress during pregnancy related to ADHD symptoms in children? Journal of child psychology and psychiatry, and allied disciplines. 2005;46(3):246-54.

47. Cnattingius S. The epidemiology of smoking during pregnancy: smoking prevalence, maternal characteristics, and pregnancy outcomes. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2004;6 Suppl 2:S125-40.

48. Thapar A, Cooper M, Eyre O, Langley K. What have we learnt about the causes of ADHD? Journal of child psychology and psychiatry, and allied disciplines. 2013;54(1):3-16.

49. Fredriksen M, Halmoy A, Faraone SV, Haavik J. Long-term efficacy and safety of treatment with stimulants and atomoxetine in adult ADHD: a review of controlled and naturalistic studies. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology. 2013;23(6):508-27.

50. Daley D, van der Oord S, Ferrin M, Danckaerts M, Doepfner M, Cortese S, et al. Behavioral interventions in attention-deficit/hyperactivity disorder: a meta-analysis of randomized controlled trials across multiple outcome domains. Journal of the American Academy of Child and Adolescent Psychiatry. 2014;53(8):835-47, 47 e1-5.

51. Kollins SH. A qualitative review of issues arising in the use of psycho-stimulant medications in patients with ADHD and co-morbid substance use disorders. Current medical research and opinion. 2008;24(5):1345-57.

52. Connor DF, Fletcher KE, Swanson JM. A meta-analysis of clonidine for symptoms of attention-deficit hyperactivity disorder. Journal of the American Academy of Child and Adolescent Psychiatry. 1999;38(12):1551-9.

53. Wilens TE, Morrison NR, Prince J. An update on the pharmacotherapy of attention-deficit/hyperactivity disorder in adults. Expert review of neurotherapeutics. 2011;11(10):1443-65.

54. Del Campo N, Chamberlain SR, Sahakian BJ, Robbins TW. The roles of dopamine and noradrenaline in the pathophysiology and treatment of attention-deficit/hyperactivity disorder. Biological psychiatry. 2011;69(12):e145-57.

55. Kooij SJ, Bejerot S, Blackwell A, Caci H, Casas-Brugue M, Carpentier PJ, et al. European consensus statement on diagnosis and treatment of adult ADHD: The European Network Adult ADHD. BMC psychiatry. 2010;10:67.

56. Martinez-Raga J, Knecht C, Szerman N, Martinez MI. Risk of serious cardiovascular problems with medications for attention-deficit hyperactivity disorder. CNS drugs. 2013;27(1):15-30.

57. Graham J, Coghill D. Adverse effects of pharmacotherapies for attention-deficit hyperactivity disorder: epidemiology, prevention and management. CNS drugs. 2008;22(3):213-37.

58. Clavenna A, Bonati M. Safety of medicines used for ADHD in children: a review of published prospective clinical trials. Archives of disease in childhood. 2014;99(9):866-72.

59. Chang Z, Lichtenstein P, Halldner L, D'Onofrio B, Serlachius E, Fazel S, et al. Stimulant ADHD medication and risk for substance abuse. Journal of child psychology and psychiatry, and allied disciplines. 2014;55(8):878-85.

60. Chen Q, Sjolander A, Runeson B, D'Onofrio BM, Lichtenstein P, Larsson H. Drug treatment for attention-deficit/hyperactivity disorder and suicidal behaviour: register based study. Bmj. 2014;348:g3769.

61. Dalsgaard S, Mortensen PB, Frydenberg M, Maibing CM, Nordentoft M, Thomsen PH. Association between Attention-Deficit Hyperactivity Disorder in childhood and schizophrenia later in adulthood. European psychiatry : the journal of the Association of European Psychiatrists. 2014;29(4):259-63.

62. Greenhill LL, Swanson JM, Vitiello B, Davies M, Clevenger W, Wu M, et al. Impairment and deportment responses to different methylphenidate doses in children with ADHD: the MTA titration trial. Journal of the American Academy of Child and Adolescent Psychiatry. 2001;40(2):180-7.

