



Associations between substance use disorder and attention-deficit/hyperactivity disorder

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**Lokaverkefni til BS-gráðu
Sálfræðideild
Heilbrigðisvísindasvið**



HÁSKÓLI ÍSLANDS

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Lokaverkefni til BS-gráðu í sálfræði

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Abstract

Accumulated research points to certain associations between substance use disorder (SUD) and attention-deficit/hyperactivity disorder (ADHD). The intent of this thesis was to examine associations between SUD and ADHD among Icelandic adults. In line with results of earlier studies, it was hypothesized that individuals with ADHD are diagnosed with SUD at an earlier age and show shorter times of abstinence than individuals without ADHD. A positive correlation was predicted between age at offset of stimulant medication for ADHD and age at diagnosis of SUD. No associations were predicted between ADHD diagnosis and specific SUDs (i.e. specific substances of abuse) or between diagnosis of ADHD subtype and specific SUDs. The study was retrospective and used data from a large-scale study on the genetics of SUD. Data of 931 individuals (643 men and 288 women) who had been diagnosed with SUD were analyzed, including 58 individuals with ADHD. Individuals with ADHD were diagnosed with SUD at an earlier age than individuals without ADHD and showed shorter times of abstinence from stimulants, but not from alcohol, cannabis, cocaine, opioids and sedatives. The relationship between age at offset of stimulant medication and age at onset of SUD was not tested since data about ADHD medication were available for very few individuals. Individuals with ADHD were more likely to be diagnosed with amphetamine, cannabis, cocaine and sedatives use disorder than individuals without ADHD, but there were no association between ADHD diagnosis and alcohol and opioid use disorder. However, individuals with ADHD were diagnosed with more SUDs than individuals without ADHD. No associations were found between diagnosis of ADHD subtypes and specific SUDs.

Introduction

Researchers' attention has increasingly been directed toward the comorbidity of substance use disorder (SUD) and attention-deficit/hyperactivity disorder (ADHD). A relationship between ADHD and SUD has been documented in a number of studies. Accumulated research suggests that about one fifth of people with SUD have ADHD and that individuals with ADHD often have a more severe and complicated course of SUD than individuals without ADHD (Wilens, 2007). The risk for SUD has been shown to be about twofold in individuals with ADHD, compared to individuals without ADHD (Biederman, Wilens, Mick, Milberger et al, 1995). It has been proposed that the relationship could be due to genetic factors, vulnerability for earlier substance use in individuals with ADHD or the presence of SUD in parents, but the nature of the relationship is still unclear (Wilens, 2007). This is an important topic, since the results of further investigations presumably could be utilized to prevent SUD in a high risk group. SUD is a high-cost disorder, both for the suffering individual and for society. The intent of this thesis is to investigate whether ADHD is associated with earlier age at diagnosis of SUD, longer times of abstinence or any specific SUD among those with a diagnosis of SUD. It will also be investigated whether offset of stimulant treatment for ADHD is associated with subsequent diagnosis of SUD and whether ADHD subtype is associated with any specific SUD.

Substance use disorder

Substance use disorder (SUD) is a common label for substance abuse and substance dependence (American Psychiatric Association, 2000). Any drug, medication or toxin is considered a substance. The common feature of substances of abuse is that they have

psychoactive properties, which means that they affect perception, thoughts and feelings. Alcohol, marijuana, cocaine, heroin and amphetamine are examples of commonly abused substances. The Diagnostic and Statistical Manual of Mental Disorders' (DSM-IV) criteria for substance abuse and dependence include using a substance repetitively with wide consequences: failing to take care of one's home, school or work, using in situations which could have dangerous consequences physically, legal problems and problems in one's social life. The diagnostic criteria for substance dependence also include signs of tolerance, withdrawal, failure to control the amount or time of intake and not managing to cut down using the substance.

Between 1,3% and 15 % of adults develop a substance use disorder sometime in their life (Kessler et al, 2007). Many drugs of abuse affect the transmission of dopamine and individual differences in the function of the dopamine transporter are predictive of responses to psychostimulants and new situations (Zhu and Reith, 2008). However, many interacting genetic, personal and environmental factors are likely to be involved in the development of SUD. Kreek, Nielsen, Butelman and LaForge (2005) propose a model of different factors contributing to a different degree at different stages in the development from initiation of drug use to addiction and relapse. They base the model on genetic studies and estimate that drug use is initially greatly influenced by impulsivity and risk taking and to a small degree by comorbidity and stress responsivity. The exact role of comorbidity is unclear, but stress affects the hypothalamic-pituitary-adrenal (HPA) axis in a way that may increase reinforcing effects of substances of abuse. The development of intermittent to regular use is under medium influence of all of these four factors – impulsivity, risk taking, comorbidity and stress responsivity. The development of addiction and relapse is influenced by impulsivity and risk taking to a minor degree, to a medium degree by comorbidity and to the greatest degree by stress

responsivity. They also set forth that environmental factors, genetic factors for addiction and drug induced effects increasingly have more influence from beginning of drug use to addiction or relapse (Figure 1).

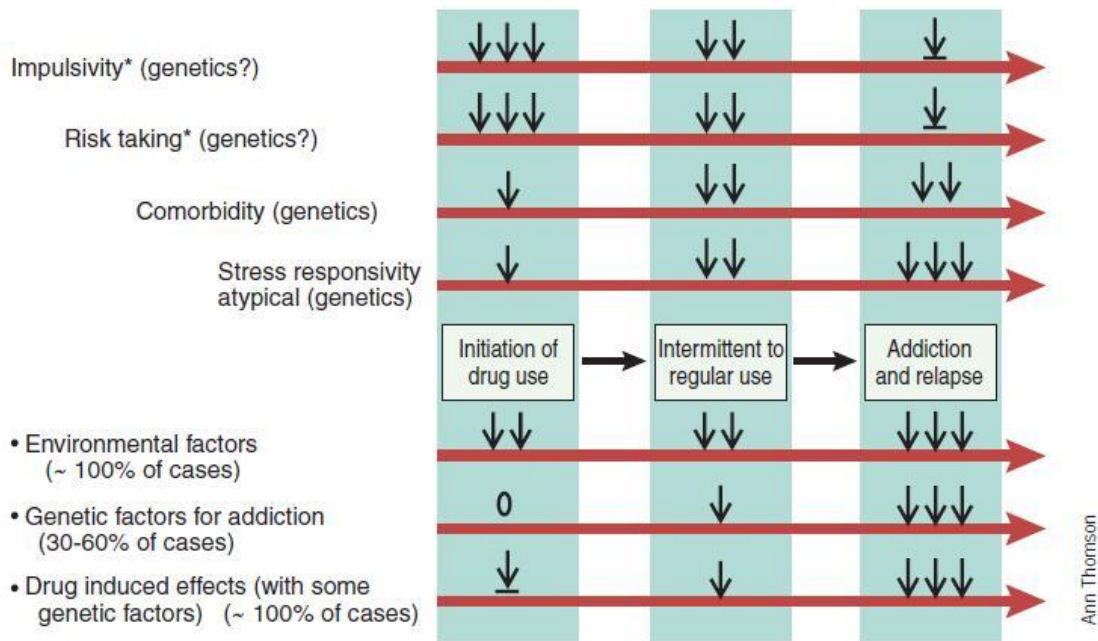


Figure 1. Factors contributing to the development of SUD. Figure is taken from Kreek et al (2005). The upper half of the figure represents personality factors and the lower half represents external factors. 0 represents no influence, an underlined arrow represents minor relative influence, one arrow represents small relative influence, two arrows represent medium relative influence and three arrows represent the greatest relative influence.

High impulsivity has indeed been associated with SUD, as well as earlier exposure to alcohol, and it seems like the age of first alcohol use is hastened by impulsivity (von Diemen et al, 2008). Substance use at an early age overall and using many kinds of substances have been found to increase the risk for developing SUD (Palmer et al,

2009). This is in line with the findings of Tarter et al (2003), who reported that SUD at age 19 was predicted by neurobehavioral disinhibition at age 16, frequency of substance use and risk group with 85% accuracy. They also found that neurobehavioral disinhibition predicted SUD to a stronger degree than frequency of substance use.

