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Do Executive Function Deficits Predict Later Substance Use Disorders Among Adolescents and Young Adults?

Dr. Timothy E. Wilens, M.D., **Ms. MaryKate Martelon, M.P.H.**, **Ms. Ronna Fried, Ed.D.**, **Mr. Carter Petty, M.A.**, **Mr. Clancey Bateman, B.A.**, and **Dr. Joseph Biederman, M.D.**
Clinical and Research Program in Pediatric Psychopharmacology, Massachusetts General Hospital, Boston, MA

Abstract

Objective—There is increasing interest regarding the risk and overlap of executive function deficits (EFDs) in stable cigarette smoking and substance use disorders (SUD). Therefore, we examined whether earlier EFD was a risk factor for subsequent cigarette smoking and SUD and further explored the relationship between EFD and SUD.

Method—We assessed 435 subjects at the five-year follow-up (232 cases of ADHD; mean age ± SD: 15.4 ± 3.43 and 203 controls: 16.3 ± 3.42 years) and again four to five years later as part of a prospective family study of ADHD youth. Individuals were assessed by structured psychiatric interview for psychopathology and SUD. EFD was categorically defined in an individual that had at least 2 out of 6 abnormal neuropsychological tests of executive functioning.

Results—At the final follow-up period, ADHD was found to be a significant predictor of stable cigarette smoking ($p<0.01$) and SUD into late adolescence and young adult years ($p<0.01$). However, EFDs were not associated with an increase in subsequent substance use outcomes. New onset stable cigarette smoking, but not SUD, was associated with subsequent EFD ($p<0.01$).

Conclusions—Our results do not support the hypothesis that EFDs predicts later stable cigarette smoking or SUD in children with ADHD growing up. However, stable cigarette smoking is associated with subsequent EFD.

Keywords

ADHD; executive function; substance-use disorders; longitudinal follow-up

Correspondence to: Timothy E. Wilens, M.D., Massachusetts General Hospital, Pediatric Psychopharmacology Unit, 55 Parkman Street., YAW 6A, Boston, MA 02114; Telephone: 617-726-1731; Fax: 617-724-3742; twilens@partners.org.

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Introduction

A large body of literature has linked Attention-deficit/Hyperactivity Disorder (ADHD) to Substance Use Disorders (SUD; including drug or alcohol abuse or dependence) and cigarette smoking (for reviews see[1–4]). Although the reasons for these associations remain unclear (it has been suggested that the link may be due to executive function deficits (EFDs) since EFDs are common in individuals with ADHD),[5] cognitive and neuropsychological disturbances have been linked with SUD.[6–9]

Executive functioning (EF) generally refers to a group of higher order cognitive processes responsible for self-regulatory and goal-oriented behaviors.[10] It includes various cognitive functions consisting of interference and effortful control, mental flexibility, organization and strategic planning, such as anticipatory, and goal oriented "preparedness to act."[11, 12] Welsh and Pennington [12, 13] have defined EF clinically "as the ability to maintain an appropriate problem solving set for attainment of a future goal, which includes the following: a) an intention to inhibit a response or to defer it to a later more appropriate time; b) a strategic plan of action sequences; and c) a mental representation of the task, including the relevant stimulant information encoded in memory and the desired future goal-state."[13] Poor EF has been hypothesized to lead to a range of inappropriate motor behavior or impulses[14] and has been implicated in the regulation of other higher-level cognitive systems, including social behavior, language production, planning, attention, and SUD.

Tarter et al. [15] have shown that youth with neurobehavioral disinhibition are at an increased risk for later SUD. In a sample of young adults with parental history of SUD, Deckel et al. [16] reported abnormal tests of executive functioning predicted alcohol consumption at a 3-year follow up. Aytaclar et al. [17] showed that a high risk group of school aged youth performed poorer on EF at baseline that subsequently predicted substance use in early adolescence. In contrast, Gale et al. [18] in a group of Vietnam veterans in early adulthood found that after controlling for other confounders, cognitive ability ceased to be significantly associated with risk of current (but not lifetime) alcohol abuse. While informative, many of the studies have used behavioral descriptions or traits of cognition and not psychometric testing and there is little overlap between behavioral rating scales of EFDs and those assessed by psychometric testing.[19] Moreover, the role of EFD in causing SUD has not been previously investigated in the context of ADHD.

