Familial Risk Analysis of the Association Between Attention-Deficit/Hyperactivity Disorder and Psychoactive Substance Use Disorders

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Objective: To test hypotheses about patterns of familial association between attention-deficit/hyperactivity disorder (ADHD) and psychoactive substance use disorders (PSUDs) by using the family study method.

Design: The first-degree relatives of clinically referred children and adolescents with ADHD (131 probands, 413 relatives) and healthy control probands (106 probands, 323 relatives) were assessed by blind raters.

Results: After stratifying the probands with ADHD and the control probands into those with PSUD (group 1 and group 3, respectively) and those without PSUD (group 2 and group 4, respectively), familial risk analyses revealed the following: (1) the risk for ADHD was not significantly different between relatives of group 2 and group 1 probands (19.6% vs 18.0%; P = .88), but these 2 risks were significantly greater than the risk to relatives of group 3 probands (1.0%; P = .01 and P = .02, respectively) and group 4 probands (7.0%; P = .001 and P = .01, respectively); (2) there were no significant differences in the risk for PSUD between relatives of group 1 (47.5%) and group 3 probands (39.7%; P = .40), but these risks were greater than the risk to relatives of group 2 (30.0%; P = .32) and group 4 probands (20.9%; P < .001); and (3) there was no evidence for nonrandom mating.

Conclusions: These findings are consistent with the hypothesis that ADHD and PSUD are transmitted independently in families. Because the probands were young adolescents, many have not lived through the age at risk for PSUD. Thus, the hypothesis stating that ADHD and PSUD represent variable expressions of a common underlying risk factor cannot be ruled out.

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Editor’s Note: Studies dealing with potential comorbid problems or illnesses will be valuable in identifying possible genetic linkages.

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METHODS

The study method has been described in detail elsewhere. Briefly, we sampled families of white, non-Hispanic male probands between the ages of 6 and 17 years. The original sample of siblings had been ascertained through 2 groups of index children: 140 probands with ADHD and 120 comparison probands without ADHD. These groups had 453 and 369 first-degree biological relatives, respectively. Potential probands were excluded if they had been adopted or if their nuclear family was not available for study. We excluded probands if they had major sensorimotor handicaps (eg, paralysis, deafness, or blindness), psychosis, autism, or a Full Scale IQ score less than 80. Subjects from the lowest socioeconomic class (class VI) were excluded to minimize the potential confounding of social adversity.

Two independent sources provided the proband children. We selected psychiatrically referred probands with ADHD from consecutive referrals to the Pediatric Psychopharmacology Unit at the Massachusetts General Hospital (MGH), Boston. The MGH is a nonprofit, Harvard Medical School–affiliated medical center serving the New England area. The patient population served by MGH derives from inner-city Boston and its suburbs. The Pediatric Psychopharmacology Unit is not a tertiary care clinic; approximately 50% of referrals have never been diagnosed or treated. At MGH, we recruited control probands from the MGH Pediatric Ambulatory Service.

The Harvard Community Health Plan (HCHP) provided the pediatriically referred probands with ADHD. The HCHP is one of the largest health maintenance organizations in the Boston area. We recruited subjects from its centers in Boston, Wellesley, and West Roxbury, Mass. These centers serve approximately 32,000 pediatric patients from inner-city and suburban areas.

A 3-stage ascertainment procedure selected the probands. For probands with ADHD, the first stage was the patient’s referral to a psychiatric or pediatric clinic resulting in a clinical diagnosis of ADHD by a child psychiatrist or pediatrician as recorded in the clinic record. Because these diagnoses had been made by many different clinicians using different clinical standards of diagnosis, we included a second systematic screening using the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R). This second stage confirmed the diagnosis of ADHD by screening all children considered positive for ADHD at the first stage by using a telephone questionnaire with their mothers. The questionnaire asked about the 14 DSM-III-R symptoms of ADHD. The third stage involved the comprehensive assessment battery described later in this section. This assessment battery collected data for the final DSM-III-R diagnoses used in this article. Only patients who received a positive diagnosis of ADHD at all 3 stages were included in the final analysis.