63. Wilens T, McBurnett K, Stein M, Lerner M, Spencer T, Wolraich M. ADHD treatment with once-daily OROS methylphenidate: final results from a long-term open-label study. Journal of the American Academy of Child and Adolescent Psychiatry. 2005;44(10):1015-23.

64. Markowitz JS, Straughn AB, Patrick KS, DeVane CL, Pestreich L, Lee J, et al. Pharmacokinetics of methylphenidate after oral administration of two modified-release formulations in healthy adults. Clinical pharmacokinetics. 2003;42(4):393-401.

65. Gonzalez MA, Pentikis HS, Anderl N, Benedict MF, DeCory HH, Dirksen SJ, et al. Methylphenidate bioavailability from two extended-release formulations. International journal of clinical pharmacology and therapeutics. 2002;40(4):175-84.

66. Swanson J, Kinsbourne M, Roberts W, Zucker K. Time-response analysis of the effect of stimulant medication on the learning ability of children referred for hyperactivity. Pediatrics. 1978;61(1):21-9.

67. Swanson J, Gupta S, Lam A, Shoulson I, Lerner M, Modi N, et al. Development of a new once-a-day formulation of methylphenidate for the treatment of attention-deficit/hyperactivity disorder: proof-of-concept and proof-of-product studies. Archives of general psychiatry. 2003;60(2):204-11.

68. Crocq MA. Historical and cultural aspects of man's relationship with addictive drugs. Dialogues in clinical neuroscience. 2007;9(4):355-61.

69. Berridge V, Mars S. History of addictions. Journal of epidemiology and community health. 2004;58(9):747-50.

70. UNODC. World Drug Report 2014 https://www.unodc.org/wdr2014/ Accsessed 2015-10-30.

71. DSM-5 A. American Psychiatric Association. Diagnostic and statistical mannual of mental disorders 5th ed. Washington. DC: American Psychiatric Association; 2013 http://psychiatry.org/psychiatrists/practice/dsm Accessed 2015-10-30.

72. CAN. Drogutvecklingen i Sverige 2014 Rapport http://can.se/sv/Undersokningar/Drogutvecklingen-i-Sverige/ Accsessed 2015-10-15.

73. Degenhardt L, Whiteford HA, Ferrari AJ, Baxter AJ, Charlson FJ, Hall WD, et al. Global burden of disease attributable to illicit drug use and dependence: findings from the Global Burden of Disease Study 2010. Lancet. 2013;382(9904):1564-74.

74. Ball D. Addiction science and its genetics. Addiction. 2008;103(3):360-7.

75. Lynskey MT, Agrawal A, Heath AC. Genetically informative research on adolescent substance use: methods, findings, and challenges. Journal of the American Academy of Child and Adolescent Psychiatry. 2010;49(12):1202-14.

76. Agrawal A, Verweij KJ, Gillespie NA, Heath AC, Lessov-Schlaggar CN, Martin NG, et al. The genetics of addiction-a translational perspective. Translational psychiatry. 2012;2:e140.

77. Wise RA, Koob GF. The development and maintenance of drug addiction. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2014;39(2):254-62.

78. Goodwin DW, Schulsinger F, Knop J, Mednick S, Guze SB. Psychopathology in adopted and nonadopted daughters of alcoholics. Archives of general psychiatry. 1977;34(9):1005-9.

79. Goodwin DW, Schulsinger F, Moller N, Hermansen L, Winokur G, Guze SB. Drinking problems in adopted and nonadopted sons of alcoholics. Archives of general psychiatry. 1974;31(2):164-9.

80. Kendler KS, Karkowski LM, Neale MC, Prescott CA. Illicit psychoactive substance use, heavy use, abuse, and dependence in a US population-based sample of male twins. Archives of general psychiatry. 2000;57(3):261-9.

81. Karkowski LM, Prescott CA, Kendler KS. Multivariate assessment of factors influencing illicit substance use in twins from female-female pairs. American journal of medical genetics. 2000;96(5):665-70.

82. Tsuang MT, Bar JL, Harley RM, Lyons MJ. The Harvard Twin Study of Substance Abuse: what we have learned. Harvard review of psychiatry. 2001;9(6):267-79.