Whether EFDs moderate the risk for SUD in children with and without ADHD is of clinical, research, and public health significance. Since EF can be determined objectively by psychometric tests, their dysfunction could alert families and clinicians to higher risk in individuals with or without ADHD of these deficits. The elucidation of cognitive perturbations that predict SUD in children will help in identifying etiological factors and subgroups at risk for SUD. Given the high rates of both EFDs and of SUD in youth with ADHD, identifying those at highest risk for SUD by virtue of their EF could potentially help in the prevention of SUD.

The main aim of this study was to evaluate whether EFDs affect the risk for SUD in children with ADHD. We also examined if EFDs increase the risk for SUD in subjects without ADHD. To this end we used data from two large longitudinal, case-control samples of aging ADHD boys and girls.[20, 21] Based on the literature, we hypothesized that EFDs identified in childhood would predict subsequent SUD in aging children with ADHD independent of ADHD status. We also examined the relationship between EFDs and current or past SUD.

Method

Detailed methodological information has been previously reported.[20–22] Briefly, subjects were derived from two identically designed longitudinal case-control family studies of children with and without ADHD of both sexes ascertained from pediatric and psychiatric sources. These studies recruited male and female probands aged 6 to 17 years with (N=140 boys, N=140 girls) and without (N=120 boys, N=122 girls) DSM-III-R ADHD. Male subjects were assessed at baseline, 1-year, 4-year, and 10-year follow-ups while female subjects were assessed at baseline, 5-year, and 11-year follow-ups. The current sample includes information from the 4 and 5-year follow-ups through the 10 and 11-year follow-ups (from 1997–2008) for the boys and girls studies, respectively.

We excluded potential subjects if they had major sensorimotor handicaps (paralysis, deafness, blindness), psychosis, autism, inadequate command of the English language, a Full Scale IQ less than 80, if their nuclear family was not available for study or if they were adopted. All of the ADHD subjects met full DSM-III-R diagnostic criteria for ADHD at the time of the clinic referral; at the time of recruitment they all had active symptoms of the disorder. At all assessment periods, 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 MGH approved the initial assessments as well as all aspects of the follow-up study.

Follow-up Assessment Procedures

Lifetime psychiatric assessment at the 4 – 5 and 10 – 11 year follow-ups relied on the Schedule for Affective Disorder and Schizophrenia for Children (K-SADS-E) [23] for subjects younger than 18 years of age and the Structured Clinical Interview for the DSM-IV (SCID)[24, 25] supplemented with modules from the KSADS-E to assess childhood diagnoses for subjects 18 years of age and older. We conducted indirect interviews with subject's mothers and direct interviews with subjects. We combined data from indirect and direct interviews by considering a diagnostic criterion positive if it was endorsed in either interview.

As previously reported,[20, 21] we considered a disorder positive if DSM-IV diagnostic criteria were unequivocally met. SUD and stable smoking were diagnosed on the basis of DSM-IV criteria using the KSADS-E and SCID. To meet a positive diagnosis of stable smoking, subjects under 18 needed to endorse any amount of smoking daily for over a month, whereas subjects over 18 needed to endorse smoking at least a pack of cigarettes per day. Recent evidence suggests the utility of structured interview data compared to objective data for "lifetime" SUD determination.[26] Rates of disorders reported are lifetime prevalence. Duration of disorders is expressed in years based on ages of onset and offset. Onsets and offsets for all disorders as well as stable cigarette smoking were the age at which the subject began meeting criteria for that disorder.

