

# Prospective Effects of Attention-Deficit/Hyperactivity Disorder, Conduct Disorder, and Sex on Adolescent Substance Use and Abuse

Irene J. Elkins, PhD; Matt McGue, PhD; William G. Iacono, PhD

**Context:** Attention-deficit/hyperactivity disorder (ADHD), an early manifestation of externalizing behavior, may identify children at high risk for later substance abuse. However, the ADHD–substance abuse relationship often disappears when co-occurring conduct disorder (CD) is considered.

**Objective:** To determine whether there is a prospective relationship between ADHD and the initiation of substance use and disorders, and whether this relationship depends on the ADHD subtype (hyperactive/impulsive or inattentive), CD, or sex.

**Design, Setting, and Participants:** Dimensional and categorical measures of ADHD and CD were examined via logistic regression analyses in relation to subsequent initiation of tobacco, alcohol, and illicit drug use by 14 years of age and onset of substance use disorders by 18 years of age in a population-based sample of 11-year-old twins (760 female and 752 male twins) from the Minnesota Twin Family Study.

**Main Outcome Measures:** Structured interviews were administered to adolescents and their mothers regarding substance use and to generate diagnoses.

**Results:** For boys and girls, hyperactivity/impulsivity predicted initiation of all types of substance use, nicotine dependence, and cannabis abuse/dependence (for all,  $P < .05$ ), even when controlling for CD at 2 time points. By contrast, relationships between inattention and substance outcomes disappeared when hyperactivity/impulsivity and CD were controlled for, with the possible exception of nicotine dependence. A categorical diagnosis of ADHD significantly predicted tobacco and illicit drug use only (adjusted odds ratios, 2.01 and 2.82, respectively). A diagnosis of CD between 11 and 14 years of age was a powerful predictor of substance disorders by 18 years of age (all odds ratios,  $> 4.27$ ).

**Conclusions:** Hyperactivity/impulsivity predicts later substance problems, even after growth in later-emerging CD is considered, whereas inattention alone poses less risk. Even a single symptom of ADHD or CD is associated with increased risk. Failure in previous research to consistently observe relationships between ADHD and substance use and abuse outcomes could be due to reliance on less-sensitive categorical diagnoses.

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## Author Affiliations:

Department of Psychology, University of Minnesota Twin Cities Campus, Minneapolis (Drs Elkins, McGue, and Iacono); and Department of Epidemiology, University of Southern Denmark, Odense (Dr McGue).

**A**TENTION-DEFICIT/HYPERACTIVITY disorder (ADHD) is one of the most common<sup>1</sup> and highly heritable<sup>2</sup> childhood behavioral disorders. Recently, concern over the contribution of ADHD to substance abuse has generated considerable interest.<sup>3</sup> However, a comprehensive review<sup>4</sup> and subsequent prospective studies in adolescents<sup>5</sup> and young adults<sup>6</sup> have found that the relation between childhood ADHD and substance abuse disappears when the overlap between ADHD and conduct disorder (CD) and other externalizing problems is taken into account. Childhood ADHD thus appears unimportant to substance abuse apart

from its role in increasing the risk for CD because comorbid CD has been reported in 30% to 50% of adolescents with ADHD.<sup>7</sup> Nonetheless, other studies have found ADHD to be prospectively associated with cigarette smoking<sup>8,9</sup> and nicotine dependence,<sup>10</sup> even after controlling for CD, and ADHD and CD in combination may contribute to a higher risk for substance abuse than either disorder alone.<sup>4</sup> The role of ADHD in adolescent substance use and abuse consequently remains uncertain.

