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

Charlotte Skoglund, Qi Chen, Johan Franck, Paul Lichtenstein, and Henrik Larsson

ABSTRACT

BACKGROUND: Previous research indicates that attention-deficit/hyperactivity disorder (ADHD) is highly associated with substance use disorders (SUD). However, these studies have failed to clarify the nature of the overlap. The main aim of this study was to explore whether the overlap between ADHD and SUD could be explained by shared genetic and environmental factors or by harmful effects of ADHD medication.

METHODS: We employed a matched cohort design across different levels of family relatedness recorded from 1973–2009. By linking longitudinal Swedish national registers, 62,015 ADHD probands and first-degree and second-degree relatives were identified and matched 1:10 with control subjects without ADHD and their corresponding relatives. Any record of SUD was defined by discharge diagnoses of the International Classification of Diseases or a purchase of any drug used in the treatment of SUD.

RESULTS: First-degree relatives of ADHD probands were at elevated risk for SUD (odds ratios 2.2 and 1.8) compared with relatives of control subjects. The corresponding relative risk in second-degree relatives was substantially lower (odd ratios 1.4 and 1.4). The familial aggregation patterns remained similar for first-degree and second-degree relatives after excluding individuals with coexisting disorders such as schizophrenia, bipolar disorder, depression, and conduct disorder.

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

Keywords: ADHD, Alcohol use disorder, Comorbidity, Drug abuse, Family study, Substance use disorder

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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 with individuals without ADHD (3). However, previous studies have failed to clarify the nature of the overlap.

A 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). Comparisons across studies are difficult because some previous studies have used broad definitions of SUD (4–7), whereas others have explored the relationship between ADHD and specific SUD subtypes (e.g., psychoactive drug abuse, alcohol use disorder, and nicotine dependence) (8–13). Additionally, because SUD, particularly alcohol use disorder, is rare in childhood but increases 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 suggested a strong genetic predisposition for both ADHD (14) and SUD (5,6,10) but 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), whereas 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). Additional research is needed to resolve the conflicting results of previous research.

Although many epidemiologic 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 result in the withholding of effective pharmacologic 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 accept ADHD pharmacotherapy more readily in patients with SUD.

In this register-based family study, we aimed to explore further the extent to which genetic and environmental factors are shared between the two disorders. By excluding individuals with ADHD from relatives of both case subjects and

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control subjects, 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 are shared with other major psychiatric disorders previously shown to share genetic risk factors with ADHD (e.g., schizophrenia and bipolar disorder) as well as 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-degree and second-degree relatives, and approximately 10 control subjects matched on birth year, sex, and residential information and their corresponding relatives.

METHODS AND MATERIALS

Data Sources

We used 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 inpatient care since 1973 (International Classification of Diseases (ICD)-8 to ICD-10) and outpatient 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 contains information on the identity of the parents of all residents born in Sweden since 1932. The Cause of Death Register provides information on dates of all registered deaths since 1958. The Migration Register includes information on dates of all registered migrations into or out of Sweden since 1969. The Total Population Register 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 No. 2009/5:10.

Measures

We identified 47,794 patients with ADHD from the NPR (ICD-9 314, ICD-10 F90) and 46,186 patients with ADHD treated with stimulant or nonstimulant medication (methylphenidate [ATC code N06BA04], atomoxetine [ATC code N06BA09], amphetamine [ATC code N06BA01], dexamphetamine [ATC code N06BA02]) at any time between July 2005 and December 2009 from the PDR. Patients 3–65 years old at the time of the first ADHD diagnosis (or first prescription of stimulant or nonstimulant medication for ADHD) were included. Among the 62,015 patients with 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 during the years 1992–2001) with psychiatric symptom information from the Swedish Twin Registry (26). Symptoms of ADHD 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, 303; ICD-9 291, 303, 305A; 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, 305X; ICD-10 F11.0–F16.9) and ATC codes from the PDR (N02AE01 [buprenorphine], N07BC51 [buprenorphine + naltrexone], and N07BC02 [methadone]).

For each case, we randomly selected 10 unaffected control subjects. By matching control subjects with no lifetime history of ADHD 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), control subjects were alive and living in Sweden with no diagnosis of 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 control subjects matched on birth year, sex, and residential information. This method allows equal follow-up periods of the relatives of the probands and control subjects 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-degree and second-degree relatives based on the following assumptions: 1) first-degree relatives share ~50% of their cosegregating genes and are more genetically similar than second-degree relatives, who share only ~25% of their cosegregating genes, and 2) maternal half-siblings are more similar with regard to shared environmental exposures than paternal half-siblings because children continue to live predominantly with their mothers after parental separation (28).

We controlled for the possibility that the familial association was due to ADHD medication by excluding ADHD in relatives of both case subjects and control subjects from the analyses. In the main analyses, relatives with ADHD of ADHD probands were excluded to avoid counting an ADHD case twice. We also excluded index persons (ADHD case or control subjects) with SUD and their relatives with ADHD to minimize the possibility that the co-occurrence of the two disorders could reflect an etiologically distinct “ADHD plus SUD” subsyndrome.

We performed several different sensitivity analyses to test the robustness of our results. First, we 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–296W; ICD-10 F30–F31)