Board-certified child and adult psychiatrists who were blind to the subject's ADHD status, referral source and all other data resolved diagnostic uncertainties. We estimated the reliability of the diagnostic review process by computing kappa coefficients of agreement for clinician reviewers. For these diagnoses in children and adults, the median reliability between individual clinicians and the review committee assigned diagnoses was 0.87. To assess the reliability of our overall diagnostic procedures, we computed kappa coefficients of agreement by having experienced, blinded, board-certified child and adult psychiatrists diagnose subjects from audiotaped interviews made by the assessment staff. Based on 500 assessments from interviews of children and adults, the median kappa coefficient was 0.98.

Kappa coefficients for individual diagnoses included: major depression (1.0), mania (0.95), ADHD (0.88), conduct disorder (CD; 1.0), oppositional defiant disorder (ODD; 0.90), antisocial personality disorder (ASPD; 0.80), major depression (1.0), and SUD (1.0).

Interviewers assessed the degree of impairment on daily functioning associated with each disorder that subjects endorsed on a three-level ordinal scale: minimal (e.g., little to no impairment), moderate (e.g., difficulties in daily life tasks), or severe (e.g., unable to perform essential daily tasks). Consistent with our prior work, we considered major depression only if the depressive episode was associated with severe impairment, in order to avoid false positive diagnoses. As there is not a similar precedent for bipolar or substance use disorders, we adopted a less stringent approach and made the diagnosis only when associated with at least moderate impairment.

Neuropsychological Assessments

As reported previously,[5] we defined executive functioning deficits as at least 2 of 6 abnormal neuropsychological tests of executive function. These tests are thought to assess the following executive functioning components: vigilance and distractibility; planning and organization; response inhibition; set shifting and categorization; selecting attention; visual scanning; and verbal learning. The tests used are as follows: the copy organizations and delay organization of the Rey-Osterrieth Complex Figure[27, 28] (scored by the Waber-Holmes method), which are meant to test planning and organization. The total errors score (sum of omission, commission, and late errors) of the Auditory Continuous Performance Test,[29] which is intended to measure auditory sustained attention, vigilance, and impulsivity. Perseverative errors and loss of set of the computerized Wisconsin Card Sorting Test,[30] which measures reasoning ability, concept formation, and cognitive flexibility. The percentage of words learned (number of words recalled across all trials divided by total number of words) of the Wide Range Achievement of Memory and Learning test for children less than 17 years of age[31] or the California Verbal Learning Test in children greater than or equal to 17 years of age,[32] which is intended to be an index of left prefrontal systems and a measure of verbal learning and working memory. The color-word raw score of the Stroop test[33] which is meant to measure response inhibition - impairments on this scale could be due to inhibitory difficulties and/or problems with reading and rapid naming. We consider rapid naming relevant to ADHD, given that such difficulties are also found in participants with ADHD, even in the absence of a learning disability (LD).[34] Lastly, the Freedom from Distractibility Index[35, 36] gauges attention and working memory.

The justification and validation of the consolidation of these tests as a measure of EF dysfunction for analytical purposes has been reported previously.[5] Analyses by Biederman et al.[5] showed that these variables all measure a single latent construct. Therefore, even though in general EF is considered to be made up of several factors, the subtests from these measures collectively measure a single factor. In defining EFDs, we were compelled to attend to conceptual and methodological issues. Briefly, we wanted our definition to be clinically applicable, such that practitioners could readily apply our apply our algorithm without excessive cumbersome computation and because performance on tests of EF improves with age; [37] our method took into account the age of subjects.