Several factors contribute further to the uncertainty over the nature of the relationship of ADHD with adolescent substance use and abuse. First, the prospective studies of ADHD involve clinically ascertained samples

in which comorbid conditions predominate and girls are omitted or represented in insufficient numbers (see Barman et al<sup>11</sup> for an exception). Therefore, whether ADHD and CD contribute to substance problems differently in girls than in boys or in less severely afflicted populations is unknown. Second, although both categorical and dimensional approaches to the ADHD phenotype have been productive in genetic studies,<sup>12</sup> it is not clear whether varying definitions of ADHD, as a discrete clinical entity or as an extreme along a quantitative dimension of inattention (IN) and hyperactivity/impulsivity (HI), affects its relationship with substance problems. Third, although some studies find that it is primarily the IN symptoms of ADHD that are most predictive of substance problems,<sup>8,13</sup> others find that the HI symptoms<sup>14,15</sup> are most predictive. Finally, studies of substance abuse often depend on retrospective self-report of ADHD symptoms in older adolescents or young adults, although parental reports remain important,<sup>16</sup> whereas studies of individuals with ADHD often lack a detailed assessment of substance abuse (as noted by Molina and Pelham<sup>13</sup>). Prospective research extending through the end of adolescence, using multiple reporters in a population-based sample including female subjects and using dimensional as well as categorical representations of ADHD, is needed to help resolve these issues.

The present study sought to address these limitations of previous research. We investigated the relationship between ADHD and adolescent substance initiation and abuse in a large prospective study of more than 1500 individual twins followed up from 11 years of age, when few have initiated substance use, through 18 years of age, when substance abuse may begin to develop. We are unaware of any previous study that included a large sample of girls and that has investigated the following questions prospectively: (1) Is ADHD a risk factor for adolescent initiation and abuse of tobacco, alcohol, and marijuana, and does this depend on whether it is measured as a categorical diagnosis or symptom dimension? (2) Does ADHD predict substance outcomes when comorbidity with CD is considered? (3) Is the risk associated with ADHD attributable to a particular subtype of ADHD symptoms (IN vs HI)? and (4) Is the risk associated with ADHD comparable in boys and girls?

## METHODS

### PARTICIPANTS

The sample consisted of 760 female and 752 male twins from reared-together, same-sex twin pairs initially undergoing assessment at 11 years of age as part of the Minnesota Twin Family Study, a longitudinal study of the origins of substance use disorders. The sample was ascertained from Minnesota state birth records and was broadly representative of families with children born in Minnesota in the birth years sampled (eg, 97.9% of the twins were white). Of eligible twin-families, 17.3% declined to complete an in-person intake assessment, but non-participating families differed minimally from participating families in socioeconomic status and mental health indicators (see Iacono et al<sup>17</sup> for a more detailed description of the Minnesota Twin Family Study sample and assessment). The research protocol was approved by the University of Minnesota's institutional review board.

For the present investigation, data from the intake and first 2 follow-up assessments were used. At intake, twins ranged in age from 10.7 to 12.8 years (for boys, mean [SD] age was 11.7 [0.39] years; for girls, mean [SD] age was 11.7 [0.46] years). At the first follow-up, twins ranged in age from 13.6 to 16.9 years (for boys, mean [SD] age was 14.8 [0.49] years; for girls, mean [SD] age was 14.8 [0.57] years), although most were aged 14 to 15 years. For ease of presentation, the first follow-up is hereinafter referred to as the age-14 follow-up. At the second follow-up, twins ranged in age from 16.6 to 20.3 years (for boys, mean [SD] age was 18.0 [0.66] years; for girls, mean [SD] age was 18.3 [0.71] years). For ease of presentation, the second follow-up is hereinafter referred to as the age-18 follow-up. Of the 752 male twins in the intake sample, 694 (92.3%) had data on the substance outcomes investigated at the age-14 follow-up and 666 (88.6%) had data at the age-18 follow-up. Of the 760 female twins in the intake sample, 710 (93.4%) at the age-14 follow-up and 693 (91.2%) at the age-18 follow-up had data on the substance outcomes investigated. Although all intake and most follow-up assessments were completed in person, some twins moved out of state or were otherwise unavailable to visit the University of Minnesota. Because of such circumstances, 14% of the boys and 20% of the girls completed the age-14 follow-up by telephone and 23% of the boys and 25% of the girls completed the age-18 follow-up by telephone.

