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Attention-Deficit Hyperactivity Disorder and Risk for Substance Use Disorders in Relatives

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Abstract

Background: Previous research indicates that Attention-deficit hyperactivity disorder (ADHD) is highly associated with Substance Use Disorders (SUD). These studies however, have failed to clarify the nature of the overlap. The main aim was to explore if the overlap between ADHD and SUD could be explained by shared genetic and environmental factors or by harmful effects of ADHD medication.

Method: Matched cohort design across different levels of family relatedness recorded from 1973 to 2009. By linking longitudinal Swedish national registers, 62,015 ADHD probands and their first and second degree relatives were identified and matched 1:10 with non-ADHD controls and their corresponding relatives. Any record of SUD defined by discharge diagnoses of the International Classification of Diseases and/or a purchase of any drug used in the treatment of SUD.

Result: 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 (OR_{SUD2nd} 1.4 and 1.4). The familial aggregation patterns remain similar for first degree and second degree relatives after excluding cases and controls with SUD as well as relatives with an ADHD diagnosis, and individuals with schizophrenia, bipolar disorder, depression and conduct disorder.

Conclusion: Our findings suggest that the co-occurrence of ADHD and SUD are due to genetic factors shared between the two disorders, rather than to a general propensity for psychiatric disorders or harmful effects of ADHD medication.

Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a highly prevalent neuropsychiatric disorder characterized by impairing symptoms of hyperactivity, impulsivity and inattention (1). Individuals with ADHD are at increased risk for substance use disorders (SUD) (2) and they tend to have more serious SUD related problems and poorer treatment outcomes compared to individuals without ADHD (3). Previous studies however, have failed to clarify the nature of the overlap.

A recent meta-analysis suggests that the association between ADHD and SUD varies across the different SUD-subtypes, possibly supporting a substance preference hypothesis in people with ADHD (2). The fact that some previous studies have used broad definitions of SUD (4-7), while others have explored the relationship between ADHD and specific SUD subtypes (such as psychoactive drug abuse, alcohol use disorder and nicotine dependence) (8-13) makes comparisons across studies difficult. Furthermore, since SUD, and particularly alcohol use disorder, is rare in childhood but increasing in prevalence with age through adolescence and into adulthood, short follow-up time is a serious limitation of many previous studies looking at the association between ADHD and SUD (4, 9).

Previous family and twin studies have suggested a strong genetic predisposition for both ADHD (14) and SUD (5, 6, 10), but have produced inconsistent results regarding the nature of the overlap between the two disorders. Some genetically informed studies suggest shared genetic risk factors for ADHD and SUD (11, 15, 16), while other family-based studies indicate independent transmission of SUD and ADHD, or alternatively, the presence of an etiologically distinct ADHD plus SUD syndrome (7, 9, 12). Clearly, additional research is needed to resolve the conflicting results of previous research.

Although many epidemiological studies seem to find no or possibly even protective, effects of ADHD medication on SUD (17, 18), there are still some lingering

concerns about harmful effects of stimulant treatment stemming primarily from findings of animal and imaging studies (19-21). The fear that stimulant ADHD treatment may put susceptible individuals at risk for future SUD might, in fact, result in the withholding of effective pharmacological treatment in these individuals (22). A better understanding of the relationship between these two disorders might influence individuals with ADHD, their families, and clinicians to more readily accept ADHD pharmacotherapy in SUD patients.

In this register-based family study, we aimed to further explore the extent to which genetic and environmental factors are shared between the two disorders. Importantly, by excluding individuals with ADHD from relatives to both cases and controls, we made attempts to rule out harmful effects of ADHD medication as a potential explanation to an observed familial association between ADHD and SUD. We also investigated whether ADHD is more strongly associated with any of the specific SUD subtypes, and the extent to which familial factors for ADHD and SUD were shared with other major psychiatric disorders previously shown to share genetic risk factors with ADHD (e.g. schizophrenia and bipolar disorder), and psychiatric disorders frequently coexisting with ADHD and SUD such as depression and conduct disorder. To this end, using nationwide register linkages, we identified 62,015 ADHD probands, their first and second degree relatives as well as approximately ten controls matched on birth year, sex, and residential information and their corresponding relatives.