Socioeconomic status (SES) was measured using the 5-point Hollingshead scale.[38]

Statistical Analysis

We created a binary measure of EFD that we previously found to be a valid measure of analyzing EFDs.[5] We assessed differences at the 4 and 5-year follow-ups between ADHD and control subjects using t-tests for continuous outcomes, the Wilcoxon rank-sum test for

SES, and the Pearson χ^2 tests for binary outcomes. We used Cox proportional hazards model to assess the risk of SUD (moderate/severe impairment) while controlling for SES. To properly assess this risk, any subject who endorsed any SUD or stable cigarette smoking at the 4 and 5-year follow-ups were dropped from the Cox analysis for that outcome. Because we assessed multiple outcomes, the number of dropped subjects varied across the different outcomes: any alcohol use disorders (N=44), any drug use disorders (N=38), any SUD (N=62), and stable cigarette smoking (N=38).

To examine differences between current SUD status and current EFD status we used logistic regression controlling for SES and age. We used logistic regression to test whether the development of new cases of any SUD or cigarette smoking was associated with a subject's current EFD status. Subjects were dropped from this analysis if at the 4/5-year assessment they had an EFD or an alcohol, drug, or nicotine use disorder that was the predictor in the model. For the aforementioned analyses, we conducted pairwise comparisons. Exact logistic was used in the event of small numbers. Data are expressed as mean ± standard deviation (SD) unless otherwise specified. All tests were two-tailed, and our alpha level was set at 0.05 for all analyses, unless otherwise noted. We calculated all statistics using STATA, version 10.0.

Results

There were 435 subjects available for study at the respective 4 and 5-year follow-ups (232 cases of ADHD; mean age at follow-up 15.36 ± 3.43 years) and 203 controls (16.26 ± 3.42 years). Twenty-three subjects (5%) were dropped due to missing neuropsychological information. Therefore, our final sample size included 412 subjects. Among those without any SUD or an endorsement of stable cigarette smoking at the 5-year follow-up (N=343), ADHD subjects were significantly younger, had a significantly lower socioeconomic status, and were more likely to be diagnosed with mood disorders, multiple anxiety disorders, and oppositional defiant disorder than controls (see Table 1). There was also a significant difference in the number of subjects who had EFD: 41% (N=72) of ADHD cases (N=174) and 11 % (N=18) of controls (N=169; $\chi^2 = 41.83$, $p<0.001$). We found no significant differences across the groups for gender (p=0.43) or conduct disorder (p=0.10)

EFDs and risk of subsequent SUD

We first examined whether ADHD and EFDs were associated with an increased risk of subsequent SUD. The overall comparison between controls, ADHD subjects without EFD, subjects with only EFD, and ADHD subjects with EFD was significant for any SUD, drug use disorders, alcohol use disorders, and cigarette smoking (Table 2). We determined that ADHD subjects were significantly more likely to be diagnosed with an alcohol use disorder (32% vs. 21%; $p<0.01$), drug use disorder (27% vs. 10%; $p<0.001$), any SUD (38% vs. 25%; p=0.001), and cigarette smoking (19% vs. 8%; $p<0.01$) compared to controls. ADHD subjects with EFD were also more likely to smoke cigarettes than controls (23% vs. 8%; $p<0.01$). Additionally, among those with ADHD, having an EFD did not increase the prevalence of SUD, but was associated with a decrease in any SUD (ADHD alone: 38% vs. ADHD plus EFD: 21%; p=0.04) and drug use disorders (ADHD alone: 27% vs. ADHD plus EFD: 10%; p=0.01).

We did not find any significant differences between subjects with EFD and controls across all substance use outcomes. Similarly, there were no significant differences between subjects who had EFD and ADHD subjects with EFD (all p values>0.05). Results remained unchanged when we controlled for family history of substance use and IQ.

Substance Use Onset

We also examined the onset of SUD between ADHD and controls as well as between those with and without EFD. We found a significant difference between ADHD and controls in the time of any SUD onset (Difference=1.0 year; t=2.28; p=0.02), stable cigarette use onset (1.9 years; t=2.45; p=0.02), and drug use disorder onset (1.1 years; t=2.24; p=0.02) with ADHD subjects beginning use earlier than controls. We did not find a significant difference in onsets for alcohol use disorders (0.66 years; t=1.47; p=0.14). When examining individuals with and without EFDs (including all ADHD and controls), we did not find any significant difference in onsets for any of the SUD outcomes (all p values >0.05).