Including visits and telephone interviews as participation (because  $\chi^2$  comparisons of intake ADHD and CD status among those interviewed in person vs by telephone at either follow-up showed no significant differences), attrition analyses confirmed that boys and girls did not differ significantly in rate of participation at the age-14 ( $\chi^2=0.73$  [ $P=.39$ ]) or the age-18 ( $\chi^2=2.85$  [ $P=.09$ ]) follow-up. Among boys, a diagnosis of ADHD at intake did not significantly affect the likelihood of participating at the age-14 ( $\chi^2=0.02$  [ $P=.88$ ]) or the age-18 ( $\chi^2=0.00$  [ $P=.97$ ]) follow-up, but boys with a CD diagnosis at intake were more likely to participate at the age-14 ( $\chi^2=4.41$  [ $P<.05$ ]) but not the age-18 ( $\chi^2=0.04$  [ $P=.85$ ]) follow-up than boys without CD. Among girls, a diagnosis of ADHD at intake did not significantly affect the likelihood of participating at the age-14 ( $\chi^2=0.71$  [ $P=.40$ ]) or the age-18 ( $\chi^2=0.00$  [ $P=.96$ ]) follow-up, nor did a CD diagnosis at intake affect likelihood of participation at the age-14 ( $\chi^2=2.43$  [ $P=.12$ ]) or the age-18 ( $\chi^2=0.33$  [ $P=.57$ ]) follow-up.

### DIAGNOSTIC AND SUBSTANCE USE ASSESSMENT

Procedures at the intake and both follow-up assessments were very similar. A complete description of the study was followed by written informed consent from parents and adult twins or assent from minor twins. Twins were interviewed separately by different interviewers, each of whom had a bachelor of arts or master of arts degree in psychology and went through extensive training and observation. Twins underwent assessment for ADHD at intake, and for CD and substance use (of tobacco, alcohol, and 12 illicit substances) at intake and the age-14 follow-up, with a modified version of the Diagnostic Interview for Children and Adolescents-Revised.<sup>18</sup> At the age-18 follow-up, nicotine, alcohol, and illicit drug use disorders (ie, amphetamines, cannabis, cocaine, hallucinogens, inhalants, opiates, phencyclidine, or sedatives) were assessed using a modified version of the expanded Substance Abuse Module of the Composite International Diagnostic Interview.<sup>19</sup> In addition to each twin's self-report, maternal reports of ADHD, CD, and substance use disorders were obtained using a parallel parent version of the Diagnostic Interview for Children and Adolescents-

Revised. A symptom was considered present if the mother or the twin reported it as present, which has been shown to result in greater validity than either report alone.<sup>20</sup> Diagnoses at intake were lifetime, whereas diagnoses at the follow-up assessments were based on symptoms occurring in the interval since the last assessment.

Categorical diagnoses of ADHD and CD from intake and the age-14 follow-up were based on *DSM-III-R* criteria (the diagnostic system in use when the Minnesota Twin Family Study intake began). For dimensional analyses, the use of 3 additional *DSM-IV* symptoms of ADHD not present in *DSM-III-R* (which were included as part of a *DSM-III* assessment) allowed us to use the full complement of 9 *DSM-IV* HI symptoms and 6 of the *DSM-IV* symptoms of IN. Diagnoses of substance use disorders at the age-18 follow-up were based on *DSM-IV* criteria. Symptom presence was determined by consensus teams of 2 advanced clinical psychology graduate students (supervised by a PhD-level clinical psychologist), and every interview was reviewed regarding examples of the severity and frequency of each behavior. Subthreshold symptoms of ADHD and CD, or behavior unusual in severity or frequency but not sufficient to warrant a full symptom, were used in dimensional analyses, but only full symptoms were used to generate categorical diagnoses. The reliability of the consensus diagnoses ( $\kappa$  statistic) was 0.77 and 0.79 for ADHD and CD, respectively,<sup>20</sup> and greater than 0.92 for all substance use disorder diagnoses.<sup>17</sup> To maximize the sensitivity for lifetime diagnosis and for detection of emerging disorders,<sup>21,22</sup> diagnoses were made at 2 levels: definite (for all diagnostic criteria satisfied) and probable (for 1 symptom short of definite). Inclusion of probable cases and multiple reporters did not substantially inflate rates of ADHD and CD because 6.7% of the intake sample had a probable or definite diagnosis of ADHD and 11.6% had a diagnosis of CD, only slightly higher than the prevalence rates reported in *DSM-IV*.