Method and Materials

Data sources

We utilized data from a record linkage of six population-based registries in Sweden; personal identification numbers enabled accurate linkage (23). The *National Patient Register (NPR)* provides data on psychiatric in-patient care since 1973 (ICD-8 to ICD-10) and out-patient care (ICD-10) since 2001 (24). The *Swedish Prescribed Drug register (PDR)* (25) contains information on drug identity (Anatomical Therapeutic Chemical [ATC-codes]) and dates of all registered prescriptions to the entire population in Sweden since July 2005. The *Multi-Generation Register (MGR)*, contains information on the identity of the parents of all residents born in Sweden since 1932. The *Cause of Death Register* (CDR) provides information on dates of all registered deaths since 1958. The *Migration Register* (MR), includes information on dates of all registered migrations into or out of Sweden since 1969. The *Total Population Register (TPR),* includes information on sex, birth year, and migrant status for the entire Swedish population since 1969. The study was approved by the research ethics committee at The Karolinska Institute, Stockholm, Sweden Protocol Nr 2009/5:10.

Measures

We identified 47,794 patients with ADHD 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 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. Among the 62,015 unique ADHD (42,118 males (68 %), 15,829 (25.5%) were identified from the NPR alone, 14,221 (22.9 %) were identified from the PDR alone, and 31,965 (51.6 %) were identified from both the NPR and the PDR.

We have previously validated the register-based ADHD diagnosis using data from 19,150 twins (born between 1992 and 2001) with psychiatric symptom information from the Swedish Twin Registry (26). ADHD symptoms were assessed using a well-validated measure of 96 specific child psychiatric symptoms (27). About 70% of the twins with a national register-based ADHD diagnosis recorded in the NPR or the PDR were also rated as screen-positive by parents.

We acquired information on SUD using both ICD-codes from the NPR and ATC-codes in the PDR (using drugs exclusive 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 (natrexone) 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 (buprenorfine), N07BC51 (buprenorfine+naltrexone) and N07BC02 (methadone)).

For each case, we randomly selected ten unaffected control subjects. By matching life time non-ADHD control subjects on birth year, sex and residential factors we ensured equal follow-up time. According to well-established procedures for nested case-control designs (23, 28), 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.

Statistical Analyses

The statistical analyses were performed using a nested case-control design. To explore the familial overlap between ADHD and SUD, we compared relatives of ADHD probands with relatives of controls matched on birth year, sex and residential information. This method allows equal follow-up periods of the relatives to the probands and controls and

minimizes bias introduced when individuals in the population registries enter the study at different time points (i.e., left truncation) (28). We compared the risk separately for first and second degree relatives based on the following assumptions; a) first degree relatives share approximately 50% of their co-segregating genes and are thereby more genetically similar than second degree relatives who only share approximately 25% of their co-segregating genes and b) 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 (28).

We controlled for the possibility that the familial association was due to ADHD medication by excluding ADHD in relatives of both cases and controls from the analyses. We also simultaneously excluded family pairs with SUD in cases and controls to minimize the possibility that, the co-occurrence of the two disorders could reflect an etiologically distinct "ADHD plus SUD" sub syndrome.

We also explored whether the observed familial aggregation pattern remained similar after excluding all individuals with a diagnosis of schizophrenia (ICD-8: 295.0-295.4, 295.6, 295.8-295.9; ICD-9: 295A-295E, 295G, 295W, 295X; ICD-10: F20) or bipolar disorder (ICD-8: 296.1, 296.3, 296.8; ICD-9: 296A/C/D/E/W; ICD-10: F30-F31) in the NPR. This was done to explore the extent to which the familial factors for ADHD and SUD were shared with other major psychiatric disorders that have previously been found to share genetic risk factors with ADHD (29, 30). Furthermore, to explore if the association was driven by other psychiatric disorders frequently coexisting with ADHD and SUD (3, 31, 32), we excluded all individuals with a diagnosis of depression (ICD8: 296.2, 298.0, 300.4; ICD9: 296B, 300E; ICD10: F32-F34 and conduct disorder (ICD9: 312; ICD-10: F91) in the NPR.

We performed two different sensitivity analyses to test the robustness of our results. First, we explored if the familial association was driven by the fact that 40,300 families contributed

with more than one case-relative pair, by selecting and analyzing a sample with only one case-relative pair per family. Secondly, we explored the validity of the ADHD diagnosis by analyzing a sample of individuals identified as ADHD cases in both the NPR and the PDR.

To describe associations, we used odds ratios (ORs) with 95% confidence intervals (95% CIs) obtained from conditional logistic regression models in PROC PHREG in SAS version 9.3. When studying associations within the same families (e.g. not statistically independent of one another), CIs were obtained with a robust sandwich estimator function to adjust for non-independence (PROC PHREG, covsandwich option).