We also screened potential control probands in 3 stages. First, we selected referrals to medical clinics for routine physical examinations. Second, to the mothers of referred control probands we administered the DSM-III-R ADHD telephone questionnaire. Potential control probands were deemed ineligible based on our exclusion criteria or because they met the telephone interview diagnosis of ADHD. Eligible subjects who consented to participate in additional assessments were recruited for the study; they received the same assessment battery as that used for the ADHD sample. We screened control probands only for the presence of ADHD. Screening for other conditions is inappropriate; it could spuriously produce evidence for familial coaggregation between the screened conditions and ADHD. We used 3-stage ascertainment to maximize the probabilities of probands with ADHD being “true cases” and of control probands not having ADHD. Persons who seek treatment and are given a clinical diagnosis are more likely to have experienced the level of distress and disability that DSM-III-R requires for psychiatric illness. This fact combined with the fact that persons free of illness are rarely referred means that psychiatric clinic populations have a higher base rate of all psychiatric illnesses than does the general population.

Likewise, our 3-stage screening of control probands decreases the probability of misclassifying a child with ADHD as a control proband. Of course, since our screened control probands were selected for the absence of ADHD, they cannot be considered representative of the general population. However, work in psychiatric epidemiology indicates that screened control probands are very effective when the goal of a project is to delineate factors that differentiate control probands from cases. Furthermore, unscreened controls frequently have rates of psychopathologic disease and its correlates that are higher than the population expectation. Thus, unscreened control groups of alcoholism in parents and second-degree relatives of children with ADHD. Similar findings have been seen in 2 large double-blind family-genetic studies of ADHD, in which higher rates of PSUD in the relatives of ADHD probands were reported.

Although these studies suggest important associations between ADHD and PSUD, the nature of this association remains unclear. To this end, we conducted a familial risk analysis based on the model of Pauls et al, testing competing hypotheses about the familial relationship between ADHD and PSUD. In stating these hypotheses, the expected differences are relative to population rates or healthy controls. The hypotheses were as follows:

1. ADHD and PSUD are etiologically independent.

If this were the case, we would expect to find high rates of ADHD in the relatives of probands with ADHD, regardless of the proband’s PSUD status, but an increased...
often are heavily contaminated with cases, thereby obscuring the effects of the variable of interest. We emphasize that control probands were screened only for ADHD, not for other psychiatric disorders or conditions related to cognitive functioning. With the exception of the diagnosis of ADHD, all exclusions applied to the control group also were applied to the ADHD group.

Our goal in selecting control probands was to satisfy the comparability principles required for meaningful inference in case-control epidemiological studies. Since it was not possible to establish a primary study base with a geographically defined population, we chose to use 2 secondary study bases defined by the MGH and HCHP sampling sources. The use of secondary study bases limits generalizability and does not produce a representative sample from a geographic population. Nevertheless, it does allow for meaningful case-control comparisons if the control probands are persons who could have been cases had ADHD developed during the time of the study.31-34 When sampling from a clinic, this requires that if our control probands required treatment for ADHD, they would have been referred to the clinics from which we selected our ADHD probands. This is true for our control probands. Children from the HCHP in whom ADHD develops are treated at HCHP, and children from the MGH pediatric practice in whom ADHD develops are referred to the Pediatric Psychopharmacology Unit.

Probands and their siblings were assessed at baseline and again 1 and 4 years later. Parents of probands were assessed at baseline only. As described previously by Biederman et al,23 the rates of successful follow-up at 4 years did not differ between proband groups (93.6% [131] for probands with ADHD and 88.3% [106] for control probands). Moreover, at the 4-year follow-up, 87.4% (152) of the siblings of probands with ADHD and 90.7% (117) of the siblings of control probands assessed at baseline had been successfully recruited. Rates of successful follow-up at 4 years and acquisition of new siblings did not differ significantly between the groups. There were no significant differences between siblings successfully recruited and those unavailable for follow-up on any of the measures used in this study (detailed information is available from the authors on request).

All diagnostic assessments were made by using DSM-III-R-based structured interviews. Psychiatric assessments of probands and siblings were made with the Schedule for Affective Disorders and Schizophrenia for School-Age Children: Epidemiologic 4th Version.31 All assessments were made by raters who were blind to the proband diagnosis (ADHD or control) and ascertainment site (MGH or HCHP). All efforts were made to sequence the mothers’ interviews about their children after the direct interviews with the mothers about themselves had been completed and to have different interviewers conduct the direct interview of children and the interviews with mothers about their children. All follow-up assessments were made blind to prior evaluations of the same subject. All diagnoses in this article refer to lifetime diagnoses at follow-up. We defined PSUD as having any alcohol abuse or dependence or drug abuse or dependence.