83. Tsuang MT, Lyons MJ, Eisen SA, Goldberg J, True W, Lin N, et al. Genetic influences on DSM-III-R drug abuse and dependence: a study of 3,372 twin pairs. American journal of medical genetics. 1996;67(5):473-7.

84. Kendler KS, Bulik CM, Silberg J, Hettema JM, Myers J, Prescott CA. Childhood sexual abuse and adult psychiatric and substance use disorders in women: an epidemiological and cotwin control analysis. Archives of general psychiatry. 2000;57(10):953-9.

85. Moran PB, Vuchinich S, Hall NK. Associations between types of maltreatment and substance use during adolescence. Child abuse & neglect. 2004;28(5):565-74.

86. Alati R, Al Mamun A, Williams GM, O'Callaghan M, Najman JM, Bor W. In utero alcohol exposure and prediction of alcohol disorders in early adulthood: a birth cohort study. Archives of general psychiatry. 2006;63(9):1009-16.

87. Wakschlag LS, Pickett KE, Cook E, Jr., Benowitz NL, Leventhal BL. Maternal smoking during pregnancy and severe antisocial behavior in offspring: a review. American journal of public health. 2002;92(6):966-74.

88. Gorwood P, Wohl M, Le Strat Y, Rouillon F. Gene-environment interactions in addictive disorders: epidemiological and methodological aspects. Comptes rendus biologies. 2007;330(4):329-38.

89. Cadoret RJ, Troughton E, O'Gorman TW, Heywood E. An adoption study of genetic and environmental factors in drug abuse. Archives of general psychiatry. 1986;43(12):1131-6.

90. Cloninger CR, Bohman M, Sigvardsson S. Inheritance of alcohol abuse. Cross-fostering analysis of adopted men. Archives of general psychiatry. 1981;38(8):861-8.

91. National Board of Health and Welfare. Nationella riktlinjer för vård och stöd vid missbruk och beroende – Stöd för styrning och ledning http://www.socialstyrelsen.se/nationellariktlinjermissbrukochberoende Accessed 2015-10-30.

92. Martin GW, Rehm J. The effectiveness of psychosocial modalities in the treatment of alcohol problems in adults: a review of the evidence. Canadian journal of psychiatry Revue canadienne de psychiatrie. 2012;57(6):350-8.

93. Douaihy AB, Kelly TM, Sullivan C. Medications for substance use disorders. Social work in public health. 2013;28(3-4):264-78.

94. Stinson FS, Grant BF, Dawson DA, Ruan WJ, Huang B, Saha T. Comorbidity between DSM-IV alcohol and specific drug use disorders in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Drug and alcohol dependence. 2005;80(1):105-16.

95. Najt P, Fusar-Poli P, Brambilla P. Co-occurring mental and substance abuse disorders: a review on the potential predictors and clinical outcomes. Psychiatry research. 2011;186(2-3):159-64.

96. Frodl T. Comorbidity of ADHD and Substance Use Disorder (SUD): a neuroimaging perspective. Journal of attention disorders. 2010;14(2):109-20.

97. Cortese S, Castellanos FX. Neuroimaging of attention-deficit/hyperactivity disorder: current neuroscience-informed perspectives for clinicians. Current psychiatry reports. 2012;14(5):568-78.

98. Volkow ND, Fowler JS, Wang GJ, Baler R, Telang F. Imaging dopamine's role in drug abuse and addiction. Neuropharmacology. 2009;56 Suppl 1:3-8.

99. Volkow ND, Swanson JM. Variables that affect the clinical use and abuse of methylphenidate in the treatment of ADHD. The American journal of psychiatry. 2003;160(11):1909-18.

100. Volkow ND, Fowler JS, Wang GJ, Swanson JM, Telang F. Dopamine in drug abuse and addiction: results of imaging studies and treatment implications. Archives of neurology. 2007;64(11):1575-9.

101. Volkow ND, Wang GJ, Kollins SH, Wigal TL, Newcorn JH, Telang F, et al. Evaluating dopamine reward pathway in ADHD: clinical implications. Jama. 2009;302(10):1084-91.