Results

Table 1 shows distribution for study variables among ADHD probands, matched controls and their corresponding relatives and odds ratios for ADHD associated with each comorbid disorder. 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 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).

Table 2 shows the numbers and percentages of SUD for first and second degree relatives to ADHD probands versus 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).

Table 3 shows that the risk for SUD still was higher in first degree compared to second degree relatives of ADHD probands even after excluding disorders that share genetic risk factors with ADHD such as bipolar disorder or schizophrenia (OR_{SUD1st} 2.2 and 1.7; OR_{SUD2nd} 1.4 and 1.4). **Table 4** shows that the increased risk for SUD remains after exclusion of coexisting disorders such as depression (OR_{SUD1st} 2.2 and 1.7; OR_{SUD2nd} 1.4 and 1.3). **Table 5** and **6** shows the results of the two different sensitivity analyses. As can be seen, the results were robust not only when a sample with one case-relative pair per family was used (OR_{SUD1st} 2.2 and 1.8; OR_{SUD2nd} 1.3 and 1.2), but also in a sample with ADHD cases identified in the NPR and the PDR (OR_{SUD1st} 2.4 and 1.9; OR_{SUD2nd} 1.5 and 1.4).

Discussion

This population-based case-cohort study found a strong familial association between ADHD and SUD. Our results show that the risk for SUD increases considerably with increased genetic relatedness to an ADHD proband. The familial aggregation patterns remained similar after excluding cases and controls with SUD as well as relatives with an ADHD diagnosis and thereby support the hypothesis that the association between ADHD and SUD is explained by shared familial risk factors rather than the harmful effects of ADHD medication. Furthermore, since our results show similar risks between maternal and paternal half-siblings, the familial effect most probably reflects genetic factors rather than shared environmental factors. The understanding of the shared and specific genetic and environmental risk factors underlying co-occurring psychiatric disorders is still limited. Based on the findings of this study, we predict that future molecular genetic studies will identify genetic risk variants that are shared across ADHD and SUD, perhaps reflecting variants involved in dopaminergic mesolimbic reward pathways, or neural systems involved in impulse control (20). This, in turn, may generate a better understanding of the pathophysiological mechanisms that are common to ADHD and SUD.

Our finding has potentially important implications for clinical practice and future research. The main clinical implication is that the overlap between ADHD and SUD is likely not explained by harmful effects of stimulant medication. This is important, given that concerns around the safety of central stimulant treatment in ADHD might result in the withholding of essential and effective pharmacological treatment in affected individuals. The main research implication is the clarification of inconclusive results from previous family studies of ADHD and SUD (5, 7, 9, 10, 12, 15). That is, some of the previous family studies have found that only relatives of ADHD probands with co-occurring SUD had an increased risk of SUD, but not relatives to probands with ADHD alone. This has been interpreted as

support for ADHD plus SUD being a distinct sub-syndrome influenced by a specific pattern of genetic and environmental risk factors. In contrast to these previous findings, we found that pure ADHD in probands actually predicted pure SUD in relatives, which supports the hypothesis of shared familial risk factors for the co-occurrence of the two disorders. A potential explanation for the conflicting results is that previous studies might have been underpowered to detect a true familial association between ADHD and SUD.

Since previous studies (29, 30) have shown pleiotropic effects of genetic risk variants across a broad range of diagnostic categories, including schizophrenia, bipolar disorder and ADHD, we also explored the extent to which the genetic factors for ADHD and SUD were shared with bipolar disorder and schizophrenia. We found 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. Also, both ADHD and SUD are known to frequently co-occur with depression (3, 31) and conduct disorder (32). However, our results were robust after excluding these conditions suggesting that the association are not primarily driven by co-existing depression or conduct disorders.

In this study we also addressed the issue of short follow-up time, which has been a serious limitation of some of the previous family-based studies (4, 9). SUD is unusual in children but gets more frequent with increasing age. Insufficient follow up time is a possible explanation to previous inconsistent results. By providing a maximal follow-up time of 36 years (1973-2009) the possibility of capturing SUD cases increases dramatically.