Further, strong associations have been found between SUD and a variety of mental disorders worldwide (Merikangas et al, 1998). Chan, Dennis and Funk (2008) found that two thirds of 6886 adolescents and adults who were seeking treatment for substance abuse had had mental problems during the prior year. Between 78 and 90% reported either an internalizing problem, like anxiety or depression, or an externalizing problem, like attention-deficit/hyperactivity disorder or conduct disorder, and 42%-61% reported both internalizing and externalizing problems. Grant et al (2004) found that SUD was positively associated with mood and anxiety disorders and that the mood and anxiety disorders were not dependent on the SUD or some other medical condition. Wilens et al (2007) found that more than one third of individuals between 15 and 25 years old were using substances as an attempt to change mood or aid sleep, that is to say as an attempt to self-medicate. Gudjonsson, Sigurdsson, Sigfusdottir and Young (2012) recently conducted a large epidemiological study in Iceland and found that anxiety and depression were associated with substance use in youth. These findings fit nicely with the roles of comorbidity and stress responsivity in Kreek et al's (2005) model of the development of SUD.

Attention-deficit/hyperactivity disorder

Attention-deficit/hyperactivity disorder (ADHD) is a cognitive, emotional, behavioral and social disorder, with symptoms of inattentiveness, impulsivity or hyperactivity

(American Psychiatric Association, 2000). Inattentiveness may be expressed as difficulties keeping attention on school work or taking instructions, impulsivity as breaking into conversations and taking actions without thinking them fully through, and hyperactivity as difficulties sitting in one's seat without moving around or continually fiddling with things. Symptoms need to be present for at least 6 months since before 7 years of age and cause impairment in daily functioning in a number of areas and settings. The expression of ADHD is individual, since individuals may show symptoms of inattention, hyperactivity or impulsivity to a varying degree. DSM-IV recognizes three subtypes of ADHD: predominantly inattentive type, predominantly hyperactive/impulsive type and combined type. The distinction between subtypes is made on the frequency of symptoms. A diagnosis of predominantly inattentive type requires six or more symptoms of inattentiveness and predominantly hyperactive/impulsive type requires six or more symptoms of hyperactivity/impulsivity. The combined type requires six or more symptoms of both inattentiveness and hyperactivity/impulsivity and is thus a more severe form of ADHD.

Between 3% and 7% (American Psychiatric Association (2000) or about 5 % of children worldwide are diagnosed with ADHD, with methodological differences in diagnosing the disorder probably being responsible for variations in prevalence rates (Polanczyk, de Lima, Horta, Biederman and Rohde, 2007). Rates of ADHD often decline with age (Costello, Mustillo, Erkanli, Keeler and Angold, 2003; Faraone, Biederman and Mick, 2006). However, Biederman, Petty, Evans, Small and Faraone (2010) analyzed boys who continued to meet some but not all of the criteria for ADHD diagnosis and revealed that almost 80% of them continued to be impaired into early adulthood due to their symptoms. Thus, even though rates of diagnoses of ADHD decline with age, many individuals may still be impaired by ADHD symptoms in adult

life. ADHD symptoms have been shown to be most likely to persist into adulthood when there is a family history of ADHD and in individuals who are also diagnosed with other psychological disorders. The expression, characteristics, neurobiology and pharmacological responsivity are similar for adolescents and adults with ADHD (Wilens, Biederman and Spencer, 2002).

There are up to ten times more boys than girls in clinical samples of children with ADHD, but the gender difference declines with age. In epidemiological and adult samples there are usually about twice as many males than females (Wilens et al, 2002). Gudjonsson et al (2012) used a self-administered questionnaire in their study and a screening diagnosis for ADHD symptoms was made if at least six of nine items were reported to occur either “often” or “very often”. The screening criteria for ADHD was met in 5,4% of Icelandic adolescents between 14 and 16 years, with similar rates for boys and girls. The small gender difference is noteworthy, since there are generally more boys than girls with ADHD and the study was large-scale with a sample that is very representative of Icelandic youth. However, it remains a question whether the similar rates could be due to the self-administered nature of the measure or properties of the screening ADHD items. The results possibly reflect an underestimation of boys with ADHD or overestimation of girls with ADHD.

Considerable research has been conducted with the aim of understanding the neurobiological underpinnings of ADHD. Evidence strongly suggests that the transmission of dopamine is not functioning normally in individuals with ADHD (Carlsson, 2010; Li, Sham, Owen and He, 2006; Volkow et al, 2007). Dopamine is an essential neurotransmitter and its correct transmission is necessary for attention and short-time memory to work properly. Deficits in the transmission of dopamine may also render immediate reinforcement more effective and delayed reinforcement less effective

than normally, which could be a reason for the impulsivity and hyperactivity in ADHD individuals (Carlsson, 2010). These deficits may be a result of abnormal brain development. Overproduction and subsequent pruning of neurons is a natural part of brain development and there is a possible connection between overproduction and delayed pruning of dopamine receptors in the forebrain and more persistent attention related problems. Differences between girls and boys in overproduction and pruning may result in differences in density of dopamine receptors, which could be a reason for gender differences in ADHD (Andersen and Teicher, 2000).

Treatment of ADHD usually includes medications. The stimulant methylphenidate, which is the active substance in Ritalin, is one of the most widely used psychopharmacological treatments today. It is thought to have behavioral and cognitive effects on individuals with ADHD by influencing the transmission of dopamine (Engert and Pruessner, 2008; Volkow et al, 2007) and it has been shown to have both short-term and long-term effects. Huang, Chao, Wu, Chen and Chen (2007) assessed ADHD children's scores on the Test of Variables of Attention (TOVA) and compared their scores before and one hour after receiving methylphenidate. They found that methylphenidate significantly improved the children's performance, particularly responses associated with impulsivity. Another study showed that school-aged children with ADHD combined type who had received stimulant medication for a mean of 21 months did better on tests of executive functioning than school-aged children with ADHD combined type who had not received stimulant treatment (Vance, Maruff and Barnett, 2003).

Higher prevalence of lifetime and current comorbid psychiatric disorders and more psychosocial impairment are observed in adults with ADHD than in adults without ADHD (Biederman, Wilens, Mick, Faraone and Spencer, 1998; Sobansky et al, 2007).

McGough et al (2005) reported that 87% of adults with ADHD have at least one other mental disorder and 56% have at least two. Mood and anxiety disorders were associated with ADHD and ADHD individuals showed earlier onset of dysthymia, major depression, conduct disorder and oppositional defiant disorder. Cumyn, French and Hechtman (2009) found that 19% of adults with ADHD currently suffered from depression, compared to 7% of adults without ADHD. Murphy, Barkley and Bush (2002) found that adults with ADHD combined and predominantly inattentive types were more likely to exhibit dysthymia and greater psychological distress than a control group without ADHD. Accumulated research also points to a strong relationship between ADHD and SUD (Wilens, 2006).

The relationship between ADHD and SUD

Attention has increasingly been directed toward the relationship between ADHD and SUD and associations between them have been found in a number of studies (Biederman et al, 1998; McGough et al, 2005; Szobot et al, 2007, Ohlmeier et al, 2008). Biederman et al (1995) found that the lifetime risk for developing SUD was 52% for adults with ADHD and 27% for adults without ADHD and that ADHD independently increased the risk for developing SUD. A follow-up study of only girls with ADHD also found that ADHD was strongly associated with a lifetime risk for SUD (Biederman et al, 2010). The odds of dependence have been shown to increase with the severity of ADHD (Lambert, 2005) and ADHD has also been found to be predictive of SUD in relatives (Biederman et al, 2008).

About 15-25% of individuals with SUD also have ADHD (Wilens, 2006).

Individuals with both ADHD and SUD have been shown to begin abusing substances at

an earlier age, for a longer time, with more severe abuse and impairment, relapsing more frequently and have more difficulty remaining abstinent (Biederman et al, 2008; Wilens, Biederman and Mick, 1998). Wilens, Biederman, Mick, Faraone and Spencer (1997) found that the association between ADHD and earlier onset of SUD was not dependent on comorbid psychiatric disorders. Many ADHD individuals develop an early alcohol use disorder and later also develop drug use disorders (Biederman et al, 1998). These findings fit well with Kreek et al's (2005) model of the development from initiation of drug use to addiction and relapse and reasonably explain why individuals with ADHD are at high risk for SUD.