Because early initiation of substance use in adolescence is a powerful predictor of substance use disorders in adulthood,<sup>23,24</sup> early initiation of substance use and onset of substance use disorders were included as outcomes for our analyses. The specific outcomes investigated included ever having tried tobacco, alcohol (without parental permission only), or at least 1 illicit drug by the age-14 follow-up and a *DSM-IV* diagnosis of nicotine dependence, alcohol abuse/dependence, and cannabis abuse/dependence by the age-18 follow-up.

## STATISTICAL ANALYSES

To develop IN and HI dimensions, given that *DSM-III-R* does not identify subtypes, all 14 *DSM-III-R* symptoms of ADHD (along with the 3 additional *DSM-IV* symptoms available) were submitted to exploratory principal components factor analyses in SPSS statistical software for Windows.<sup>25</sup> Factor analyses were conducted separately for mother-reported, child-reported, and best-estimate symptoms (based on both reports), as well as separately for male and female twins. An oblique 2-factor solution based on best-estimate symptoms was the most interpretable and consistent with the *DSM-IV* distinction between HI and IN subtypes. The HI scale consisted of all 9 *DSM-IV* criterion A2 symptoms for this subtype, as well as the *DSM-III-R* symptom "often engages in physically dangerous acts." The IN scale consisted of 6 of the *DSM-IV* criterion A1 symptoms. The ADHD subtype scales were created by summing the symptoms loading on each of the 2 factors, with 0 indicating no symptom; 0.5, subthreshold symptom; and 1, full symptom. The *DSM-III-R* symptom "often shifts from one uncompleted activity to another" had a higher loading on the HI scale but reduced scale reliability and was dropped. The re-

sulting HI and IN scales had comparable internal consistency reliabilities (0.79 and 0.72, respectively) and were substantially correlated ( $r=0.58$ ), indicating that they are not entirely distinct, consistent with the findings of others.<sup>26</sup> However, correlations between different raters (mother and child) on the same scale were modest (0.26 for HI and 0.34 for IN), suggesting that each reporter provides a unique perspective. For CD, scales corresponding to *DSM-III-R* criterion A symptoms of CD reported at intake ( $\leq 11$  years of age inclusive) and those reported from intake to the age-14 follow-up (ie, 11-14 years of age) were used. Symptom counts were log-transformed to minimize positive skewness, then converted to standard scores to facilitate interpretation of the magnitude of effects.

The association among ADHD, CD, and substance use outcomes was investigated through logistic regression models, with symptom dimensions or categorical diagnoses as predictors. To assess the utility of these dimensions and diagnoses in predicting substance use initiation or the development of a substance use disorder, a series of increasingly complex models was fitted for each of the 6 dichotomous substance outcomes: initiation of tobacco, alcohol, or illicit drug use (by the age-14 follow-up) or onset of *DSM-IV* nicotine, alcohol, and illicit drug disorders (by the age-18 follow-up). We used the generalized estimating equations (GEE) method<sup>27</sup> in PROC GENMOD from SAS statistical software<sup>28</sup> (using a logit link function) because GEE models are useful when observations on multiple individuals within a higher-order unit, such as a family or twin pair, are clustered.<sup>29</sup> When applied to twin data, GEE models correct for this by simultaneously estimating the correlation between twins with respect to the dependent variable (in this case, substance outcomes), as well as the coefficients associated with the predictor variables in the regression model (eg, ADHD and CD).

