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FAMILIAL RISK ANALYSIS OF THE ASSOCIATION BETWEEN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND PSYCHOACTIVE SUBSTANCE USE DISORDER IN FEMALE ADOLESCENTS: A CONTROLLED STUDY

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Abstract

Background—A robust and bi-directional comorbidity between attention-deficit/hyperactivity disorder (ADHD) and psychoactive substance use disorder (PSUD, alcohol or drug abuse, or dependence) has been consistently reported in the literature. However, this literature has been based almost exclusively on male only samples and, therefore, the findings may not generalize to females.

Methods—First-degree relatives from a large sample of pediatrically and psychiatrically referred girls with (123 probands, 403 relatives) and without ADHD (112 probands, 359 relatives) were comprehensively assessed by blind raters with structured diagnostic interviews. Familial risk analysis examined the risks in first-degree relatives for ADHD and PSUD (alcohol or drug abuse or dependence) after stratifying probands by the presence and absence of these disorders.

Results—ADHD in the proband significantly increased the risk for ADHD in relatives independently of the comorbidity with PSUD. PSUD in the proband was associated with a significantly increased risk for PSUD in relatives regardless of ADHD status. There was no evidence of co-segregation or non-random mating in the families of probands with ADHD and PSUD.

Conclusions—Patterns of familial risk analysis suggest that the association between ADHD and PSUD in adolescent females is most consistent with the hypothesis that these disorders are independently transmitted, although the hypothesis of variable expressivity could not be ruled out. These findings are consistent with previously reported patterns of familial associations between ADHD and PSUD found in adolescent males. Longer follow-up periods are needed to more fully

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Conflict of Interest

Dr. Joseph Biederman receives/d research support from, is on the speaker's bureau for, and/or has an advisory/consulting relationship with the following sources: Shire, Eli Lilly, Pfizer, McNeil, Abbott, Bristol-Myers-Squibb, New River Pharmaceuticals, Cephalon, Janssen, Neurosearch, Stanley Medical Institute, Novartis, Lilly Foundation, Prechter Foundation, Astra-Zeneca, Forest Laboratories, Glaxo-SmithKline, UCB Pharma, Inc, NIMH, NICHD, and NIDA. Dr. Stephen V. Faraone receives/d research support from, is on the speaker's bureau for, and/or has an advisory/consulting relationship with the following sources: Eli Lilly & Company, McNeil Pediatrics, Novartis, Shire Laboratories, the National Institute of Mental Health, the National Institute of Child Health and Development and the National Institute of Neurological Diseases and Stroke. Dr. Eric Mick receives/d grant support from the following pharmaceutical companies: McNeil Pediatrics, Shire LPC, Pfizer, and the National Institute of Mental Health. Mr. Carter R. Petty, Ms. Allison Clarke, Ms. Kristina Ten Haagen, and Dr. Michael C. Monuteaux have no competing interests to disclose.

clarify the relationship between ADHD and PSUD, as well as provide adequate power for separate analyses of alcohol and drug use.

Keywords

ADHD; substance use; female; family risk

INTRODUCTION

The co-occurrence of attention-deficit/hyperactivity disorder (ADHD) and psychoactive substance use disorder (PSUD: alcohol or drug abuse, or dependence) has been reported in a variety of clinical and research settings (Carroll & Rounsaville, 1993; Kaminer, 1992; Wilens, Biederman, Spencer, & Frances, 1994). Follow-up studies have documented a higher than expected risk for PSUD in adults with ADHD (Hechtman & Weiss, 1986; Mannuzza et al., 1991). Likewise, studies of referred and non-referred adults with ADHD have also documented a high risk for PSUD (Biederman et al., 1993; Faraone et al., 2007; Shekim, Asarnow, Hess, Zaucha, & Wheeler, 1990). Most recently, Kessler et al. (2006) reported results from the National Comorbidity Replication Survey indicating that adults with ADHD were at significantly higher risk for any substance use disorder compared to respondents without ADHD.