ADHD and specific substances

Some studies have supported the notion that individuals with ADHD use different kinds of substances compared to individuals without ADHD. It has been proposed that ADHD individuals prefer stimulants to a higher degree than depressants and that this would be due to the symptom relieving effects of stimulants on individuals with ADHD (Lambert, 2005). Biederman et al (1995) and Wilens et al (1998) reported that adults with ADHD were more frequently diagnosed with drug and drug combined with alcohol use disorders than adults without ADHD, but they did not find any difference in frequencies of alcohol use disorder. Similarly, Biederman et al (2008) found that adults with ADHD are at a greater risk for drug use disorder than alcohol use disorder and Wilens et al (2007) reported that ADHD individuals used more stimulants than individuals without ADHD. Simply put, a greater preference of stimulants seems reasonable in ADHD individuals because of its symptom relieving effects.

However, this is not necessarily the case. Alcohol use disorder is present in 17-45% of adults with ADHD, while drug use disorder is present in 9-30% of adults with ADHD (Wilens, 2006). Molina and Pelham (2003) found that adolescents with ADHD used many different substances more frequently than adolescents without ADHD. ADHD adolescents were more likely to be impaired due to alcohol consumption, but there were no differences in frequency of alcohol and marijuana use disorders between the groups. Murphy et al (2002) reported that adults with ADHD combined or predominantly inattentive types were more likely to be diagnosed with alcohol use disorder and cannabis use disorder than a control group without ADHD. Clure et al (1999) assessed treatment-seeking individuals with cocaine, alcohol or cocaine and alcohol dependence. They found no differences in drug choice between individuals with ADHD and individuals without ADHD. Faraone et al (2007) similarly found no difference in drug choice between adults with ADHD and controls. Both cigarettes and marijuana were frequently used in ADHD adults. Neither Wilens et al (1998) nor Ohlmeier et al (2008) found any significant differences in the kinds of substances abused by adults with ADHD and adults without ADHD. Gudjonsson et al (2012) reported that ADHD symptoms in Icelandic youth were related to nicotine, alcohol and illicit drug use. Thus, individuals with ADHD clearly do abuse substances other than stimulants to a high degree. A reason could be the comorbidity between mood and anxiety disorders and ADHD. Individuals with ADHD often suffer from high levels of anxiety, which reasonably make depressants attractive because of their soothing effect.

Wilens et al (1998) reported that the lifetime prevalence of severe major depression, multiple anxiety disorders and conduct disorder were significantly higher in ADHD adults with a life history of SUD than non-ADHD adults with a history of SUD. Wilens et al (2005) found that adults with both ADHD and SUD show higher rates of

comorbid psychiatric disorders, especially depressive and anxiety disorders, compared to adults with only ADHD, only SUD or neither ADHD or SUD. Adults with both ADHD and SUD also showed higher rates of conduct disorders in childhood and adult antisocial personality disorder. The SUD usually developed after comorbid psychopathology and was thus unlikely responsible for it. Wilens et al (1997) similarly found that psychiatric disorders in general were diagnosed before SUD both in adults with ADHD and adults without ADHD. Gudjonsson et al's (2012) study revealed that substance use was predicted by ADHD symptoms in addition to what was predicted by anxiety and depression, but also that depressive symptoms affected illicit substance use in youth beyond ADHD symptoms. The burden of greater comorbidity in individuals with both ADHD and SUD compared to individuals with only SUD could be a reason that ADHD individuals usually show more severe abuse, more frequent relapses and more difficulty staying abstinent.

SUD and stimulant treatment for ADHD

Different voices have been heard on the topic of stimulant medications for ADHD and the relationship with subsequent SUD. A meta-analytic review by Wilens, Faraone, Biederman and Gunawardene (2003), which included data of 674 individuals who received stimulant treatment of ADHD and 360 individuals with ADHD who did not receive stimulant medication, showed that youths who received stimulant therapy of ADHD were at a lower risk for SUD when followed into adolescence. Protective effects were also reported by Biederman (2003), Katusic et al (2005) and Wilens et al (2008). Barkley, Fischer, Smallish and Fletcher (2003) found no evidence for increased risk for

any substance use, abuse or dependence due to stimulant treatment of ADHD, either in childhood or adolescence.

Andersen, Napierata, Brenhouse and Sonntag (2008) exposed rats to methylphenidate before puberty and assessed them biochemically and behaviorally in young adulthood. The results indicated that the effectiveness of methylphenidate could be due to the altering of cortical development during a sensitive period. A reduction of D3 receptors, a dopamine receptor which is thought to be involved in drug-conditioned stimuli and motivation, may bring about increased cortical responsiveness to psychostimulants and thus decrease drug-seeking behavior. One may also reason that a reduction of ADHD symptoms, including impulsivity, decreases the risk of initiation of drug use.

However, Lambert (2005) concluded that the protective effect was short-lived, Wilens et al (2003) found that the protective effect of stimulant treatment was smaller in youths who were followed into adulthood, compared to youths who were followed only into adolescence, and Biederman et al (2008) failed to replicate protective effects in a follow-up study of adults. Mannuzza et al (2008) did follow-up assessments of boys with ADHD in late adolescence and adulthood and found an association between age of methylphenidate treatment and chances of subsequent development of SUD. The risk was greater the later the treatment was initiated.

Controversies regarding ADHD subtypes

Controversies have arisen regarding the validity and reliability of the DSM-IV diagnosis of ADHD subtypes. Evidence suggests that the DSM-IV diagnosis of ADHD subtypes is not reliable. Lahey, Pelham, Loney, Lee and Willcutt (2005) re-assessed children who

were diagnosed with ADHD seven times over a period of eight years. They found that a considerable part of children in all subtypes, especially in the predominantly hyperactive-impulsive group, were diagnosed with another subtype than the initial one in two or more assessments.

Todd et al (2001) obtained data about 4036 female twins between 13 and 23 years of age, who were diagnosed with ADHD subtypes according to DSM-IV criteria. A latent-class analysis was also done, which suggested six classes of ADHD. The primarily inattentive and combined subtype ran in the same families, but not the primarily hyperactive/impulsive subtype and the latent-class analysis subtypes.

Ostrander, Herman, Sikorski, Mascendaro and Lambert (2008) used latent profile modeling and similarly found six classes of ADHD. They suggest that disruptive behavior and/or internalizing problems could be used to diagnose ADHD subtypes more reliably.

Children with ADHD combined and predominantly inattentive types have showed similar deficiencies in inhibition (Chhabildas, Pennington and Willcutt, 2001). Similarly, Huang-Pollock, Mikami, Pfiffner and McBurnett (2007) found no differences in inhibitory control between children with the combined type and children with the predominantly inattentive type. According to the diagnostic criteria of more impulsivity symptoms, children with the combined type should do worse. Gudjonsson et al (2012) found that symptoms of inattention and hyperactivity/impulsivity were highly correlated. Thus, there is evident reason to question the distinction between ADHD subtypes, since many of the core features that they are based on clearly overlap.

There is no evident relationship between ADHD subtypes, SUD and other comorbid disorders. Cumyn, French and Hechtman (2009) found that ADHD adults with the combined type showed higher rates of both past and current Axis I and Axis II

disorders compared to ADHD adults with the inattentive type. Current and past specific phobia, panic disorder and major depression were significantly associated with the combined type, as well as past conduct disorder and antisocial personality disorder. On the other hand, Murphy et al (2002) found no differences between adults with ADHD combined type and predominantly inattentive type in prevalence of conduct disorder, major depressive disorder and dysthymia. Sobanski et al (2008) included an ADHD subtype called inattentive, anamnesticly combined type in their study. This group included ADHD adults with the inattentive type who also showed symptoms of hyperactivity or impulsivity in childhood. The lifetime prevalence of comorbid psychiatric disorders were higher in the ADHD subtypes than in the controls and there was little variation between the ADHD subtypes. ADHD subtypes showed only small differences in psychosocial adjustment and they were similar regarding education, unemployment, divorces and children. However, the frequency of lifetime SUD was higher in the combined type (48,4%) and in the inattentive, anamnesticly combined type (45,8%) than in the inattentive type (23,3%), which further support the role of impulsivity in Kreek et al's (2005) model of the development of SUD. Gudjonsson et al (2012) reported a positive relationship between severity of ADHD symptoms and the number of substances used. These findings support the concept of ADHD combined type as a more severe form of ADHD, but the definitions of ADHD hyperactive/impulsive type and ADHD inattentive type are clearly not fully supported.