Our results should also be interpreted in the context of some limitations. ADHD probands and their relatives might be more exposed to healthcare interventions resulting in an obvious risk of detection bias. Given the significant time trend in the diagnosis of ADHD (33) the observed association for parents could be overestimated due to under-diagnosis of ADHD

in older people. This might explain why the risk is higher for parents compared to siblings. Also, the ascertainment of ADHD cases 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 the 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 our proxies for ADHD most likely underestimates the incidence of ADHD and identifies severe ADHD cases. Thus, our strategies probably could not avoid producing false negatives, while we consider bias due to false positives more unlikely. By excluding individuals with ADHD from relatives to both cases and controls we draw the conclusion that familial factors rather than harmful effects of stimulant medication drive the association between ADHD and SUD. This conclusion relies on the assumption that central stimulant medication is used almost uniquely in the treatment of ADHD and that individuals without a diagnosis of ADHD are therefore not exposed to ADHD medication.

This study contributes to the growing body of genetically informed research concerning the nature of the observed overlap between ADHD and SUD by specifically addressing the hypothesis of shared genetic risk factors for ADHD and SUD. An improved understanding of the etiologic underpinnings of SUD and ADHD is crucial and will have important clinical and public health implications. Familial history of ADHD needs to be taken into account when assessing risk for future SUD since it is not only the individual themself, but also their relatives who are at risk for SUD, should an ADHD diagnosis be established.

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, thus preventing the development of a more severe addiction disorder. Also, further exploration of genetic underpinnings of both disorders is important to individualize and optimize future

psychosocial and pharmacological treatment. Theoretically, individuals with a genetic susceptibility for ADHD and SUD might benefit from different treatment options than individuals without such hereditary risk factors (34).

Finally, individuals with ADHD and SUD not only experience great personal suffering and functional impairment but are also exposed to a variety of misunderstandings, misinterpretations and misclassification regarding their ADHD symptoms and SUD disorders. Not only could a clearer understanding of the etiological overlap between ADHD and SUD increase societal acceptance for them as valid medical diagnoses, but it could also reduce the personal and psychosocial stigmatization associated with both disorders and ensure that these individuals receive effective treatment.

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Author Contributions: C Skoglund had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses

Study concept and design: Skoglund, Lichtenstein, Larsson

Acquisition of data: Lichtenstein

Analysis and interpretation of data: All authors.

Drafting of the manuscript: Skoglund

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Skoglund, Chen

Obtained funding: Franck, Lichtenstein, Larsson

Study supervision: Larsson

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Table 1 Distribution of study variables among ADHD probands and matched controls, and odds ratios for ADHD associated with each comorbid disorder

	No. (%)		
	ADHD (n=62,015)	**Controls (n=619,794)**	**Odds ratio (95% CI)**
Sex			
Male	42,118 (67.9)	420,824 (67.9)	
Female	19,897 (32.1)	198,970 (32.1)	
Relatives			
Parents (Females, %)	85,399(50.2)	760,358 (50.2)	
Full siblings (Females, %)	51,005 (50.7)	478,353 (50.9)	
Maternal half siblings (Females, %)	20,992 (50.3)	160,458 (50.7)	
Paternal half siblings (Females, %)	23,099 (50.0)	179,316 (50.1)	
Outcomes			
Substance use disorder	12,021 (19.4)	15,471 (2.5)	10.8(10.5-11.1)
Drug abuse	8349 (13.5)	5606 (0.9)	19.2 (18.5 – 19.8)
Alcohol use disorder	7574 (12.2)	11,132 (1.8)	8.3 (8.0 - 8.5)
Comorbid disorders			
Bipolar disorder	3199 (5.2)	1771 (0.3)	20.1 (19.0 - 21.1)
Schizophrenia	639 (1.0)	947 (0.2)	6.9 (6.4 - 7.6)

Depression	12,032 (19.4)	13,489 (2.2)	12.8 (12.5 - 13.1)
Conduct disorder	2990 (4.8)	1034 (0.2)	31.4 (29.5 - 33.6)

Table 2 Risk for substance use disorder, drug abuse and alcohol use disorder in relatives to ADHD probands compared to relatives to controls[a]