The association between ADHD and PSUD has also been seen in family members of children with ADHD. Morrison and Stewart (1971) and Cantwell (1972) reported elevated rates of alcoholism in relatives of children with ADHD. Similar findings have been seen in two large, family-genetic studies of ADHD that showed higher rates of PSUD in the relatives of boys (Biederman, Faraone, Keenan, Knee, & Tsuang, 1990) and girls (Biederman et al., 1992) with ADHD. Although these studies suggest important relationships between ADHD and PSUD, the nature of this association remains unclear.

In one of the few studies of its kind, Milberger, Faraone, Biederman, Chu and Wilens (1998) conducted a familial risk analysis in a longitudinal sample of boys with and without ADHD followed into adolescent years. Although results were suggestive of independent transmission between ADHD and PSUD, variable expressivity could not be ruled out. However, because this study was based on a male sample, results may not generalize to girls with ADHD. If we find that the familial association between ADHD and PSUD is different in families of females with ADHD compared to families of males with ADHD, then our results would support the development of sex-specific hypotheses about the familial and genetic etiology of ADHD.

The main aim of this study was to examine patterns of familial association between ADHD and PSUD in adolescent girls with ADHD. To this end we examined data from a longitudinal sample of pediatrically and psychiatrically referred girls with and without ADHD followed longitudinally and blindly for five years into adolescence. Based on models proposed by Pauls, Towbin, Leckman, Zahner and Cohen (1986), we tested several competing hypotheses describing the familial association between ADHD and PSUD. In stating these hypotheses, the expected differences are relative to healthy controls. The hypotheses were as follows:

1. ADHD and PSUD are etiologically independent. In this case we would expect to find high rates of ADHD in the relatives of probands with ADHD, regardless of the proband's PSUD status, and an increased rate of PSUD among the relatives of the probands with PSUD, regardless of the proband's ADHD diagnosis. In addition, there should be no co-segregation of ADHD and PSUD in these families.

2. ADHD and ADHD with PSUD share familial etiological factors, but additional factors are needed to manifest ADHD with PSUD. In this case we would expect to find a higher risk for ADHD and PSUD among the relatives of probands with ADHD and PSUD compared with the relatives of probands with ADHD alone and the relatives of control probands. There should also be evidence for co-segregation of ADHD and PSUD in these families.
3. ADHD and PSUD share common familial etiologic factors. In this case we would expect to find elevated rates of ADHD and PSUD in the relatives of probands with ADHD with PSUD, the relatives of probands with ADHD alone, and the relatives of probands with PSUD alone compared with the relatives of control probands.
4. ADHD with PSUD is a distinct familial subtype. In this case we would expect to find high rates of ADHD in the relatives of probands with ADHD, regardless of the proband's PSUD status, and an increased rate of PSUD among the relatives of the probands with PSUD, regardless of the proband's ADHD diagnosis. In addition, ADHD and PSUD co-segregate in these families.
5. ADHD with PSUD is the result of non-random mating. If this were the case, we would expect to find that spouses of individuals with ADHD have higher rates of PSUD than spouses of individuals without ADHD. Rates of disorders in the relatives of probands would resemble the patterns for independent transmission (hypothesis 1).

To the best of our knowledge this is the first comprehensive evaluation of the association between ADHD and PSUD in girls.