102. Mannuzza S, Klein RG, Truong NL, Moulton JL, 3rd, Roizen ER, Howell KH, et al. Age of methylphenidate treatment initiation in children with ADHD and later substance abuse: prospective follow-up into adulthood. The American journal of psychiatry. 2008;165(5):604-9.

103. Wise RA. Brain reward circuitry: insights from unsensed incentives. Neuron. 2002;36(2):229-40.

104. Swanson JM, Volkow ND. Serum and brain concentrations of methylphenidate: implications for use and abuse. Neuroscience and biobehavioral reviews. 2003;27(7):615-21.

105. Thapar A, Rutter M. Do prenatal risk factors cause psychiatric disorder? Be wary of causal claims. The British journal of psychiatry : the journal of mental science. 2009;195(2):100-1.

106. Elkins IJ, McGue M, Iacono WG. Prospective effects of attention-deficit/hyperactivity disorder, conduct disorder, and sex on adolescent substance use and abuse. Archives of general psychiatry. 2007;64(10):1145-52.

107. Schubiner H, Tzelepis A, Milberger S, Lockhart N, Kruger M, Kelley BJ, et al. Prevalence of attention-deficit/hyperactivity disorder and conduct disorder among substance abusers. The Journal of clinical psychiatry. 2000;61(4):244-51.

108. Ebejer JL, Medland SE, van der Werf J, Gondro C, Henders AK, Lynskey M, et al. Attention deficit hyperactivity disorder in Australian adults: prevalence, persistence, conduct problems and disadvantage. PloS one. 2012;7(10):e47404.

109. Flory K, Lynam DR. The relation between attention deficit hyperactivity disorder and substance abuse: what role does conduct disorder play? Clinical child and family psychology review. 2003;6(1):1-16.

110. Serra-Pinheiro MA, Coutinho ES, Souza IS, Pinna C, Fortes D, Araujo C, et al. Is ADHD a risk factor independent of conduct disorder for illicit substance use? A meta-analysis and metaregression investigation. Journal of attention disorders. 2013;17(6):459-69.

111. August GJ, Winters KC, Realmuto GM, Fahnhorst T, Botzet A, Lee S. Prospective study of adolescent drug use among community samples of ADHD and non-ADHD participants. Journal of the American Academy of Child and Adolescent Psychiatry. 2006;45(7):824-32.

112. Barkley RA, Fischer M, Smallish L, Fletcher K. Young adult follow-up of hyperactive children: antisocial activities and drug use. Journal of child psychology and psychiatry, and allied disciplines. 2004;45(2):195-211.

113. Kendler KS, Chen X, Dick D, Maes H, Gillespie N, Neale MC, et al. Recent advances in the genetic epidemiology and molecular genetics of substance use disorders. Nature neuroscience. 2012;15(2):181-9.

114. Kendler KS, Sundquist K, Ohlsson H, Palmer K, Maes H, Winkleby MA, et al. Genetic and familial environmental influences on the risk for drug abuse: a national Swedish adoption study. Archives of general psychiatry. 2012;69(7):690-7.

115. van den Bree MB, Johnson EO, Neale MC, Pickens RW. Genetic and environmental influences on drug use and abuse/dependence in male and female twins. Drug and alcohol dependence. 1998;52(3):231-41.

116. Biederman J, Petty CR, Wilens TE, Fraire MG, Purcell CA, Mick E, et al. Familial risk analyses of attention deficit hyperactivity disorder and substance use disorders. The American journal of psychiatry. 2008;165(1):107-15.

117. Edwards AC, Kendler KS. Twin study of the relationship between adolescent attention-deficit/hyperactivity disorder and adult alcohol dependence. Journal of studies on alcohol and drugs. 2012;73(2):185-94.

118. Biederman J, Petty CR, Monuteaux MC, Mick E, Clarke A, Ten Haagen K, et al. Familial risk analysis of the association between attention-deficit/hyperactivity disorder and psychoactive substance use disorder in female adolescents: a controlled study. Journal of child psychology and psychiatry, and allied disciplines. 2009;50(3):352-8.