All diagnostic uncertainties (including alcohol and drug abuse or dependence) were resolved by a committee of 4 board-certified child and adult psychiatrists who were unaware of the subject’s ascertainment group, ascertainment site, all data collected from other family members, and all nondiagnostic data (eg, cognitive functioning). Diagnoses presented for review were considered positive only if a consensus was achieved that criteria were met to a degree that would be considered clinically meaningful. For children older than 12 years, data from direct and indirect interviews were combined by considering a diagnostic criterion positive if it was endorsed in either interview. All parents signed written informed consent forms before participation in the study; children signed assent forms.

Interviews were conducted by raters with undergraduate degrees in psychology who had been trained to high levels of interrater reliability. We computed κ coefficients of agreement by having 3 experienced board-certified child and adult psychiatrists diagnose 173 subjects from audi-taped interviews made by the assessment staff. The κ coefficients of agreement were found to be excellent with a mean κ of 0.85. For ADHD, drug abuse, and drug dependence, κ values of 1.0 were obtained. The κ value for alcohol abuse was 0.75 and for alcohol dependence, 0.82.

Logistic regression was used to control for potential confounding variables, such as age and socioeconomic status. The statistical problems associated with correlated family data were avoided by using the Huber36 correction to produce robust statistical tests for logistic regression models. All analyses were 2-tailed. Results were considered statistically significant if the P value was .05 or less.

RESULTS

As previously reported,8 19 (14.5%) of the 131 ADHD probands and 17 (16.0%) of the 106 control probands met criteria for PSUD. Accordingly, we stratified the probands into 4 groups based on their ADHD and PSUD status: group 1, 19 probands with ADHD with PSUD who had 61 relatives;
group 2, 112 probands with ADHD without PSUD who had 352 relatives; group 3, 17 control probands with PSUD who had 59 relatives; and group 4, 89 healthy control probands without PSUD who had 264 relatives.

**SOCIODEMOGRAPHIC AND CLINICAL CHARACTERISTICS**

As indicated in the Table, group 1 probands were significantly older (17.8 years) than group 2 (14.0 years; $z = -4.9; P < .001$) and group 3 (14.7 years; $z = -3.5; P = .003$) probands. Moreover, group 3 probands were significantly older (19.9 years) than the probands in all other groups (all $z$ scores > 2.9 and $P$ values < .004). Correspondingly, the parents of group 3 probands were significantly older (46.1 years) than the parents of group 1 (43.0 years; $z = 2.3; P = .02$), group 2 (40.3 years; $z = 5.3; P = .001$), and group 4 (41.5 years; $z = -4.3; P = .001$) probands. Moreover, the parents of group 1 probands were significantly older than the parents of group 2 probands ($z = -2.3; P = .02$). Similarly, the siblings of group 3 probands (22.6 years) were significantly older than the siblings of group 2 (16.6 years; $z = 4.4; P = .001$) and group 4 (16.3 years; $z = -4.4; P = .001$) probands. In addition, more group 2 probands came from families in the lower socioeconomic class than did group 4 probands (mean ± SD, 1.8 ± 0.8 vs 1.4 ± 0.1; $z = -3.8; P = .002$).

**FAMILIAR RISK FOR ADHD**

As shown in Figure 1, A, the relatives of group 1 and group 2 probands did not differ in their risk for ADHD (18.0% vs 19.6%; $z = -0.15; P = .88$). In contrast, both of these risks were significantly higher than those seen in the relatives of group 3 probands (1.8%; $z = 2.3; P = .02$ and $z = 2.5; P = .01$, respectively) and group 4 probands (7.0%; $z = 2.5; P = .01$ and $z = 3.7; P = .001$, respectively). Similar patterns of results were seen when parents and siblings were studied separately.

**FAMILIAR RISK FOR PSUD**

As shown in Figure 1, B, there was no significant difference in the overall risk for PSUD in the relatives of group 1 probands (47.5%) compared with the relatives of group probands.

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**Figure 1.** Risks for attention-deficit/hyperactivity disorder (ADHD) (A) and psychoactive substance use disorder (PSUD) (B) in the relatives of probands with and without ADHD and with and without PSUD. All analyses controlled for age and socioeconomic status. The groups were defined as follows: 1, probands with ADHD and PSUD (n = 19); 2, probands with ADHD only (n = 112); 3, control probands with PSUD (n = 17); and 4, control probands without PSUD (n = 89). An asterisk indicates $P$ value from omnibus $x^2$ test comparing all 4 groups; dagger, $P < .05$ vs group 2; double dagger, $P < .05$ vs group 3; and section mark, $P < .05$ vs group 4. Unless indicated, pairwise comparisons were not significant at the .05 level.