Current EFD and Current Substance Use

We then examined whether current SUD status (past 30 days) was associated with a subject's most recent EFD measurement. ADHD subjects were more likely to have current stable cigarette smoking compared to controls (8% vs. 1%; p<0.01). ADHD subjects with EFD were more likely to have current SUD (7% vs. 2%; p=0.02), current drug use disorder (4% vs. 0%; p=0.03) and current cigarette smoking compared to controls (10% vs. 1%; p<0.01). We did not find significant differences between EFD subjects and controls, EFD subjects and ADHD subjects, EFD subjects and ADHD subjects with EFD, nor between ADHD subjects and ADHD subjects with EFD for all current substance use outcomes (all p values>0.05). In other words, among EFD subjects, ADHD does not add any additional SUD risk and conversely; among ADHD subjects, EFD does not add any additional SUD risk.

Potential Effect of Substance Use on Later EFD

We also investigated whether new cases of SUD or cigarette smoking were related to the development of an EFD. For this analysis, we eliminated all subjects who had an EFD or SUD/cigarette smoking at the 4/5-year assessment. We then examined whether the development of an SUD or cigarette smoking between the 4/5 and 10/11-year assessment was associated with subsequent current EFD and whether this association varied by ADHD status. We found that non-ADHD subjects who developed an alcohol use disorder (11% vs. 2%; p=0.03), a drug use disorder (22% vs. 3%; p=0.02), or cigarette smoking (22% vs. 2%; p<0.01) were more likely to have current EFD than controls. ADHD subjects who developed any SUD (16% vs. 2%; p<0.01), any alcohol use (17% vs. 2%; p<0.01), any drug use (25% vs. 3%; p<0.001), or any cigarette smoking (29% vs. 2%; p<0.01) were more likely to have current EFD than controls. We found a trend to significance between subjects who developed any SUD and controls (10% vs. 2%; p=0.05).

ADHD subjects with a drug use disorder were more likely to have a current EFD compared to ADHD subjects without a drug use disorder (25% vs. 7%; p=0.01). Non-ADHD subjects with stable cigarette smoking were more likely than ADHD subjects to have current EFD (22% vs. 2%; p=0.01). Additionally, ADHD subjects who developed cigarette smoking were more likely to have current EFD than ADHD subjects who did not develop cigarette smoking (29% vs. 2%; p<0.01). In short, among ADHD subjects, the development of a drug use disorder and cigarette smoking added an additional EFD risk.

Discussion

The result of our analyses examining whether EFD predicts subsequent SUD in aging children with ADHD did not predict subsequent SUD in late adolescent and young adult years. Similarly, we failed to find that EFDs predicted SUD in a non-ADHD sample. In either ADHD or control samples, we did not find that EFDs were associated with earlier

onset SUD or current SUD. However, stable cigarette use onsets were associated with subsequent EFD.

We found ADHD increased the risk for earlier onset SUD similar to previous reports.[3, 39–41] However, it does not appear that EF within ADHD is accounting for the increased risk or earlier onset for SUD. This is evident from the significant decrease in any SUD risk among ADHD subjects with an EFD; and EFD was not associated with earlier-onset SUD. These data suggest that non-neuropsychologically derived EF related symptoms, functional impairment, or non-EF factors [42] are accounting for SUD in ADHD samples. This does not negate others findings of inattentive symptoms being important predictors of SUD,[41] but highlights that abnormal results on tests of neuropsychological function indicative of EF may not predict SUD.