119. Groenman AP, Oosterlaan J, Rommelse N, Franke B, Roeyers H, Oades RD, et al. Substance use disorders in adolescents with attention deficit hyperactivity disorder: a 4-year follow-up study. Addiction. 2013;108(8):1503-11.

120. Biederman J, Pettye CR, Hammerness P, Woodworth KY, Faraon SV. Examining the nature of the association between attention-deficit hyperactivity disorder and nicotine dependence: a familial risk analysis. Canadian journal of psychiatry Revue canadienne de psychiatrie. 2013;58(3):177-83.

121. Volkow ND, Fowler JS, Wang GJ, Swanson JM. Dopamine in drug abuse and addiction: results from imaging studies and treatment implications. Molecular psychiatry. 2004;9(6):557-69.

122. Hyman SE, Malenka RC, Nestler EJ. Neural mechanisms of addiction: the role of reward-related learning and memory. Annual review of neuroscience. 2006;29:565-98.

123. Volkow ND, Wang GJ, Fowler JS, Logan J, Gatley SJ, Hitzemann R, et al. Decreased striatal dopaminergic responsiveness in detoxified cocaine-dependent subjects. Nature. 1997;386(6627):830-3.

124. Wang GJ, Smith L, Volkow ND, Telang F, Logan J, Tomasi D, et al. Decreased dopamine activity predicts relapse in methamphetamine abusers. Molecular psychiatry. 2012;17(9):918-25.

125. Kaye S, Darke S. The diversion and misuse of pharmaceutical stimulants: what do we know and why should we care? Addiction. 2012;107(3):467-77.

126. Levin FR. Diagnosing attention-deficit/hyperactivity disorder in patients with substance use disorders. The Journal of clinical psychiatry. 2007;68 Suppl 11:9-14.

127. US Food and Drug Administration. Controlled Substances Act. http://www.fda.gov/RegulatoryInformation/Legislation/ucm148726.htm Accessed 2015-10-30

128. Swedish Medical Products Agency. Information från Läkemedelsverket 1:2009 https://lakemedelsverket.se/malgrupp/Halso---sjukvard/Behandlings--rekommendationer/Behandlingsrekommendation---listan/ADHD/ Accessed 2015-10-30.

129. Elliott RA, Barber N, Horne R. Cost-effectiveness of adherence-enhancing interventions: a quality assessment of the evidence. The Annals of pharmacotherapy. 2005;39(3):508-15.

130. Blaschke TF, Osterberg L, Vrijens B, Urquhart J. Adherence to medications: insights arising from studies on the unreliable link between prescribed and actual drug dosing histories. Annual review of pharmacology and toxicology. 2012;52:275-301.

131. Osterberg L, Blaschke T. Adherence to medication. The New England journal of medicine. 2005;353(5):487-97.

132. Kooij JJ, Rosler M, Philipsen A, Wachter S, Dejonckheere J, van der Kolk A, et al. Predictors and impact of non-adherence in adults with attention-deficit/hyperactivity disorder receiving OROS methylphenidate: results from a randomized, placebo-controlled trial. BMC psychiatry. 2013;13:36.

133. Charach A, Ickowicz A, Schachar R. Stimulant treatment over five years: adherence, effectiveness, and adverse effects. Journal of the American Academy of Child and Adolescent Psychiatry. 2004;43(5):559-67.

134. Thiruchelvam D, Charach A, Schachar RJ. Moderators and mediators of long-term adherence to stimulant treatment in children with ADHD. Journal of the American Academy of Child and Adolescent Psychiatry. 2001;40(8):922-8.

135. Brorson HH, Ajo Arnevik E, Rand-Hendriksen K, Duckert F. Drop-out from addiction treatment: a systematic review of risk factors. Clinical psychology review. 2013;33(8):1010-24.

136. Castells X, Cunill R, Capella D. Treatment discontinuation with methylphenidate in adults with attention deficit hyperactivity disorder: a meta-analysis of randomized clinical trials. European journal of clinical pharmacology. 2013;69(3):347-56.

137. McCarthy S, Asherson P, Coghill D, Hollis C, Murray M, Potts L, et al. Attention-deficit hyperactivity disorder: treatment discontinuation in adolescents and young adults. The British journal of psychiatry : the journal of mental science. 2009;194(3):273-7.