METHODS

Subjects

Subjects were derived from a longitudinal case-control family study of ADHD described previously (Biederman et al., 1999; Biederman et al., 2006). At baseline, we studied female probands aged 6–18 years with (N=140) and without (N=122) ADHD ascertained from pediatric and psychiatric sources. Potential probands were excluded if they had been adopted, if their nuclear family was not available for study, if they had major sensorimotor handicaps (paralysis, deafness, blindness), psychosis, autism, inadequate command of the English language, or a Full Scale IQ less than 80. All of the ADHD probands met full DSM-III-R diagnostic criteria for ADHD at the time of the clinical referral; at the time of recruitment they all had active symptoms of the disorder. The present study reports on the five-year follow-up of the probands, where 123 ADHD and 112 control subjects were successfully ascertained. First-degree relatives of these probands included mothers (N=234), fathers (N=224), and siblings (N=304). Parents were assessed at baseline only (as they had passed the age of risk for most psychopathology), while the siblings were assessed at baseline (N=255) and five-year follow-up (N=302). Parents and adult offspring provided written informed consent to participate, and parents also provided consent for offspring under the age of 18. Children and adolescents provided written assent to participate. The human research committee at Massachusetts General Hospital approved this study protocol.

Two independent sources provided the index children. We selected psychiatrically referred ADHD subjects from consecutive referrals to a pediatric psychopharmacology clinic at a major academic center. The pediatrically referred ADHD subjects were consecutively ascertained outpatients from the pediatric clinics of a major Health Maintenance Organization (HMO) identified from their computerized records as either having or not having ADHD. Within each setting, we selected normal controls from consecutive outpatient referrals at pediatric medical clinics. The ADHD sample comprised 63 subjects

referred by psychiatric sources and 77 by pediatric sources. The control group comprised 55 hospital-based subjects and 67 HMO-based subjects. We previously demonstrated no clinically or statistically significant differences between ADHD subjects ascertained from these two referral sources on baseline measures of psychopathology, cognitive performance or psychosocial functioning (Busch et al., 2002).

A three-stage ascertainment procedure was used to select probands (Faraone & Tsuang, 1995). For ADHD subjects, the first stage was their referral to a psychiatric or pediatric clinic resulting in a clinical diagnosis of ADHD by a child psychiatrist or pediatrician. The second stage confirmed the diagnosis by screening all children positive at the first stage by administering a telephone questionnaire to their mothers. Eligible case children meeting study entry criteria were recruited for the study and received the third stage, a diagnostic assessment with a structured interview. Only patients who received a positive diagnosis at all three stages were included in the final analysis.

We also screened potential non-ADHD controls in three stages. First, we ascertained them from consecutive referrals to medical clinics for routine physical examinations at both the psychiatric and pediatric sources. In stage two, the control mothers responded to the DSM-III-R ADHD telephone questionnaire about their daughters. Eligible controls meeting study entry criteria were recruited for the study and received the third stage, a diagnostic assessment with a structured interview. Only subjects classified as not having ADHD at all three stages were included in the control group.

Because this study had begun prior to the finalization of DSM-IV, our baseline assessment used DSM-III-R-based structured interviews, but we supplemented these with questions that would allow us to make DSM-IV diagnoses. Psychiatric assessments at the five-year follow-up relied on the Schedule for Affective Disorders and Schizophrenia for School-Aged Children – Epidemiologic Version (K-SADS-E) (Orvaschel, 1994) for subjects younger than 18 years of age and the Structured Clinical Interview for DSM-IV (SCID) (First, Spitzer, Gibbon, & Williams, 1997) (supplemented with modules from the K-SADS-E to assess childhood diagnoses) for subjects 18 years of age and older. We conducted direct interviews with subjects and indirect interviews with their mothers. We considered a disorder positive if DSM-IV diagnostic criteria were unequivocally met in either interview.

Although standardized algorithms were used to determine each diagnosis, interviewers needed a mechanism to determine the clinical relevance of symptoms when subjects were only able to provide unclear or imprecise information. Thus, a committee of nine board-certified child and adult psychiatrists who were blind to the subject's ADHD status, referral source and all other data resolved diagnostic uncertainties. 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.

The raters were blind to the clinical status of the subject, the ascertainment site and all prior assessments. The raters had undergraduate (or first) degrees in psychology and were trained to high levels of inter-rater reliability. First, they underwent several weeks of classroom style training, learning interview mechanics, diagnostic criteria and coding algorithms. Then, they observed interviews conducted by experienced raters and clinicians. They subsequently conducted at least six practice (non-study) interviews and at least two study interviews while being observed by senior interviewers. The principal investigator (JB) supervised the interviewers throughout the study. We computed kappa coefficients of agreement by having experienced, board certified child and adult psychiatrists and licensed clinical psychologists diagnose subjects from audio taped interviews. Based on 500 assessments from interviews of children and adults, the median kappa coefficient was .98.