ADHD subtypes and specific SUDs

A literature search does not reveal many studies with the aim of comparing differences in the kinds of substances used in different ADHD subtypes. Clure and associates (1999)

found no associations between ADHD subtypes and drug of choice. Murphy, Barkley and Bush (2002) found no differences in prevalence of alcohol and cannabis use disorder between adults with ADHD combined type and predominantly inattentive type. Any association between ADHD subtype and specific substance use disorders seem unlikely in light of the similarities between ADHD subtypes discussed above.

Hypotheses

The intent of this study is to investigate associations between ADHD and SUD in a sample of Icelandic adults who have been diagnosed with SUD. In line with earlier research, it is hypothesized that individuals with ADHD will show an earlier onset of SUD than individuals without ADHD. This seems likely in light of the evidence for the role of impulsivity in children and adolescent's initiation of drug use and the connection between early use and SUD.

Based on earlier research indicating that ADHD individuals usually stay abstinent with more difficulty, another hypothesis is that ADHD individuals will show shorter periods of abstinence than individuals without ADHD. A possible explanation for this relationship could be the burden of more frequent comorbid mental disorders in individuals with ADHD, compared to individuals without ADHD.

It is predicted that ADHD diagnosis will not be associated to any specific SUD (that is to say to specific substances of abuse or dependency). This is grounded in results from earlier studies and the fact that little is known about the nature or the underpinnings of the relationship between ADHD and SUD. It does not seem likely that individuals with ADHD will be more likely than individuals without ADHD to abuse for example

stimulants, since many individuals with ADHD apparently suffer from comorbid anxiety disorders and thus should find the effects from depressants relieving.

It is hypothesized that there will be an association between age at offset of stimulant medication for ADHD and age at onset of SUD. A positive correlation is predicted, such that the earlier the offset of stimulant treatment, the earlier the onset of SUD. This is grounded in the effectiveness of stimulant medications in reducing ADHD symptoms and the evidence for their protective effects against development of SUD in individuals with ADHD.

In regard to earlier results pointing to the many similarities between DSM-IV ADHD subtypes, it is predicted that no association will be found between ADHD subtypes and any specific SUD.

Methods

Subjects

Participants were recruited from a large-scale 5-year study on the genetics of SUD. The original study was conducted by SÁÁ National Center of Addiction Medicine in Iceland and deCODE genetics. The aim of the study was to detect genes coding for SUD, thereof alcohol, tobacco and other drug use disorders, and to examine associations between SUD and various mental disorders. Both probands and relatives participated. Probands had met at least once in a rehabilitation program at Vogur, where 9,4% of all living Icelandic men and 4% of all living Icelandic women over 15 years of age have come for rehabilitation.

A randomized sample of 6500 probands was selected from medical records at Vogur and called by phone. Three thousand probands agreed to participate in the study and gave informed consent and permission to talk to relatives. Probands and relatives gave blood samples and roughly 2600 (1863 probands and 750 relatives) completed a questionnaire at Vogur. Of the 1863 probands who completed the questionnaire, 1098 were chosen, based on genetics, to complete the Semi Structured Assessment for the Genetics of Alcoholism-II (SSAGA-II) and two additional parts from the Semi-structured Assessment for Drug Dependence and Alcoholism (SSADDA). Even though this sample was not randomized, it is presumed to be representative of the Icelandic population because of its large size.

Data from the 1098 Icelandic adults who completed SSAGA-II and the additional parts from SSADDA were analyzed in this thesis. According to inclusion criteria subjects had to be 20 years old or older.

Measurements

Participants were interviewed with the Semi Structured Assessment for the Genetics of Alcoholism – II (SSAGA-II). SSAGA was originally developed in the collaborative study on the genetics of alcoholism (COGA) by Begleiter et al (1995). It is an interview utilized to assess social, psychological, physical and psychiatric indications of SUD and various mental disorders in adults. SSAGA has been shown to possess high test-retest reliability, especially for substance dependence and depression (Bucholz et al, 1994). It showed high validity when compared to the Schedule for Clinical Assessment in Neuropsychiatry (SCAN), a cross-culturally valid instrument (Hesselbrock, Easton, Bucholz, Schuckit and Hesselbrock, 1999).

Two parts of the Semi-structured Assessment for Drug Dependence and Alcoholism (SSADDA), which yield diagnoses of ADHD and pathological gambling, were added to the interview. SSADDA was originally generated from SSAGA with the aim to assess opioid and cocaine dependence and common comorbid DSM-IV disorders (Pierucci-Lagha et al, 2005). Inter-rater and test-retest reliability has been shown to be excellent for ADHD.

The interview was translated to Icelandic and back translated. Interviewers were given special training in using the interview, which consisted of 40 hours of lectures and 20 hours of vocational training. A preliminary study revealed that the Icelandic version possess both high sensitivity and predictive value of alcohol dependency diagnosis, compared to the original SSAGA interview (Bjornsdottir et al, 2008).

Measurement of the independent variables ADHD diagnosis and ADHD subtype diagnosis included meeting diagnostic criteria for ADHD and ADHD subtypes according to DSM-IV. The question “At what age did you stop taking medication?” was

used to measure the independent variable age at offset of stimulant medication for ADHD and age was recorded in years.

The question “How old were you the first time you had experiences from three or more boxes occur together within a period lasting 12 months or longer [i.e. met criteria for diagnosis of SUD]?” was used to measure the dependent variable age at onset of SUD and age was recorded in years. The dependent variable longest time of abstinence was recorded for different substances separately. The question “Since (age of regular drinking), what is the longest period of time you have gone without drinking?” was used to quantify subjects’ longest time of abstinence from alcohol and the time was recorded in months. “Since the age of (ONS [i.e. onset of SUD]), has there ever been a period of time lasting 3 months or longer when you did not use marijuana at all?” and “When did that/these occur?” were used to quantify individuals’ longest times of abstinence from marijuana. “Since the age of (ONS [i.e. onset of SUD]), has there ever been a period of time lasting 3 months or longer when you did not use drug at all?” and “When did that/these occur?” were used to quantify times of abstinence from cocaine, stimulants, sedatives, opioids and other drugs separately. Four periods of abstinence from each substance were recorded. It was recorded what month and year the periods started and what month and year they ended. The dependent variable specific SUD includes meeting diagnostic criteria for substance abuse or substance dependence of specific substances according to DSM-IV.

Procedure

The current study is retrospective and uses data from a study on the genetics of SUD (described above). The data did not include any personal information about participants.

A between-group comparison was made and the independent variables were diagnoses of ADHD and ADHD subtype. An in-group design was also used in the analysis of individuals with ADHD and the independent variable were age at offset of stimulant medication for ADHD. Dependent variables were age at onset of SUD, longest time of abstinence from specific substances and diagnoses of specific SUDs.

Statistical analysis

Statistical analyses were done in Statistical Package for the Social Sciences (SPSS) 20.0. Descriptive statistics and histograms were used to examine the variance of age, age at onset of SUD, longest time of abstinence and age at offset of stimulant medication. Frequency statistics, crosstabs and bar graphs were used to examine frequency and proportions of individuals diagnosed with specific SUDs, ADHD and ADHD subtypes.

Mann-Whitney U test were used to examine whether individuals with and without ADHD significantly differ in age at onset of SUD and longest time of abstinence. Correlation was used to examine whether a positive relationship exists between age at offset of stimulant medication for ADHD and age at onset of SUD. Chi-square tests were used to examine whether there is an association between ADHD diagnosis and specific SUDs and between diagnosis of ADHD subtype and specific SUDs. Statistical significance was set at $\alpha = 0,05$ and Bonferroni adjustment was used when several tests of significance were used to test hypotheses.

Results

Background variables

Data were obtained from 1098 individuals, thereof 778 (70,9%) men and 320 (29,1%) women. There were more than twice as many men than women, but this reflects the frequencies of men and women coming to Vogur for treatment and is no reason for concern in this study. Subjects were between 20 and 86 years old, with a mean age of 51 years and a standard deviation of 14 years. Age was normally distributed and there is no evident reason for the high mean age (Figure 2).