138. Zetterqvist J, Asherson P, Halldner L, Langstrom N, Larsson H. Stimulant and non-stimulant attention deficit/hyperactivity disorder drug use: total population study of trends and discontinuation patterns 2006-2009. Acta psychiatrica Scandinavica. 2013;128(1):70-7.

139. Wong IC, Asherson P, Bilbow A, Clifford S, Coghill D, DeSoysa R, et al. Cessation of attention deficit hyperactivity disorder drugs in the young (CADDY)--a pharmacoepidemiological and qualitative study. Health technology assessment. 2009;13(50):iii-iv, ix-xi, 1-120.

140. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. European journal of epidemiology. 2009;24(11):659-67.

141. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC public health. 2011;11:450.

142. Wettermark B, Hammar N, Fored CM, Leimanis A, Otterblad Olausson P, Bergman U, et al. The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiology and drug safety. 2007;16(7):726-35.

143. Odlind V, Haglund B, Pakkanen M, Otterblad Olausson P. Deliveries, mothers and newborn infants in Sweden, 1973-2000. Trends in obstetrics as reported to the Swedish Medical Birth Register. Acta obstetricia et gynecologica Scandinavica. 2003;82(6):516-28.

144. Axelsson O. The Swedish medical birth register. Acta obstetricia et gynecologica Scandinavica. 2003;82(6):491-2.

145. Ekbom A. The Swedish Multi-generation Register. Methods in molecular biology. 2011;675:215-20.

146. Cause of Death Register. The National Board of Health and Wellfare. http://www.socialstyrelsen.se/register/dodsorsaksregistret
Accessed 2015-10-30.

147. LISA. Statistics Sweden http://www.scb.se/lisa/
Acsessed 2015-10-30.

148. D'Onofrio BM, Lahey BB, Turkheimer E, Lichtenstein P. Critical need for family-based, quasi-experimental designs in integrating genetic and social science research. American journal of public health. 2013;103 Suppl 1:S46-55.

149. Lindmark G, Cnattingius S. The scientific basis of antenatal care. Report from a state-of-the-art conference. Acta obstetricia et gynecologica Scandinavica. 1991;70(2):105-9.

150. D'Onofrio BM, Singh AL, Iliadou A, Lambe M, Hultman CM, Grann M, et al. Familial confounding of the association between maternal smoking during pregnancy and offspring criminality: a population-based study in Sweden. Archives of general psychiatry. 2010;67(5):529-38.

151. Lundberg F, Cnattingius S, D'Onofrio B, Altman D, Lambe M, Hultman C, et al. Maternal smoking during pregnancy and intellectual performance in young adult Swedish male offspring. Paediatric and perinatal epidemiology. 2010;24(1):79-87.

152. Lichtenstein P, Bjork C, Hultman CM, Scolnick E, Sklar P, Sullivan PF. Recurrence risks for schizophrenia in a Swedish national cohort. Psychological medicine. 2006;36(10):1417-25.

153. Lichtenstein P, Yip BH, Bjork C, Pawitan Y, Cannon TD, Sullivan PF, et al. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. Lancet. 2009;373(9659):234-9.

154. Lynskey MT, Hall W. Attention deficit hyperactivity disorder and substance use disorders: Is there a causal link? Addiction. 2001;96(6):815-22.

155. Statistics Sweden. Fakta om den svenska familjen. Demografiska rapporter. Stockholm: 1994. http://www.scb.se/statistik/BE/BE0701/2000I02/BE51ST0202.pdf Accessed 2015-10-30.

156. D'Onofrio BM, Van Hulle CA, Waldman ID, Rodgers JL, Harden KP, Rathouz PJ, et al. Smoking during pregnancy and offspring externalizing problems: an exploration of genetic and environmental confounds. Development and psychopathology. 2008;20(1):139-64.

157. Lindblad F, Hjern A. ADHD after fetal exposure to maternal smoking. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2010;12(4):408-15.