	Substance use disorders in relatives			**Drug abuse in relatives**			**Alcohol use disorders in relatives**		
	ADHD N (%)	**Control N (%)**	**OR (95 % CI)**	**ADHD N (%)**	**Control N (%)**	**OR (95 % CI)**	**ADHD N (%)**	**Control N (%)**	**OR (95 % CI)**
1° relatives									
Parent	7555(8.9)	31,748(4.2)	2.2 (2.2 - 2.3)	3514 (3.8)	12,921 (1.6)	2.4 (2.4-2.5)	6024 (6.5)	24,868 (3.0)	2.3 (2.2-2.3)
Full sibling	1805(3.5)	9564(2.0)	1.8 (1.7 - 1.9)	870 (1.6)	3563 (0.7)	2.4 (2.2-2.5)	1553 (2.8)	8137 (1.5)	1.8 (1.7-1.9)
2° relatives									
Maternal half-sibling	1098(5.2)	6291(3.9)	1.4 (1.3 - 1.5)	585 (2.6)	3003 (1.7)	1.6 (1.5-1.8)	849 (3.6)	5080 (2.8)	1.4 (1.3-1.5)
Paternal half-sibling	1170(5.1)	7068(3.9)	1.4 (1.3 - 1.4)	602 (2.4)	3474 (1.7)	1.5 (1.4-1.6)	914 (3.5)	5467 (2.6)	1.4 (1.3-1.5)

[a] after exclusion of probands and controls with SUD and relatives to probands or controls with ADHD and after exclusion of probands and controls with SUD, relatives to probands or controls with ADHD.

Table 3 Risk for SUD, in relatives to ADHD probands compared to relatives to controls, after exclusion of individuals with bipolar disorder and schizophrenia

	Substance use disorder in relatives		
	ADHD N (%)	**Control N (%)**	**OR (95 % CI)**
1° relatives			
Parent	6805 (8.4)	28,109 (4.0)	2.2 (2.2-2.3)
Full sibling	1562 (3.2)	8409 (1.9)	1.7 (1.7-1.8)
2° relatives			
Maternal half-sibling	1017 (5.1)	5657 (3.7)	1.4 (1.3-1.5)
Paternal half-sibling	1050(4.8)	6228 (3.7)	1.4 (1.3-1.4)

SUD= Substance use disorder; ADHD=attention deficit-hyperactivity disorder; OR=Odds Ratio; CI=Confidence Interval

Table 4 Risk for SUD, in relatives to ADHD probands compared to relatives to controls, after exclusion of individuals with depression and conduct disorder

	Substance use disorder in relatives		
	ADHD N (%)	**Control N (%)**	**OR (95 % CI)**
1° relatives			
Parent	4450 (7.0)	17,113 (3.2)	2.2 (2.2-2.3)
Full sibling	1007 (2.5)	5369 (1.5)	1.7 (1.6-1.8)
2° relatives			
Maternal half-sibling	664 (4.1)	3455 (3.0)	1.4 (1.3-1.5)
Paternal half-sibling	687 (3.9)	3905 (3.1)	1.3 (1.2-1.4)

SUD= Substance use disorder; ADHD=attention deficit-hyperactivity disorder; OR=Odds Ratio; CI=Confidence Interval

Table 5 Risk for SUD in relatives to ADHD probands compared to relatives to controls using a sample with one case-relative pair per family[a]

	Substance use disorder in relatives		
	ADHD N (%)	**Control N (%)**	**OR (95 % CI)**
1° relatives			
Parent	4002 (9.0)	16,679 (4.2)	2.2 (2.2-2.3)
Full sibling	1044 (3.3)	5611 (1.9)	1.8 (1.7-1.9)
2° relatives			
Maternal half-sibling	607 (4.8)	3737 (3.9)	1.3 (1.2-1.4)
Paternal half-sibling	566 (4.5)	3758 (3.8)	1.2 (1.1-1.3)

SUD= Substance use disorder; ADHD=attention deficit-hyperactivity disorder; OR=Odds Ratio; CI=Confidence Interval

[a]40300 families > one case-parent pair ,12940 families > one case-sibling pair,5578 families > one case-maternal sibling pair, 6502 families > one case-paternal sibling pair.

Table 6 Risk for SUD in relatives to ADHD probands compared to relatives to controls using a sample with ADHD cases identified from the NPR and the PDR

	Substance use disorder in relatives		
	ADHD N (%)	**Control N (%)**	**OR (95 % CI)**
1° relatives			
Parent	4211 (9.6)	17,686 (4.2)	2.4 (2.3-2.5)
Full sibling	935 (3.7)	4849 (2.0)	1.9 (1.8-2.0)
2° relatives			
Maternal half-sibling	659 (5.5)	4020 (3.8)	1.5 (1.4-1.7)
Paternal half-sibling	669 (5.2)	4403 (3.9)	1.4 (1.3-1.5)

SUD= Substance use disorder; ADHD=attention deficit-hyperactivity disorder; OR=Odds Ratio; CI=Confidence Interval