Kappa coefficients for individual diagnoses included: ADHD (0.88), conduct disorder (1.0), major depression (1.0), mania (0.95), separation anxiety (1.0), agoraphobia (1.0), panic (.95), substance use disorder (1.0), and tics/Tourette's (0.89).

Socioeconomic status (SES) was measured using the 5-point Hollingshead scale (Hollingshead, 1975).

Statistical Procedures

We conducted a familial risk analysis by comparing four groups of relatives defined by probands' ADHD and PSUD status (i.e., Neither, ADHD alone, PSUD alone, both ADHD and PSUD). Using Cox proportional hazards models, we compared the relatives of the four proband groups on estimated rates of ADHD and PSUD. Using Cox models, co-segregation was established if the presence of ADHD in the relative significantly increased the risk for PSUD in the same relative within the subset of families having a proband with both ADHD and PSUD. We tested for non-random mating of ADHD and PSUD using Fisher's exact test. To account for the non-independence of family members, we used the Huber correction (Huber, 1967) to produce robust variances for all statistical tests using family members. All tests were two-tailed with alpha set at 0.05.

RESULTS

Attrition and Demographics

As previously reported (Biederman et al., 2006), 88% (123/140) of the ADHD and 92% (112/122) of the control subjects recruited at baseline were successfully reassessed at the five-year follow-up ($\chi^2_{(1)}=1.1$, $p=0.30$). Among ADHD and control subjects, there were no significant differences between those successfully followed up and those lost to follow-up on socioeconomic status (SES), age, GAF score, familial intactness, ascertainment source, or psychiatric comorbidity (all p values >0.05).

All probands (age range 10–25 years) were included in this analysis because ages of onset of psychoactive substance use disorder (PSUD) were reported as young as 9 years of age. Four groups were used for the familial risk analysis of PSUD and ADHD: relatives of 89 control probands without PSUD (Control Relatives, $N=285$), relatives of 23 control probands with PSUD (Controls+PSUD Relatives, $N=74$), relatives of 90 ADHD probands without PSUD (ADHD Relatives, $N=291$), and relatives of 33 ADHD probands with PSUD (ADHD +PSUD Relatives, $N=112$).

At the five-year follow-up, there were significant differences in age between the four groups (Table 1). Specifically, the Controls+PSUD and ADHD+PSUD groups had older probands and relatives. Therefore, we controlled for proband age in all subsequent analyses. The Cox models used for the familial risk analysis adjusted for the differences in the relatives' ages. There were no differences between groups in race or family SES.

Familial Risk for ADHD and PSUD

Figure 1A shows that age-adjusted rates of ADHD in the ADHD+PSUD Relatives and ADHD Relatives were significantly higher compared to Control Relatives (37% and 23% versus 11%; Hazard Ratio (HR)=1.5, 95% Confidence Interval [1.2, 1.8], $p<0.001$ and $HR=1.5$ [1.2,1.9], $p<0.001$, respectively) and Controls+PSUD Relatives (37% and 23% versus 5%, $HR=2.8$ [1.8,4.4], $p<0.001$ and $HR=4.4$ [1.8,11.1], $p=0.001$, respectively). A test of the proportion hazards assumption revealed that the risk for ADHD between ADHD Relatives and Control Relatives was not proportional over time ($\chi^2_{(1)}=5.20$, $p=0.02$). Based on a plot of the observed and predicted values, we calculated a hazard ratio for ages one to

five years and ages six years and older. This analysis showed that the risk for ADHD in the ADHD Relatives was significant in the first five years of life (HR=1.8 [1.4,2.5], $p<0.001$) but not following this period (HR=1.1 [0.7,1.7], $p=0.73$). All other comparisons of ADHD did not violate the proportion hazards assumptions (all $p>0.20$).