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*Group 1 includes 19 probands with attention-deficit/hyperactivity disorder (ADHD) with psychoactive substance use disorder (PSUD) who had 38 parents and 23 siblings; group 2, 112 probands with ADHD only who had 223 parents and 129 siblings; group 3, 17 control probands with PSUD who had 33 parents and 26 siblings; and group 4, 89 control probands without PSUD who had 176 parents and 88 siblings. Three of the 117 siblings for groups 3 and 4 had missing data and were not included in the analysis. Data are given as mean ± SD unless otherwise specified.

†$P < .05$ vs group 2.
‡$P < .05$ vs group 3.
§$P < .05$ vs group 4.
In contrast, the risk for PSUD in the relatives of group 1 probands (47.5%) was significantly higher than the risk in the relatives of group 2 probands (30.0%; \( z = 2.9; P = .004 \)) and the relatives of group 4 probands (20.9%; \( z = 3.4; P = .001 \)). In addition, the risk for PSUD in the relatives of group 3 probands (39.7%) was significantly greater than in the relatives of group 4 probands (20.9%; \( z = 2.1 \) and \( P = .03 \) for both groups).

With 1 exception, \textbf{Figure 2} shows that similar results were observed when findings were studied separately by specific subcategories of PSUD (drug or alcohol dependence, drug or alcohol abuse, alcohol abuse or dependence, and drug abuse or dependence); in the case of any drug abuse or dependence, no difference was seen in the rate in the relatives of group 1 probands (14.7%) and in the relatives of group 2 probands (16.2%; \( P = .76 \)). When parents and siblings were studied separately, similar findings were seen in both groups of relatives.

**Cosegregation of ADHD and PSUD**

No evidence of cosegregation between ADHD and PSUD was observed. Among the relatives of all probands, the presence of ADHD in the relative significantly increased the risk for PSUD in the same relatives (41.2% vs 26.0%; \( \chi^2 = 10.8; P = .001 \)). In contrast, among the relatives of group 1 probands, the presence of ADHD in the relative did not significantly increase the risk for PSUD in the same relative (45.4% vs 48.0%; \( \chi^2 = 0.02; P = .88 \)).

**Nonrandom Mating Among Parents of ADHD Probands**

Nonrandom mating occurs when having one disorder increases the likelihood that one will marry a person with another disorder. In this context, nonrandom mating occurs when a parent with ADHD marries a parent with PSUD more often than expected by chance alone. Fathers with ADHD were not more likely to have a spouse with PSUD than fathers without ADHD (21.4% vs 16.6%; \( \chi^2 = 0.41; P = .52 \)). Similarly, the presence of ADHD in mothers did not predict PSUD in the father (52.9% vs 48.3%; \( \chi^2 = 0.14; P = .71 \)).

**Antisocial Disorders in Families**

Since conduct disorder was found to be associated with PSUD in probands,\(^6\) we studied associations between PSUD and antisocial disorders in relatives. This analysis showed...
that although the relatives of group 1 and 2 probands did not differ from each other in their rates of conduct or antisocial personality disorder (23.3% vs 15.8%; \( \chi^2 = 2.1; P = .15 \)), the relatives of group 1 and 2 probands had significantly higher rates of conduct or antisocial personality disorder compared with the relatives of group 3 and 4 probands (6.1%; all \( z \) scores > 13.4 and \( P \) scores = .001).

In a systematic evaluation of the familial relationship between ADHD and PSUD using a sample of well-characterized probands with ADHD and their first-degree relatives, we found the following: (1) the risk for ADHD among the relatives of probands with ADHD did not differ by the presence of PSUD in the proband; (2) the risk for PSUD was similar among the relatives of group 1 and group 3 probands, and these risks were higher than the risk to the relatives of group 2 and group 4 probands; and (3) the association between ADHD and PSUD could not be accounted for by nonrandom mating. These findings are most consistent with the hypothesis that ADHD and PSUD are transmitted independently in families, ie, that they do not share familial risk factors (hypothesis 1).

While our findings are most consistent with independent transmission, we cannot completely rule out hypothesis 3 (shared familial etiological factors), since the probands were still young at follow-up (mean age, 15 years) and had not traversed through the period of risk for developing PSUD. The rate of PSUD in probands (15%) was considerably lower than the rate of PSUD in siblings with ADHD (41%) and adults with ADHD (52%). Considering that the mean age of the proband sample was 15 years and that of the sibling sample was 17 years, this finding supports the notion that PSUD dramatically increases during the late adolescent and young adult years.