158. Obel C, Olsen J, Henriksen TB, Rodriguez A, Jarvelin MR, Moilanen I, et al. Is maternal smoking during pregnancy a risk factor for hyperkinetic disorder?--Findings from a sibling design. International journal of epidemiology. 2011;40(2):338-45.

159. Frisell T, Oberg S, Kuja-Halkola R, Sjolander A. Sibling comparison designs: bias from non-shared confounders and measurement error. Epidemiology. 2012;23(5):713-20.

160. Konstenius M, Jayaram-Lindstrom N, Guterstam J, Beck O, Philips B, Franck J. Methylphenidate for attention deficit hyperactivity disorder and drug relapse in criminal offenders with substance dependence: a 24-week randomized placebo-controlled trial. Addiction. 2014;109(3):440-9.

161. Levin FR, Mariani JJ, Specker S, Mooney M, Mahony A, Brooks DJ, et al. Extended-Release Mixed Amphetamine Salts vs Placebo for Comorbid Adult Attention-Deficit/Hyperactivity Disorder and Cocaine Use Disorder: A Randomized Clinical Trial. JAMA psychiatry. 2015.

162. Cassidy TA, McNaughton EC, Varughese S, Russo L, Zulueta M, Butler SF. Nonmedical use of prescription ADHD stimulant medications among adults in a substance abuse treatment population: early findings from the NAVIPPRO surveillance system. Journal of attention disorders. 2015;19(4):275-83.

163. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. The Cochrane database of systematic reviews. 2014;2:CD002207.

164. Longo M, Wickes W, Smout M, Harrison S, Cahill S, White JM. Randomized controlled trial of dexamphetamine maintenance for the treatment of methamphetamine dependence. Addiction. 2010;105(1):146-54.

165. Galloway GP, Buscemi R, Coyle JR, Flower K, Siegrist JD, Fiske LA, et al. A randomized, placebo-controlled trial of sustained-release dextroamphetamine for treatment of methamphetamine addiction. Clinical pharmacology and therapeutics. 2011;89(2):276-82.

166. Miles SW, Sheridan J, Russell B, Kydd R, Wheeler A, Walters C, et al. Extended-release methylphenidate for treatment of amphetamine/methamphetamine dependence: a randomized, double-blind, placebo-controlled trial. Addiction. 2013;108(7):1279-86.

167. Tiihonen J, Kuoppasalmi K, Fohr J, Tuomola P, Kuikanmaki O, Vorma H, et al. A comparison of aripiprazole, methylphenidate, and placebo for amphetamine dependence. The American journal of psychiatry. 2007;164(1):160-2.

168. Mariani JJ, Khantzian EJ, Levin FR. The self-medication hypothesis and psychostimulant treatment of cocaine dependence: an update. The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions. 2014;23(2):189-93.

169. Ermer JC, Adeyi BA, Pucci ML. Pharmacokinetic variability of long-acting stimulants in the treatment of children and adults with attention-deficit hyperactivity disorder. CNS drugs. 2010;24(12):1009-25.

170. Wilens TE, Adler LA, Adams J, Sgambati S, Rotrosen J, Sawtelle R, et al. Misuse and diversion of stimulants prescribed for ADHD: a systematic review of the literature. Journal of the American Academy of Child and Adolescent Psychiatry. 2008;47(1):21-31.

171. Simpson DD. The relation of time spent in drug abuse treatment to posttreatment outcome. The American journal of psychiatry. 1979;136(11):1449-53.

172. Simpson DD, Joe GW, Rowan-Szal GA. Drug abuse treatment retention and process effects on follow-up outcomes. Drug and alcohol dependence. 1997;47(3):227-35.

173. Perez de Los Cobos J, Sinol N, Puerta C, Cantillano V, Lopez Zurita C, Trujols J. Features and prevalence of patients with probable adult attention deficit hyperactivity disorder who request treatment for cocaine use disorders. Psychiatry research. 2011;185(1-2):205-10.

174. Delavenne H, Ballon N, Charles-Nicolas A, Garcia FD, Thibaut F, Lacoste J, et al. Attention deficit hyperactivity disorder is associated with a more severe pattern of cocaine consumption in cocaine users from French West Indies. Journal of addiction medicine. 2011;5(4):284-8.