Our findings that psychometrically defined EFDs in mid-adolescence in both ADHD and non-ADHD samples did not predict subsequent SUD at follow-up into late adolescence and young adult years are partially consistent with the extant literature. A number of studies have shown impaired neuropsychological functioning in individuals with ongoing SUD that normalized with the cessation of SUD.[43, 44] For instance, Gonzalez et al.[6] highlighted in a comprehensive review that cognitive changes associated with marijuana were typically observed only during acute intoxication and often returned to normal with abstinence.

In contrast, Aytaclar et al. [17] showed that a high-risk group of youth by virtue of their paternal SUD performed poorer on measures of EF, and that EFDs in these children predicted the subsequent development of SUD in adolescence independently of the behavioral status of the children. Tarter et al. [15] showed that a proxy of neurobehavioral disinhibition predicted SUD. Differences in substance use versus disorder, tests of EF, and sample sizes may account for discordant results between studies.

Our lack of findings of EFD and current SUD is also partially supported by the literature. For instance, Gale et al. [18] in a large sample of Vietnam veterans (N=3258) showed that cognitive functioning was inconsistently associated with alcohol abuse (i.e. lifetime, but not current). Most of the literature showing EFD in SUD has been in relatively heavy users and has been often transient. [6] For instance, Schwieinsburg and colleagues [43] reported that in adolescents heavily using marijuana, only subtle deficits in working memory, learning and attention were noted with some evidence of improvement by 3 months after abstinence. Contrarily, in a sample with a mean age of 17 years, Medina et al. [45] showed that marijuana users had slower psychomotor speed, poorer attention, memory, planning and sequencing ability compared to nonusers.

Interestingly, we found a reduction in the risk of drug use disorders specifically among ADHD subjects with EFD. While these findings may represent a chance finding it also possible that this group by nature by of their EFD, manifest LD and are often experience special placement and classes that are linked to parental monitoring. This parental monitoring may then indirectly reduce the likelihood of later drug use disorders. It is also plausible that these children with ADHD and EFD may be less socially accepted and hence, associate with a younger more immature peer group that is less exposed to drugs of abuse. Clearly more work is necessary to disentangle this important issue.

Our data punctuate the high risk that stable cigarette smoking may partake on later EFD. More specifically, children and adolescents without cigarette smoking, SUD, or EFD who then started cigarette smoking during the five-year interval were at an increased risk for a subsequent EFD. Interestingly, the presence of EFD did not predict subsequent stable cigarette smoking; however, high rates of EFD were noted in previous smokers. While there is a large literature linking nicotine use, cigarette smoking and cognitive functioning, [46, 47]

including more recent work highlighting the treatment of cognitive dysfunction with nicotinic agents,[46, 47] less is known about cigarettes *causing* EFD and much of that work is in older adults. Ernst and associates[48] in a small sample of young adults showed poorer working memory associated with cigarette smoking. In comparing smokers, ex-smokers, and non-smokers, smoking was shown to have an adverse effect on information processing and verbal memory.[49] Similarly, Cherbuin et al.[50] recently showed that past smoking was associated with a 2 – 3 fold increase in mild cognitive impairment or disorder; and in a sample of Mexican-Americans, smoking predicted cognitive decline over a period of 7 years.[51] That stable cigarette smoking may predispose individuals to the development of EFD is of great concern given the high rate of cigarette smoking initiation during this time period, the stability of neuropsychologically defined EFD, [52] and the impairment associated with EFD.[5] Clearly, more work examining the relationship between early cigarette smoking and later EFD and other cognitive dysfunction needs to be examined.