The findings showing no difference in the risk for drug abuse or dependence in the relatives of group 1 and group 2 probands (Figure 2, D) are more consistent with hypothesis 3 (that probands with ADHD with and without PSUD share familial etiological factors) rather than with hypothesis 1 (independent transmission). This finding is concordant with the findings of Biederman et al for adults showing that relative to the risk in comparison subjects, the subjects with ADHD had a much higher risk for drug abuse or dependence than for alcohol abuse or dependence; their risk for drug abuse or dependence only was twice as high as that of the comparison subjects. The finding that ADHD may preferentially increase the risk for drug abuse or dependence relative to alcohol abuse or dependence is consistent with findings reported by Mannuzza et al showing that grown-up ADHD children have a high risk for drug use disorders and not alcohol use disorders. Clearly, additional work is needed, including the follow-up of the probands into young adulthood to better understand the familial relationship between ADHD and PSUD.

In contrast, other hypotheses can be rejected more clearly. The hypothesis that ADHD with PSUD is a more severe form of ADHD (hypothesis 2) can be rejected, because it incorrectly predicts a higher risk for ADHD and PSUD among the relatives of probands with ADHD with PSUD compared with relatives of probands with only ADHD. Since there was an increased risk for PSUD in the group 2 probands, it is unlikely that ADHD with PSUD represents a distinct subtype (hypothesis 4). Hypothesis 5 also can be rejected, since the association between ADHD and PSUD could not be accounted for by nonrandom mating.

Our findings should be interpreted with caution since they are subject to a number of limitations. Since the rates of PSUD were relatively low (15%, \( n = 19 \)), this study has limited power for studying the complex interrelationship between ADHD and PSUD. Thus, these results should be viewed as preliminary until replicated in larger clinical samples and in community samples.

Moreover, our findings, based on a clinical population, should be interpreted with caution since they may not generalize to nonclinical settings. Clinically referred children and adolescents with ADHD seeking treatment from a health professional are more likely to be more severely ill than children not referred. However, the rates of comorbidity with antisocial disorders and PSUD found in the sample of clinically referred probands with ADHD in the present study are consistent with those observed in children meeting the diagnostic criteria for ADHD in epidemiological studies of children not referred, suggesting that the probands with ADHD in the present study may, in many respects, be representative of children with ADHD in the community. Moreover, the rates of PSUD in the control probands (15%) and their first-degree relatives (20%) are consistent with those in epidemiological samples.

The diagnosis of ADHD in parents was made retrospectively. The validity of adult ADHD often has been questioned because of the hypothesis that adults incorrectly report having ADHD symptoms as a consequence of overidentifying with a child who has the disorder. However, family studies and of children with ADHD found that only a minority of parents of affected children report such symptoms themselves. Moreover, the clinical and cognitive characteristics of parents with a history of childhood-onset ADHD revealed a pattern of demographic, psychosocial, psychiatric, and cognitive features identical to those of children with the disorder. Furthermore, Zametkin and colleagues showed that even never-diagnosed, never-treated parents with ADHD whose children also had the disorder had evidence on a positron emission tomographic scan of brain dysfunction during attentional tasks. Living with a child with ADHD is highly unlikely to produce this pattern of results.

In addition, although raters were blind to the diagnosis of the probands, parents were not. The parents of children with ADHD might be more likely to recall similar problems in their own childhood than are the parents of the control probands. It is noteworthy, however, that although the possibility of recall bias may have affected the diagnosis of ADHD, such bias probably is not operative for the diagnosis of PSUD, since PSUD in probands was reported with similar frequency by parents with and without PSUD. Another potential source of bias stems from the indirect interviews with the mothers about the probands and their siblings. This method for assessment of psychopathologic disease characteristics in the children may have led to underrepresentation of psychopathologic disease in the children. In addition, while probands and their siblings were assessed at baseline and follow-up, parents were assessed only at baseline. Thus, it is pos-
sible that additional cases of PSUD that were not captured emerged in the parents during the 4-year follow-up period. Nevertheless, our findings retain considerable validity. The assessment of psychopathologic disease characteristics in probands and relatives was based on criterion-based structured interviews, and diagnoses were made by raters who were blind to the diagnoses of the probands. The instruments used are similar to those used in large epidemiological studies of adults and children, and the rates of disorders found in healthy comparison children and their relatives are compatible with those studies.37,47

Despite these considerations, in a sample of clinically referred children and adolescents with ADHD, familial risk analyses suggest that ADHD is likely to be causally independent from PSUD. However, it is possible, that ADHD and drug use disorders (ie, drug abuse or dependence) may share familial etiological factors. Additional work is needed to clarify the familial transmission of ADHD and PSUD since the probands in the sample were still young at follow-up.

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