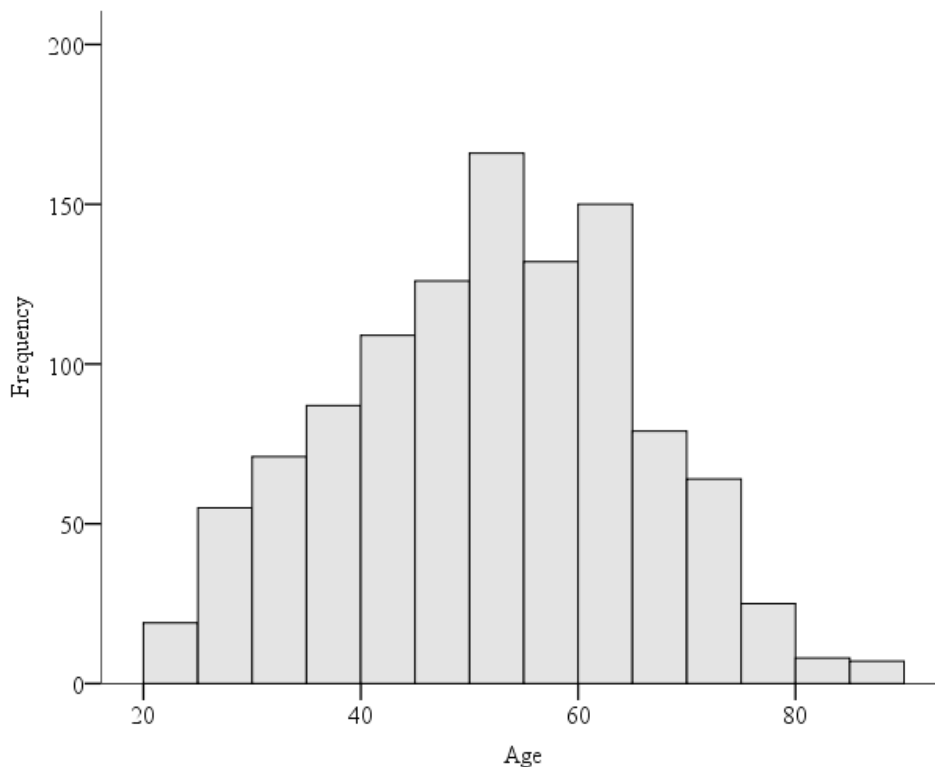


Figure 2. Age distribution of subjects.

Independent variables

ADHD was diagnosed in 58 (5,3%) subjects. Forty-four (75,9%) of them were men and 14 (24,1%) women. This gender difference is in line with earlier research using adult samples. Their age span was 21-64 years, with a mean age of 41 years and standard deviation of 12 years. To minimize the possibility of age acting as a confounding variable, an aged matched comparison group was used. Individuals older than 65 years were excluded from the statistical analyses and the final sample included 931 subjects, thereof 643 (69,1%) men and 288 (30,9%) women. Their age span was 20-65 years, with a mean age of 48 years and a standard deviation of eleven years. The age distribution is negatively skewed as a result of the exclusion of individuals over 65 years of age (Figure 3).

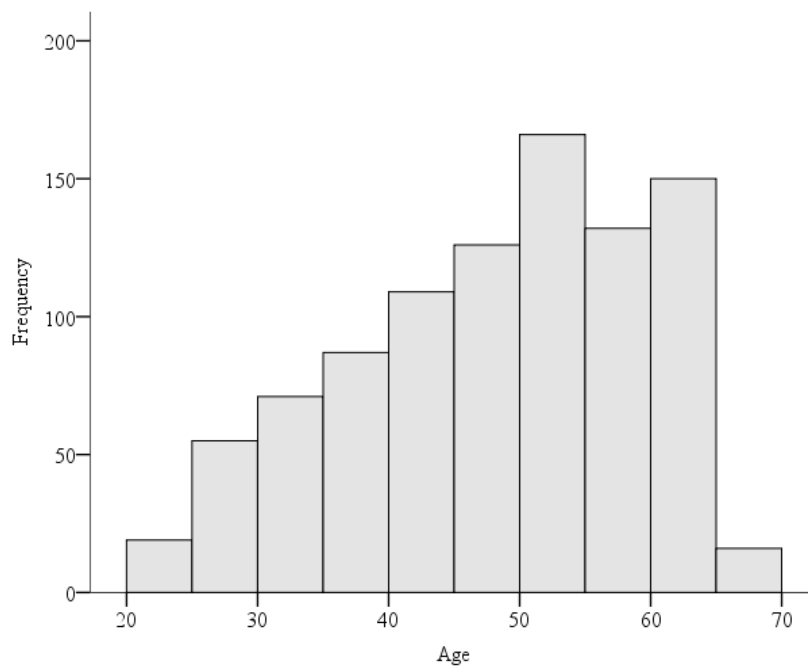


Figure 3. Age distribution in the final sample.

The frequency of different ADHD subtype diagnoses varied somewhat. Rates of ADHD predominantly inattentive type and predominantly hyperactive/impulsive type were similar and fewer individuals were diagnosed with ADHD combined type. The lower rates of ADHD combined type is a bit surprising, since research suggest that the odds of dependence increase with the severity of ADHD and one may thus conclude that more individuals with ADHD combined type would be diagnosed with SUD. Gender distributions were quite similar in all ADHD subtypes (Table 1).

Table 1. Diagnoses of ADHD subtypes and gender distributions.

ADHD subtype	N	Men	Women
Combined	13	10 (76,9%)	3 (23,1%)
Hyperactive/impulsive	23	16 (69,6%)	7 (30,4%)
Inattentive	22	18 (81,8%)	4 (18,2%)

Age distributions were also similar in all ADHD subtypes (Table 2).

Table 2. Age distributions in ADHD subtypes (years).

ADHD subtype	Minimum	Maximum	Mean	Standard deviation
Combined	22	64	45	13
Hyperactive/impulsive	26	64	42	11
Inattentive	21	64	38	11

Of the 58 individuals with ADHD, data about ADHD medication were available for 55 individuals. Only ten (18%) of them had received any medication for ADHD and 45 individuals (82%) had not received any medication for ADHD. Four individuals had received Ritalin and six had received another ADHD medication (data about what

medication was only available from one). Such a low number of subjects do not permit any conclusion and thus the hypothesis that a positive correlation would be found between age at offset of stimulant medication for ADHD and age at onset of SUD was not tested.

Dependent variables

Data about age at onset of SUD were available from 860 subjects. Age at onset of SUD ranged from eleven to 61 years, with a mean of 25 years and a standard deviation of ten years. The distribution was undoubtedly positively skewed (skewness was 1,14 and kurtosis was 0,68; see depiction in Figure 4) and the Shapiro-Wilk test of normality revealed that it clearly deviated from a normal distribution (sig. < 0,001).

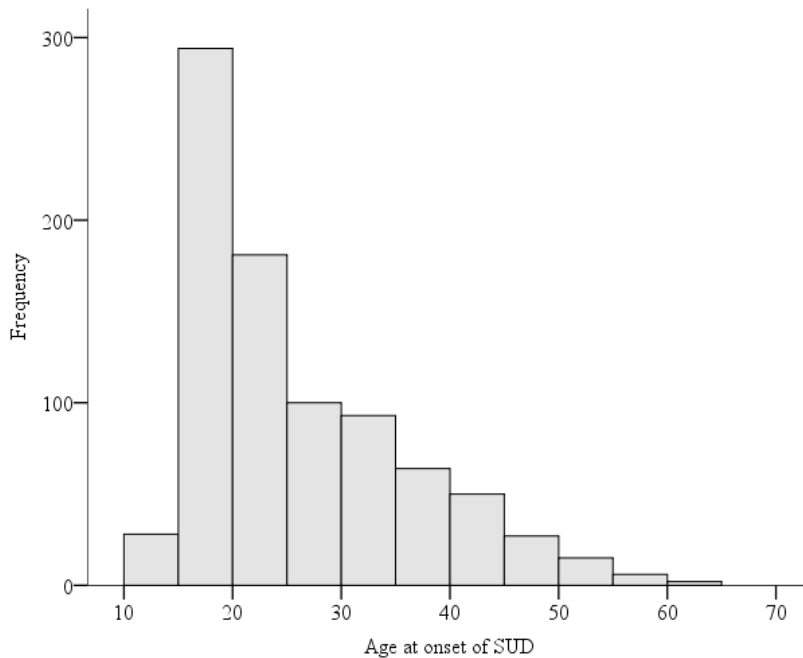


Figure 4. Distribution of age at onset of SUD.