Figure 1B shows that the ADHD+PSUD Relatives and Controls+PSUD Relatives had significantly higher age-adjusted rates of PSUD compared to Control Relatives (62% and 48% versus 42%; HR=1.2 [1.0,1.4], $p=0.01$ and HR=1.5 [1.0,2.3], $p=0.04$, respectively, Figure 1B). The ADHD+PSUD Relatives also had a significantly higher age-adjusted rate of PSUD compared to the ADHD Relatives (62% versus 48%; HR=1.7 [1.0,2.7], $p=0.04$). The Controls+PSUD Relatives and ADHD Relatives did not have significant differences in PSUD (48% versus 48%, $p=0.11$). None of the comparisons of PSUD violated the proportion hazards assumption (all $p>0.30$).

There was no evidence for co-segregation in the ADHD+PSUD Relatives (Figure 1C, 67% PSUD in subjects with ADHD versus 59% PSUD in subjects without ADHD, $p=0.44$). This test of co-segregation did not violate the proportion hazards assumption ($p=0.20$). Co-segregation, the likelihood that two disorders are inherited together through families more often than expected by chance, was examined in order to distinguish between the familial transmission patterns of independent transmission (no co-segregation) or family subtype (the disorders co-segregate). There was also no evidence for non-random mating in the ADHD+PSUD Relatives. The rate of PSUD in fathers was not significantly different in mothers with or without ADHD (73% versus 70%, respectively, $p=1.00$). The rate of ADHD in fathers was not significantly different in mothers with or without PSUD (42% versus 16%, respectively, $p=0.21$). The tests for non-random mating are used to determine if the comorbidity of ADHD and PSUD in the probands is a result of parents with ADHD who are more likely to have spouses with PSUD (or vice versa).

DISCUSSION

In a systematic evaluation of the familial relationship between ADHD and PSUD using a well-characterized, large, longitudinal sample of ADHD girls and their first-degree relatives, we found that ADHD in the proband was consistently associated with a significantly increased risk for ADHD in relatives irrespective of comorbidity with PSUD. Likewise, PSUD in the proband predicted PSUD in relatives irrespective of the comorbidity with ADHD. There was no evidence for co-segregation or non-random mating between these disorders. Taken together these findings are most consistent with the hypothesis of independent transmission between ADHD and PSUD in girls with ADHD (hypothesis 1).

The findings of familial association between ADHD and PSUD identified in this sample of girls with ADHD are remarkably consistent with those previously reported by our group in a sample of boys with ADHD using identical ascertainment and assessment methodology. These results support the hypothesis that the nature of the familial association between ADHD and PSUD is not moderated by gender.

The finding that ADHD in the proband consistently increased the risk for ADHD in relatives irrespective of PSUD status is consistent with the well-documented familiarity of this disorder (Biederman et al., 1992; Biederman et al., in press; Faraone et al., 2000; Faraone et al., 2006). Also consistent with the extant literature is the finding the PSUD in probands increases the risk for PSUD in relatives (Merikangas et al., 1998; Rounsaville et al., 1991; Tsuang et al., 1998).

However, although not reaching our threshold for statistical significance, the risk for PSUD in relatives was also increased in ADHD probands without PSUD. Thus, although our

results are most consistent with the hypothesis of independent transmission between ADHD and PSUD, considering that the probands are still young and transiting through the age of risk for PSUD, we cannot rule out the variable expressivity hypothesis (hypothesis 2) positing that ADHD and PSUD may share common risk factors. Future long-term follow-up findings will help clarify this important issue.