175. Levin FR, Evans SM, Vosburg SK, Horton T, Brooks D, Ng J. Impact of attention-deficit hyperactivity disorder and other psychopathology on treatment retention among cocaine abusers in a therapeutic community. Addictive behaviors. 2004;29(9):1875-82.

176. Humfleet GL, Prochaska JJ, Mengis M, Cullen J, Munoz R, Reus V, et al. Preliminary evidence of the association between the history of childhood attention-

deficit/hyperactivity disorder and smoking treatment failure. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2005;7(3):453-60.

177. Sobanski E, Retz W, Fischer R, Ose C, Alm B, Hennig O, et al. Treatment adherence and persistence in adult ADHD: results from a twenty-four week controlled clinical trial with extended release methylphenidate. European psychiatry : the journal of the Association of European Psychiatrists. 2014;29(5):324-30.

178. Hakansson A, Schlyter F, Berglund M. Characteristics of primary amphetamine users in Sweden: a criminal justice population examined with the Addiction Severity Index. European addiction research. 2009;15(1):10-8..

179. D'Onofrio BM, Rickert ME, Langstrom N, Donahue KL, Coyne CA, Larsson H, et al. Familial confounding of the association between maternal smoking during pregnancy and offspring substance use and problems. Archives of general psychiatry. 2012;69(11):1140-50.

180. Johnson B, Richert T. Diversion of methadone and buprenorphine by patients in opioid substitution treatment in Sweden: prevalence estimates and risk factors. The International journal on drug policy. 2015;26(2):183-90.

181. Covey LS, Hu MC, Weissman J, Croghan I, Adler L, Winhusen T. Divergence by ADHD subtype in smoking cessation response to OROS-methylphenidate. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2011;13(10):1003-8.

182. Larsson H, Anckarsater H, Rastam M, Chang Z, Lichtenstein P. Childhood attention-deficit hyperactivity disorder as an extreme of a continuous trait: a quantitative genetic study of 8,500 twin pairs. Journal of child psychology and psychiatry, and allied disciplines. 2012;53(1):73-80.

183. Gottesman, II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. The American journal of psychiatry. 2003;160(4):636-45.

184. Franke B, Faraone SV, Asherson P, Buitelaar J, Bau CH, Ramos-Quiroga JA, et al. The genetics of attention deficit/hyperactivity disorder in adults, a review. Molecular psychiatry. 2012;17(10):960-87.

185. Perez-Mana C, Castells X, Torrens M, Capella D, Farre M. Efficacy of psychostimulant drugs for amphetamine abuse or dependence. The Cochrane database of systematic reviews. 2013;9:CD009695.

186. Kakko J, Svanborg KD, Kreek MJ, Heilig M. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial. Lancet. 2003;361(9358):662-8.

187. Eisenberg MJ, Filion KB, Yavin D, Belisle P, Mottillo S, Joseph L, et al. Pharmacotherapies for smoking cessation: a meta-analysis of randomized controlled trials. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2008;179(2):135-44.

188. Ling W, Chang L, Hillhouse M, Ang A, Striebel J, Jenkins J, et al. Sustained-release methylphenidate in a randomized trial of treatment of methamphetamine use disorder. Addiction. 2014;109(9):1489-500.

189. Konstenius M, Jayaram-Lindstrom N, Beck O, Franck J. Sustained release methylphenidate for the treatment of ADHD in amphetamine abusers: a pilot study. Drug and alcohol dependence. 2010;108(1-2):130-3.

190. McCabe SE, Teter CJ, Boyd CJ. Medical use, illicit use and diversion of prescription stimulant medication. Journal of psychoactive drugs. 2006;38(1):43-56.

191. Deventer K, Roels K, Delbeke FT, Van Eenoo P. Prevalence of legal and illegal stimulating agents in sports. Analytical and bioanalytical chemistry. 2011;401(2):421-32.

192. Smith ME, Farah MJ. Are prescription stimulants "smart pills"? The epidemiology and cognitive neuroscience of prescription stimulant use by normal healthy individuals. Psychological bulletin. 2011;137(5):717-41.