Data were not available about subjects' longest times of abstinence from any kind of substance, only data about subjects' longest times of abstinence from specific substances. Since many individuals were diagnosed with more than one SUD and some stayed abstinent from one substance for a long time but during that time stayed abstinent from other substances for considerably shorter times, it was not regarded as correct to select the longest time of abstinence or compute a mean time of abstinence. The variable longest time of abstinence was thus computed for each specific substance respectively. The distributions of subjects' longest times of abstinence from specific substances all deviated significantly from normal distribution and were positively skewed (Table 3).

Table 3. Descriptive statistics of subjects' longest times of abstinence from specific substances (means and standard deviations in years).

Substance (n)	Mean	Standar deviation	Skewness	Kurtosis	Shapiro-Wilk (sig.)
Alcohol (n = 802)	7,34	6,10	0,88	0,09	< 0,001
Cannabis (n = 213)	8,61	7,29	0,98	0,21	< 0,001
Cocaine (n = 122)	7,52	5,93	1,22	1,29	< 0,001
Opiods (n = 118)	6,59	5,80	1,27	1,34	< 0,001
Sedatives (n = 175)	8,46	7,09	1,08	1,05	< 0,001
Stimulants (n = 217)	7,85	7,12	1,37	2,13	< 0,001

Rates of specific SUDs varied and the most commonly diagnosed SUD was alcohol use disorder (Table 4).

Table 4. Frequencies and proportions of subjects diagnosed with specific SUDs.

Specific SUD	N (% of sample)
Alcohol	899 (96,6%)
Amphetamine	219 (23,5%)
Cannabis	219 (23,5%)
Sedatives	183 (19,7%)
Cocaine	114 (12,2%)
Opioids	108 (11,6%)

ADHD and onset of SUD

Individuals with ADHD were usually diagnosed with SUD at 19,38 years of age, with a standard deviation of 4,94 years. Individuals without ADHD were usually diagnosed with SUD at 25,43 years of age, with a standard deviation of 9,84 years. See depiction of means in Figure 5.

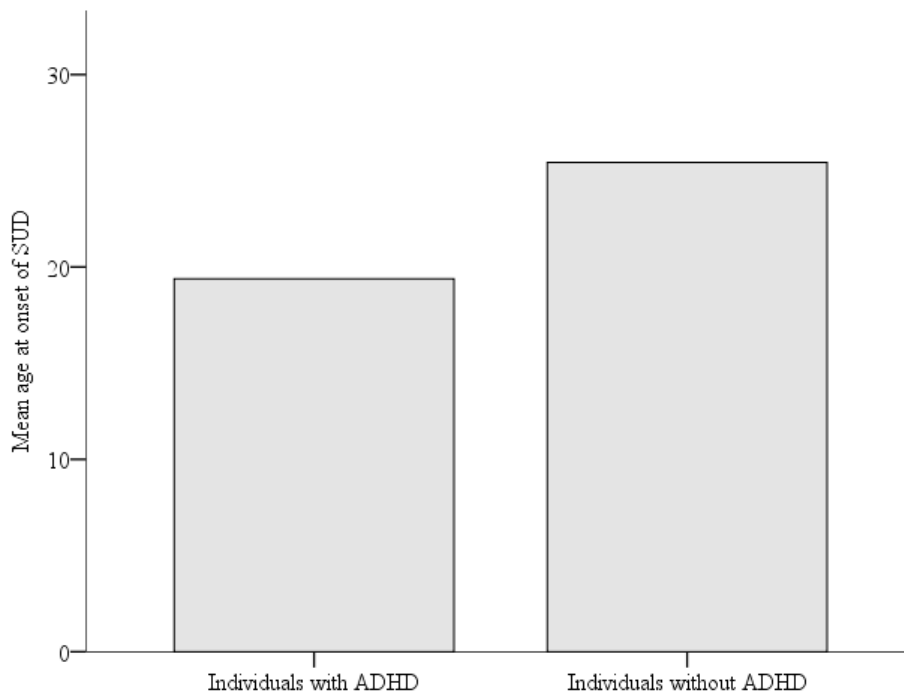


Figure 5. Individuals with and without ADHD's mean age at onset of SUD.

Confidence intervals (95%) suggest that individuals with ADHD usually develop SUD at 18,05-20,72 years of age, while individuals without ADHD usually develop SUD at 24,75-26,11 years of age. Since data clearly deviated from a normal distribution and group sizes were very unequal the non-parametric Mann-Whitney U test was used. Individuals with ADHD had a median of 18 years and a mean rank of 275,3 while individuals without ADHD had a median of 22 years and a mean rank of 441,1. The difference between the groups were statistically significant ($U = 13599,5$, $Z = -4,80$, $p < 0,001$) and thus the hypothesis that individuals with ADHD will show an earlier onset of SUD than individuals without ADHD was supported.

ADHD and times of abstinence

Individuals' longest times of abstinence varied somewhat between substances in individuals with ADHD, but not so much in individuals without ADHD (Table 5).

Table 5. Descriptive statistics for individuals with and without ADHD's longest times of abstinence from specific substances (years).

Substance	Individuals with ADHD			Individuals without ADHD		
	Mean	Standard deviation	95% confidence interval for mean	Mean	Standard deviation	95% confidence interval for mean
Alcohol	6,12	4,81	4,71-7,53	7,41	6,16	6,97-7,85
Cannabis	6,14	6,56	3,23-9,04	8,89	7,33	7,84-9,94
Cocaine	5,29	5,11	2,34-8,23	7,81	5,99	6,67-8,96
Opioids	4,75	3,37	1,93-7,57	6,72	5,93	5,60-7,85
Sedatives	4,69	3,88	2,35-7,04	8,76	7,21	7,64-9,88
Stimulants	3,50	3,17	2,02-4,98	8,29	7,26	7,27-9,31

Mann-Whitney U tests were used since the distributions of abstinence times clearly deviated from normal distribution and group sizes were very unequal. Bonferroni adjustment was used and statistical significance was thus set at $p = 0,008$. The Mann-Whitney U tests did not detect significant differences between individuals with and without ADHD's longest time of abstinence from alcohol ($U = 16146, Z = -1,04, p = 0,150$), cannabis ($U = 1586,5, Z = -1,88, p = 0,030$), cocaine ($U = 531,5, Z = -1,81, p = 0,036$), opioids ($U = 378,5, Z = -0,62, p = 0,267$) and sedatives ($U = 711,5, Z = -1,95, p = 0,026$), but a significant difference was detected in their longest time of abstinence from stimulants ($U = 1142,5, Z = -3,10, p = 0,001$). Medians and mean ranks are shown in Table 6.

Table 6. Medians and mean ranks of individuals with and without ADHD's longest times of abstinence from specific substances (years).

Substances	Individuals with ADHD		Individuals without ADHD	
	Median	Mean rank	Median	Mean rank
Alcohol	5	367,5	6	403,6
Cannabis	4	83,6	7	109,7
Cocaine	4	45,5	6	63,6
Opioids	3,5	51,8	5	59,5
Sedatives	4	61,7	7	90,1
Stimulants	2,5	67,6	7	113,2

Thus the hypothesis that individuals with ADHD will show shorter times of abstinence than individuals without ADHD is only supported regarding abstinence from stimulants, but not from alcohol, cannabis, cocaine, opioids and sedatives. The means of individuals with and without ADHD's longest times of abstinence from specific substances are depicted in Figure 6.

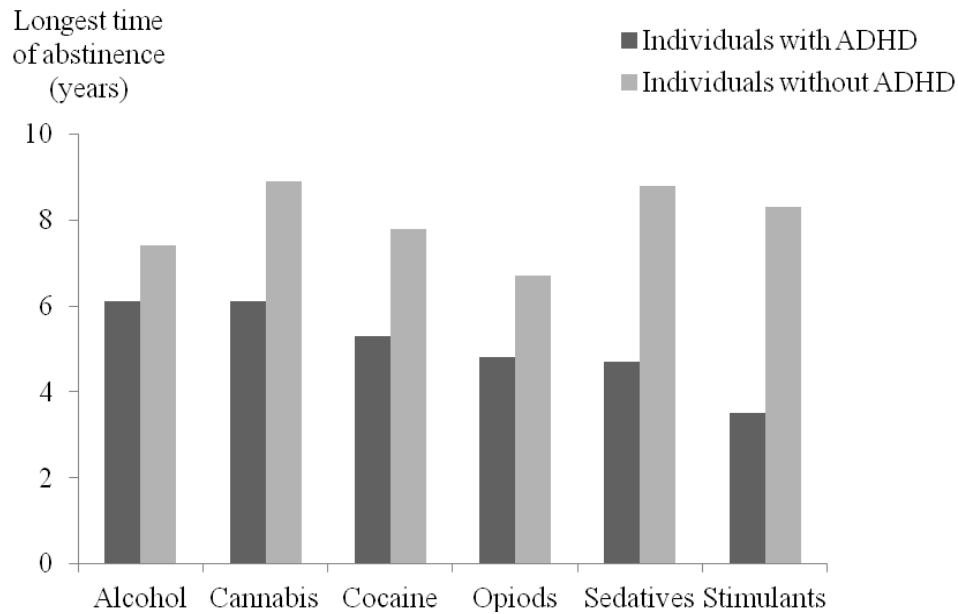


Figure 6. Means of individuals with and without ADHD's longest times of abstinence.