In contrast, other hypotheses can be rejected more clearly. The hypothesis that ADHD with PSUD is, from a familial perspective, a more severe form of ADHD 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. Furthermore, since there was no evidence of co-segregation between ADHD and PSUD in relatives, it is unlikely that ADHD with PSUD represents a distinct familial subtype. Likewise we can reject the hypothesis that the association between ADHD and PSUD is due to non-random mating, since we detected no significant evidence that parents with ADHD were more likely to be married to someone with PSUD, and vice versa. Thus, these results should be viewed as preliminary until replicated in larger clinical samples and in community samples.

Our findings should be interpreted in the context of several limitations. While probands and their siblings were assessed at baseline and follow-up assessments, parents were assessed only at baseline. Thus, it is possible that additional cases of substance use disorders emerged in the parents during the follow-up period. However, the use of Cox models to calculate age-adjusted rates somewhat mitigates this concern. In addition, the retrospective reports of ADHD symptoms in parents may have been subject to recall bias and therefore had an effect on the precision of our findings. Our sample was originally ascertained with DSM-III-R criteria, so findings may have differed had DSM-IV been used. However, Biederman et al. (1997) showed that 93% of children with a DSM-III-R diagnosis also received a DSM-IV diagnosis. Power limitations precluded our ability to examine individual PSUDs. Future long-term studies could benefit from such analyses. Since the sample consisted of largely Caucasian subjects, our findings may not generalize to other minority or ethnic groups. Finally, community based studies should determine if these findings extend to the general population.

Despite these considerations, in a sample of pediatrically and psychiatrically referred adolescent girls with ADHD, familial risk analysis suggests that the association between ADHD and PSUD is most consistent with the hypothesis of independent transmission between these disorders. Longer follow-ups are needed to confirm this finding and examine the alternative possibility of variable expressivity between ADHD and PSUD.

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Abbreviations

PSUD psychoactive substance use disorder

References

Biederman J, Faraone SV, Keenan K, Benjamin J, Krifcher B, Moore C, Sprich-Buckminster S, Ugaglia K, Jellinek MS, Steingard R, Spencer T, Norman D, Kolodny R, Kraus I, Perrin J, Keller MB, Tsuang MT. Further evidence for family-genetic risk factors in attention deficit hyperactivity