Our findings need to be viewed in light of their methodological limitations. Our proxy of EFD was based on 2 of 6 abnormal tests of EFD. We may have had greater power by using each test in a continuous manner to examine more subtle differences in EF and subsequent risk for SUD. Additionally, our proxy of EFD solely relied on EF tests and not EF rating scales (BRIEF) therefore, our results are based on psychometrically defined EFD,[5] not a more general or behaviorally defined EFD. Previous research has found that rating-scales may be more important in predicting functioning in major life activities compared to neuropsychological tests.[53]

Our use of psychometrically defined EFD did not capture emotional self-regulation, a manifestation of prefrontal functioning and a component of EF. As such we are unable to determine if deficits in emotional self-regulation maybe related to SUD. Further work examining clinical, patient-related symptoms of EF and their role in SUD development needs to be clearly defined. Our sample was relatively young and may not have been fully through the age of risk for SUD. When neuropsychologically testing our subjects, we did not evaluate for signs or symptoms of active intoxication or withdrawal in the subjects during the time of their assessments. We do not discuss in detail the characterization of the substance use; this information however will be addressed in a future publication. Our findings with cigarettes and EFD could be confounded by acute withdrawal from cigarettes. However, individuals were allowed to smoke prior to their testing and we did not prohibit smoking in subjects being tested. Because the sample consisted of referred largely middle-class Caucasian subjects, our results may not generalize to community samples and other ethnic groups.

Despite these methodological shortcomings, our findings suggest that psychometrically defined EFD in mid-adolescence does not predict SUD in older adolescence and young adult years. Stable cigarette smoking may increase the likelihood for subsequent EFDs. Further studies examining our sample through the full age of risk and identifying predictors of persistence and remission of EFD in relation to cigarette smoking and SUD are necessary to further evaluate this issue.

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Table 1

Demographics Among Those Without Any Substance Use Disorders or an Endorsement of Cigarette Smoking at the 4/5-year Follow-up (N=343)

	ADHD (N=174)	Control (N=169)	t	p-value
Age	14.46 ± 3.21	15.67 ± 3.30	3.44	<0.001
Socioeconomic Status	1.82 ± 0.89	1.59 ± 0.81	−2.55	0.01
Intelligence Quotient (IQ)	105.69 ± 14.32	115.21 ± 12.16	6.51	<0.01
	N (%)	N (%)	χ^2	
Gender (% male)	97 (56)	87 (51)	0.63	0.43
Lifetime Comorbidity				
Conduct Disorder	7 (4)	2 (1)	2.71	0.10
Mood Disorders [a]	12 (7)	2 (1)	7/15	<0.01
Multiple Anxiety Disorders [b]	49 (28)	14 (8)	22.58	<0.01
Oppositional Defiant Disorder	71 (41)	7 (4)	65.59	<0.01

Note: ADHD=attention deficit/hyperactivity disorder

[a] includes major depression, bipolar disorder

[b] includes generalized anxiety disorder, panic disorder, social phobia, simple phobia, agoraphobia, obsessive compulsive disorder, post traumatic stress disorder, separation anxiety, and avoidance disorder

Table 2

The Risk of Subsequent Substance Use Disorders (SUD) Associated with ADHD, EFD, or the Combination (N=412)[a]

	Controls		ADHD		EFD		ADHD and EFD		Overall Significance
									p value
Lifetime Prevalence	**N**	**N (%) with outcome**	**N**	**N (%) with outcome**	**N**	**N (% with outcome)**	**N**	**N (% with outcome)**	
Alcohol Use Disorders	165	35 (21)	127	41 (32)[b]	23	4 (17)	85	17 (20)	0.03
Drug Use Disorders	171	17 (10)	126	34 (27)[b, c]	22	3 (14)	86	9 (10)	<0.01
Any Substance Use Disorder	161	40 (25)	120	45 (38)[b, c]	19	5 (26)	84	18 (21)	<0.01
Cigarette Smoking	159	12 (8)	108	20 (19)[b]	21	1 (5)	74	17 (23)[b]	<0.01

Abbreviations: ADHD=attention deficit/hyperactivity disorder

EFD=Neuropsychologically defined executive function deficits

[a] Cox proportional hazards model controlling for socioeconomic status among those without any alcohol, drug, or nicotine use disorder at the 4/5-year follow-up.

Pairwise Comparisons:

[b] p<0.05 vs. Controls

[c] p < 0.05 vs. both ADHD and EFD