ADHD and specific SUDs

Chi-square tests revealed that ADHD diagnosis was associated with amphetamine use disorder ($\chi^2(1, N = 931) = 15,606, p < 0,001$), cannabis use disorder ($\chi^2(1, N = 931) = 13,182, p = < 0,001$), cocaine use disorder ($\chi^2(1, N = 931) = 10,674, p = 0,001$) and sedatives use disorder ($\chi^2(1, N = 931) = 10,728, p = 0,001$), but not with alcohol use disorder ($\chi^2(1, N = 931) = 0,547, p = 0,460$) and opioid use disorder ($\chi^2(1, N = 931) = 0,925, p = 0,336$). The frequencies and proportions of individuals with and without ADHD diagnosed with specific SUDs are shown in Table 7. The proportions are also depicted in Figure 7.

Table 7. Frequencies and proportions of individuals with and without ADHD diagnosed with specific substance use disorders.

Specific SUD	n (%) of individuals with ADHD (N = 58)	n (%) of individuals without ADHD (N = 873)
Alcohol	57 (98,3%)	842 (96,4%)
Amphetamine	26 (44,8%)	193 (22,1%)
Cannabis	25 (43,1%)	194 (22,2%)
Cocaine	15 (25,9%)	99 (11,3%)
Opioids	9 (15,5%)	99 (11,3%)
Sedatives	21 (36,2%)	162 (18,6%)

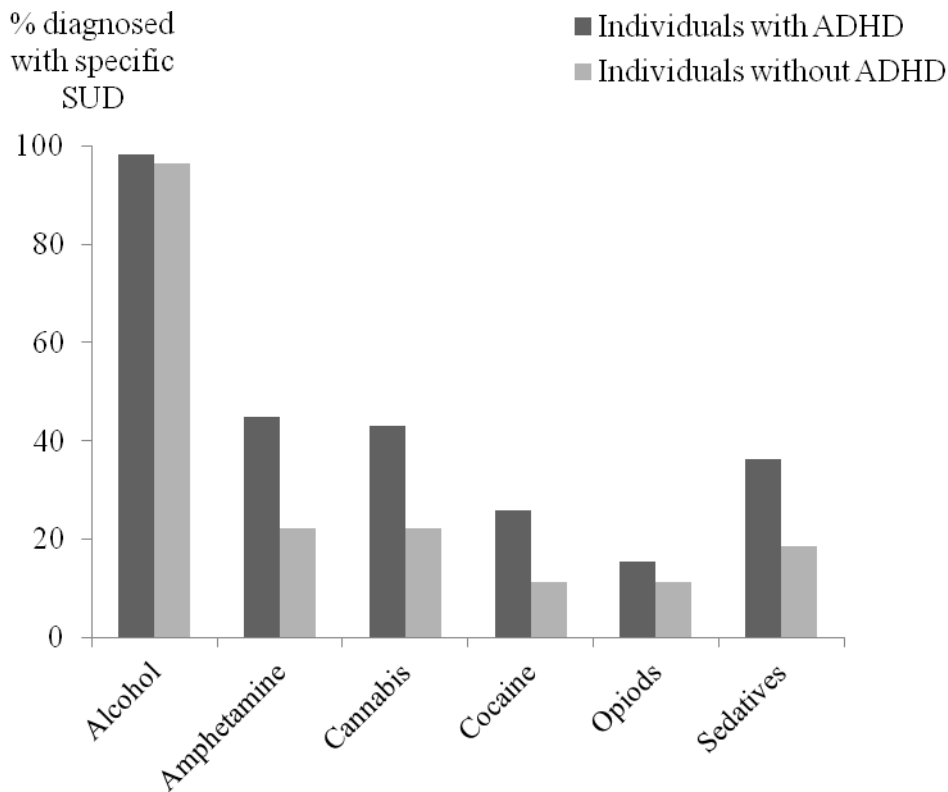


Figure 7. Proportions of individuals with and without ADHD diagnosed with specific substance use disorders.

The hypothesis that ADHD diagnosis will not be associated with any specific SUD was thus not supported.

An additional, interesting fact is that individuals with ADHD were diagnosed with a mean of 2,64 SUDs (with a standard deviation of 1,72), while individuals without ADHD were diagnosed with a mean of 1,82 SUDs (with a standard deviation of 1,37). Confidence intervals (95%) suggest that individuals with ADHD are usually diagnosed with 2,18-3,09 SUDs, while individuals without ADHD are usually diagnosed with 1,73-1,91 SUDs. The distribution of the variable frequency of SUDs clearly deviated from a normal distribution (skewness was 1,44, kurtosis was 1,20 and the p -value of the Shapiro-Wilk test was $< 0,001$) and thus the non-parametric Mann-Whitney U test was used. Individuals with ADHD had a median of 2 SUDs and a mean rank of 589,4 while individuals without ADHD had a median of 1 SUD and a mean rank of 457,8. The difference was statistically significant ($U = 18161,5$, $Z = -4,06$, $p < 0,001$) and thus it may be concluded that individuals with ADHD are usually diagnosed with more SUDs than individuals without ADHD.

ADHD subtypes and specific SUDs

Chi-square tests revealed that diagnosis of ADHD subtype was not related to diagnosis of alcohol use disorder ($\chi^2(2, N = 58) = 1,665$, $p = 0,435$), amphetamine use disorder ($\chi^2(2, N = 58) = 3,227$, $p = 0,199$), cannabis use disorder ($\chi^2(2, N = 58) = 3,858$, $p = 0,145$), cocaine use disorder ($\chi^2(2, N = 58) = 1,812$, $p = 0,404$), opioid use disorder ($\chi^2(2, N = 58) = 1,346$, $p = 0,510$) or sedatives use disorder ($\chi^2(2, N = 58) = 1,266$, $p = 0,531$). Frequencies and proportions of individuals diagnosed with specific SUDs within each ADHD subtype are shown in Table 8.

Table 8. Frequencies and proportions of individuals diagnosed with specific SUDs within ADHD subtypes.

Specific SUD	CT (N = 13)	HT (N = 23)	IT (N = 22)
Alcohol	13 (100%)	23 (100%)	21 (95,5%)
Amphetamine	3 (23,1%)	12 (52,2%)	11 (50%)
Cannabis	3 (23,1%)	13 (56,5%)	9 (40,9%)
Cocaine	2 (15,4%)	8 (34,8%)	5 (22,7%)
Opioids	1 (7,7%)	5 (21,7%)	3 (13,6%)
Sedatives	3 (23,1%)	9 (39,1%)	9 (40,9%)

Note: CT = combined type. HT = hyperactive/impulsive type. IT = inattentive type.

There is some variation in the proportions of individuals diagnosed with specific SUDs within each ADHD subtype (Figure 8).