- disorder. Patterns of comorbidity in probands and relatives in psychiatrically and pediatrically referred samples. *Archives of General Psychiatry*. 1992; 49:728–738. [PubMed: 1514878]
- Biederman J, Faraone SV, Keenan K, Knee D, Tsuang MT. Family-genetic and psychosocial risk factors in DSM-III attention deficit disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1990; 29:526–533. [PubMed: 2387786]
- Biederman J, Faraone SV, Mick E, Williamson S, Wilens TE, Spencer TJ, Weber W, Jetton J, Kraus I, Pert J, Zallen B. Clinical correlates of ADHD in females: findings from a large group of girls ascertained from pediatric and psychiatric referral sources. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1999; 38:966–975. [PubMed: 10434488]
- Biederman J, Faraone SV, Spencer T, Wilens T, Norman D, Lapey KA, Mick E, Lehman BK, Doyle AE. Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with attention deficit hyperactivity disorder. *American Journal of Psychiatry*. 1993; 150:1792–1798. [PubMed: 8238632]
- Biederman J, Faraone SV, Weber W, Russell RL, Rater M, Park K. Correspondence between DSM-III-R and DSM-IV Attention Deficit Hyperactivity Disorder (ADHD). *Journal of the American Academy of Child and Adolescent Psychiatry*. 1997; 36:1682–1687. [PubMed: 9401329]
- Biederman J, Monuteaux M, Mick E, Spencer T, Wilens T, Klein K, Price JE, Faraone SV. Psychopathology in females with attention-deficit/hyperactivity disorder: A controlled, five-year prospective study. *Biological Psychiatry*. 2006; 60:1098–1105. [PubMed: 16712802]
- Biederman J, Petty CR, Wilens TE, Fraire MG, Purcell CA, Mick E, Monuteaux MC, Faraone SV. Familial risk analysis of ADHD and substance use disorders. *American Journal of Psychiatry*. (in press).
- Busch B, Biederman J, Cohen L, Faraone S, Sayer J, Monuteaux M, Mick E, Zallen B. Similar Correlates of ADHD in Children from Pediatric and Psychiatric Clinics. *Psychiatric Services*. 2002; 53:1103–1111. [PubMed: 12221308]
- Cantwell DP. Psychiatric illness in the families of hyperactive children. *Archives of General Psychiatry*. 1972; 27:414–417. [PubMed: 5051632]
- Carroll K, Rounsaville B. History and significance of childhood attention deficit disorder in treatment-seeking cocaine abusers. *Comprehensive Psychiatry*. 1993; 34:75–82. [PubMed: 8485984]
- Faraone SV, Biederman J, Mick E, Williamson S, Wilens T, Spencer T, Weber W, Jetton J, Kraus I, Pert J, Zallen B. Family study of girls with attention deficit hyperactivity disorder. *American Journal of Psychiatry*. 2000; 157:1077–1083. [PubMed: 10873914]
- Faraone SV, Biederman J, Spencer TJ, Mick E, Murray K, Petty C, Adamson JJ, Monuteaux MC. Diagnosing Adult attention deficit hyperactivity disorder: Are Late Onset and Subthreshold Diagnoses Valid? *American Journal of Psychiatry*. 2006; 163:1720–1729. [PubMed: 17012682]
- Faraone, SV.; Tsuang, MT. Methods in Psychiatric Genetics. In: Tohen, M.; Tsuang, MT.; Zahner, GEP., editors. *Textbook in Psychiatric Epidemiology*. New York, NY: John Wiley; 1995. p. 81–134.
- Faraone SV, Wilens TE, Petty C, Antshel K, Spencer T, Biederman J. Substance use among ADHD adults: Implications of late onset and subthreshold diagnoses. *American Journal on Addictions*. 2007; 16:24–34. [PubMed: 17453604]
- First, M.; Spitzer, R.; Gibbon, M.; Williams, J. *Structured Clinical Interview for DSM-IV Axis I Disorders*. Washington, D.C: American Psychiatric Press; 1997.
- Hechtman L, Weiss G. Controlled prospective fifteen year follow-up of hyperactives as adults: non-medical drug and alcohol use and anti-social behaviour. *Canadian Journal of Psychiatry*. 1986; 31:557–567.
- Hollingshead, AB. *Four Factor Index of Social Status*. New Haven: Yale Press; 1975.
- Huber PJ. The behavior of maximum likelihood estimates under non-standard conditions. *Proceedings of the Fifth Berkeley Symposium on Mathematical Statistics and Probability*. 1967; 1:221–233.
- Kaminer Y. Clinical implications of the relationship between attention-deficit hyperactivity disorder and psychoactive substance use disorders. *American Journal on Addictions*. 1992; 1:257–264.
- Kessler RC, Adler L, Barkley R, Biederman J, Conners CK, Demler O, Faraone SV, Greenhill LL, Howes MJ, Secnik K, Spencer T, Ustun TB, Walters EE, Zaslavsky AM. The prevalence and

- correlates of adult ADHD in the United States: Results from the national comorbidity survey replication. *American Journal of Psychiatry*. 2006; 163:716–723. [PubMed: 16585449]
- Mannuzza S, Gittelman Klein R, Bonagura N, Malloy P, Giampino TL, Addalli KA. Hyperactive boys almost grown up: V. Replication of psychiatric status. *Archives of General Psychiatry*. 1991; 48:77–83. [PubMed: 1984764]
- Merikangas K, Stolar M, Stevens D, Goulet J, Preisig M, Fenton B, Zhang H, O'Malley S, Rounsaville B. Familial transmission of substance use disorders. *Archives of General Psychiatry*. 1998; 55:973–979. [PubMed: 9819065]
- Milberger S, Faraone SV, Biederman J, Chu MP, Wilens T. Familial risk analysis of the association between attention- deficit/hyperactivity disorder and psychoactive substance use disorders. *Archives of Pediatric and Adolescent Medicine*. 1998; 152:945–951.
- Morrison JR, Stewart MA. A family study of the hyperactive child syndrome. *Biological Psychiatry*. 1971; 3:189–195. [PubMed: 5163807]
- Orvaschel, H. Schedule for Affective Disorder and Schizophrenia for School-Age Children Epidemiologic Version. 5. Ft. Lauderdale: Nova Southeastern University, Center for Psychological Studies; 1994.
- Pauls DL, Towbin KE, Leckman JF, Zahner GE, Cohen DJ. Gilles de la Tourette's Syndrome and obsessive-compulsive disorder: Evidence supporting a genetic relationship. *Arch Gen Psychiatry*. 1986; 43:1180–1182. [PubMed: 3465280]
- Rounsaville BJ, Kosten TR, Weissman MM, Prusoff B, Pauls D, Anton SF, Merikangas K. Psychiatric disorders in relatives of probands with opiate addiction. *Archives of General Psychiatry*. 1991; 48:33 – 42. [PubMed: 1984760]
- Shekim WO, Asarnow RF, Hess E, Zaucha K, Wheeler N. A clinical and demographic profile of a sample of adults with attention deficit hyperactivity disorder, residual state. *Comprehensive Psychiatry*. 1990; 31:416–425. [PubMed: 2225800]
- Tsuang M, Lyons M, Meyer J, Doyle T, Eisen S, Goldberg J, True W, Lin N, Toomey R, Eaves L. Co-occurrence of abuse of different drugs in men. *Archives of General Psychiatry*. 1998; 55:967–972. [PubMed: 9819064]
- Wilens T, Biederman J, Spencer T, Frances R. Comorbidity of attention deficit hyperactivity and psychoactive substance use disorders. *Hospital and Community Psychiatry*. 1994; 45:421–435. [PubMed: 8045536]

Figure 1.
Familial risk analysis of ADHD and psychoactive substance use disorder (PSUD)

Table 1

Demographics of probands and their first-degree relatives. Values in table represent mean $\pm$ sd or frequency (percent).

	Controls		Controls+PSUD		ADHD		ADHD+PSUD		Test Statistic	p-value
	N=89 Probands	N=285 Relatives	N=23 Probands	N=74 Relatives	N=90 Probands	N=291 Relatives	N=33 Probands	N=112 Relatives		
Age at last assessment (years)										
Probands	16.4 ± 2.7		19.9 ± 2.5 <i>a***</i>		15.2 ± 3.3 <i>a**b***</i>		19.6 ± 2.7 <i>ac***</i>		$F_{(3,234)}=31.28$	<0.001
Mothers	42.0 ± 5.3		45.0 ± 4.8 <i>a**</i>		39.8 ± 5.7 <i>a**b***</i>		44.1 ± 5.8 <i>c***</i>		$F_{(3,233)}=8.92$	<0.001
Fathers	43.7 ± 5.8		48.0 ± 5.6 <i>a***</i>		42.5 ± 6.0 <i>b***</i>		45.1 ± 5.8 <i>c*</i>		$F_{(3,223)}=6.14$	<0.001
Siblings	15.9 ± 5.1		19.4 ± 5.2 <i>a**</i>		15.1 ± 5.9 <i>b**</i>		20.4 ± 6.7 <i>a**c***</i>		$F_{(3,194)}=6.83$	<0.001
Family Caucasian	118 (96)		118 (96)		118 (96)		102 (91)		Fisher's Exact	0.26
Family Socioeconomic Status	1.9 ± 0.9		1.9 ± 0.9		1.9 ± 0.9		1.7 ± 0.8		$\chi^2_{(3)}=3.37$	0.34

a vs. Controls,

b vs. Controls+PSUD,

c vs. ADHD;

* $p \leq 0.05$,

** $p \leq 0.01$,

*** $p \leq 0.001$