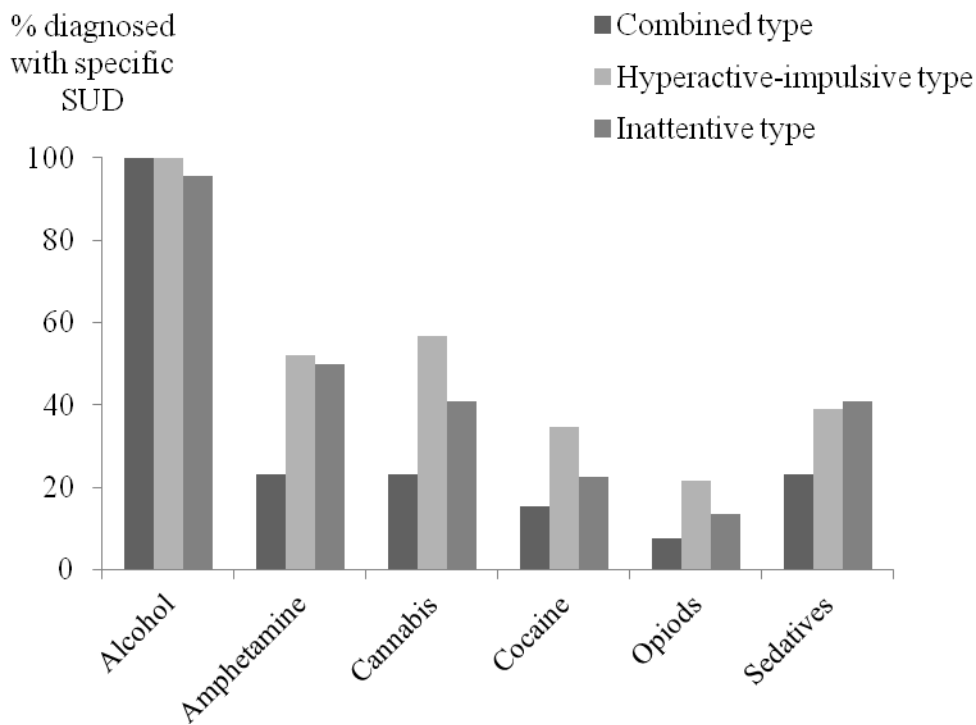


Figure 8. Proportions of individuals diagnosed with specific SUDs within ADHD subtypes.

These results support the hypothesis that no association exists between ADHD subtypes and any specific SUD.

Discussion

ADHD was diagnosed in a surprisingly low number of individuals in this study. Around five percent of subjects were diagnosed with ADHD, which is a proportion that could be expected in the general Icelandic population. This is not in line with earlier studies that suggest that about one fifth of individuals with SUD also have ADHD. According to earlier research, one could reasonably expect a group of approximately 200 individuals in this large-scale study of adults with SUD. There are at least two reasonable explanations for why this did not turn out to be the case. It could be due to the fact that the sample was not a randomized sample, but a sample chosen based on genetics. The sample was very large and thus thought to be representative of Icelandic adults with SUD, but a genetic predisposition to SUD but not ADHD could possibly be a mediating variable affecting the frequency of ADHD.

Another possibility is that ADHD may be under-diagnosed in this sample. Adults with ADHD commonly suffer from other psychiatric disorders as well and there is for example a possibility that symptoms of inattentiveness are interpreted as symptoms of depression or anxiety. This has been stressed as a cause of under-diagnosis of adult ADHD and the importance of specific training in diagnosing adult ADHD has been pointed out (Asherson, 2005). Another reason for undetected ADHD cases in individuals diagnosed with SUD is that substance abuse could be masking the symptoms of ADHD. Cocaine and amphetamine have been shown to mask ADHD symptoms, which makes sense since stimulants have relieving effects on ADHD symptoms. The impairment of memory in individuals with long lasting SUD could also be a reason that ADHD is not diagnosed. ADHD symptoms need to be present since childhood and if an individual cannot remember any signs of ADHD since then, no diagnosis is made.

The first hypothesis was supported since individuals with ADHD usually developed SUD earlier than individuals without ADHD. A reason for this could be that individuals with ADHD are by definition higher in impulsivity than individuals without ADHD. High impulsivity has been linked to earlier substance use and earlier substance use has been linked to the development of SUD.

The hypothesis that individuals with ADHD stay abstinent with more difficulty than individuals without ADHD was only supported by one of six tests of significance. Individuals with ADHD showed shorter times of abstinence from stimulants than individuals without ADHD, but not from alcohol, cannabis, sedatives, cocaine and opioids. The fact that individuals with ADHD seem to have a harder time staying abstinent from stimulants is possibly explained by the relieving effect of stimulants on ADHD symptoms, which reasonably makes it an attractive substance to individuals with ADHD. In fact, individuals with ADHD had also had significantly shorter times of abstinence from cocaine, which also has stimulant properties, if that test had been done separately and Bonferroni adjustment had not been used (the p -value was lower than 0,05). However, if all the tests had been done separately, individuals with ADHD had also had significantly shorter times of abstinence from cannabis and sedatives (these p -values were also lower than 0,05). Thus, these results do not support the idea that individuals with ADHD prefer stimulants rather than depressants. A systematic pattern is evident in the depiction of individuals with and without ADHD's longest times of abstinence (Figure 6). A reason that individuals with ADHD possibly have more difficulties staying abstinent from substances of abuse compared to individuals without ADHD could be higher rates of comorbid psychiatric disorders. The relationship between ADHD and comorbid mental disorders among individuals with SUD has been supported (Wilens et al 1998; 2005).

The hypothesis that similar rates of individuals with and without ADHD would be diagnosed with specific SUDs was not supported, since individuals with ADHD were found to be diagnosed with some SUDs more frequently than individuals without ADHD. Higher proportions of individuals with ADHD were diagnosed with amphetamine, cannabis, cocaine and sedative use disorder, compared to individuals without ADHD. Similar proportions of individuals with and without ADHD were diagnosed with alcohol and opiod use disorder. An additional analysis revealed that individuals with ADHD were usually diagnosed with more SUDs than individuals without ADHD. This is in line with earlier studies finding that individuals with ADHD use many different substances more frequently than individuals without ADHD (Molina and Pelham, 2003). A higher frequency of SUDs in ADHD individuals could possibly be a reason for the associations between diagnosis of ADHD and specific SUDs. For example, if individuals without ADHD usually only develop alcohol use disorder and individuals with ADHD usually develop alcohol, amphetamine and cannabis use disorders there will be an association between ADHD diagnosis and amphetamine and cannabis use disorders but not with alcohol use disorder. However, this would not mean that individuals with ADHD had a preference for amphetamine and cannabis rather than alcohol. These results do not support the idea that individuals with ADHD prefer stimulants, since individuals with ADHD were more likely to be diagnosed with amphetamine, cannabis, cocaine and sedatives use disorder.

Interestingly, only ten of the 58 individuals with ADHD reported that they had received any medication for ADHD. Four of them reported that they had received stimulant medication. These are surprisingly low numbers, since medication is usually the first step in treating individuals with ADHD, both among children and adults. However, the relatively high age of many participants in this study could be a reason that

few individuals had received medication for ADHD. Knowledge of ADHD, its treatment and rates of diagnoses of ADHD have increased substantially the last decades. Thus one may conclude that individuals that are of middle age today grew up in a very different diagnostic environment and are probably not as likely to have received any medication for ADHD as children who are diagnosed with ADHD today. Even though such a low number of subjects do not permit any conclusion, it is a noteworthy fact that 82% of individuals diagnosed with ADHD in this study had not received any medication for ADHD. This fact surely does not speak against the idea that any ADHD medication could have a protective effect against the development of SUD. It does seem plausible that any medication that relieve symptoms of impulsivity could decrease the risk that ADHD individuals start using any psychoactive substance in the first place, which reasonably would decrease the risk for subsequent development of SUD.

The hypothesis that no association exists between ADHD subtypes and any specific SUD was supported, since proportions of individuals diagnosed with specific SUDs were not particularly different in individuals diagnosed with different ADHD subtypes. This is in line with earlier studies on the same topic, as well as studies pointing to similarities between individuals diagnosed with different ADHD subtypes.

The results from this study should be taken with precautions, since the group of ADHD individuals was relatively small and particularly the numbers of individuals diagnosed with different ADHD subtypes were very small. It would be interesting to replicate the study with a larger sample of adults with ADHD and interviewers with special training in diagnosing adult ADHD. It would also be interesting to replicate with a randomized sample or with a clinical sample of adults with ADHD, since this sample was based on genetics. Even though genetics was not a subject in this thesis, the study of the genetics of SUD and ADHD is a highly interesting topic and it would sure be

interesting to compare the results of a replication with a randomized sample or a clinical ADHD sample with the results from this study.

Further investigations could examine whether there are any associations between mood and anxiety disorders and specific SUDs in individuals with ADHD, as well as whether these possible associations differ in individuals with ADHD and individuals without ADHD. The effect of ADHD medication on subsequent development of SUD is another interesting and important topic that definitely merits further investigations.

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