## RESULTS

### SEX SIMILARITIES AND DIFFERENCES ON SUBSTANCE OUTCOMES

Prevalences of substance use initiation by the age-14 follow-up and *DSM-IV* substance use disorders by the age-18 follow-up are given in **Table 1**. Rates of substance initiation were similar for boys and girls (for all,  $P > .05$ ), with higher initiation of tobacco use among boys (40.5%) than girls (30.0%) as the only significant exception ( $\chi^2_1=16.97$  [ $P < .001$ ]). However, boys were significantly more likely than girls to have a diagnosis of nicotine dependence ( $\chi^2_1=21.58$  [ $P < .001$ ]), alcohol abuse/dependence ( $\chi^2_1=52.62$  [ $P < .001$ ]), and cannabis abuse/dependence ( $\chi^2_1=40.26$  [ $P < .001$ ]). Our rates of substance diagnoses appear comparable to those of other epidemiological samples. For example, 26.1% of boys and 11.0% of girls had *DSM-IV* alcohol abuse or dependence at the probable or definite level of certainty. In the National Household Survey on Drug Abuse,<sup>30</sup> 24.4% of men and 13.3% of female adults aged 18 to 23 years had alcohol abuse or dependence when diagnostic "orphans" with 2 symptoms (comparable to probable dependence) were included.

To determine whether sex differences were present in the associations among ADHD, CD, and any of the substance outcomes, a sex  $\times$  symptom dimension (or sex  $\times$  diagnosis) term was added to each logistic regression model. No significant interactions were found be-

**Table 1. Prevalence of Substance Use Initiation by Age-14 Follow-up and Substance Use Disorders by Age-18 Follow-up<sup>a</sup>**

Sample	Age-14 Follow-up				Age-18 Follow-up			
	No. of Participants	Substance Use Initiated, No. (%)			No. of Participants	DSM-IV Substance Use Disorder, No. (%) <sup>b</sup>		
		Tabacco	Alcohol	Illicit Drug		Nicotine Dependence	Alcohol Abuse/Dependence	Cannabis Abuse/Dependence
Combined sample <sup>d</sup>	1404	494 (35.2)	431 (30.7)	156 (11.1)	1359	311 (22.9)	250 (18.4)	189 (13.9)
Boys	694	281 (40.5)	226 (32.6)	87 (12.5)	666	188 (28.2)	174 (26.1)	133 (20.0)
Girls	710	213 (30.0) <sup>e</sup>	205 (28.9)	69 (9.7)	693	123 (17.7) <sup>e</sup>	76 (11.0) <sup>e</sup>	56 (8.1) <sup>e</sup>

<sup>a</sup>The age-14 follow-up and age-18 follow-up are described in detail in the "Participants" subsection of the "Methods" section.

<sup>b</sup>Diagnoses are reported at both probable and definite levels of certainty.

<sup>c</sup>Alcohol use was without parental permission only.

<sup>d</sup>The combined sample included 1400 to 1404 participants for substance use outcomes at the age-14 follow-up and 1354 to 1359 participants for substance use outcomes at the age-18 follow-up.

<sup>e</sup>Prevalence among male twins was significantly greater than among female twins ( $P < .001$ ).

tween sex and each of the ADHD and CD symptom dimensions or diagnoses in any of the models tested, suggesting similar relationships between the predictors and substance outcomes for boys and girls. This prospectively confirms recent cross-sectional findings of no significant sex differences in rates of comorbid alcohol or other drug disorders associated with ADHD.<sup>31</sup> Therefore, only results of models including main effects are reported in **Table 2**, and the data in the **Figure** is presented for boys and girls together.

#### SUBSTANCE INITIATION BY AGE-14 FOLLOW-UP

The upper half of Table 2 gives the results of the prospective regression analyses, using lifetime symptom dimensions of ADHD and CD at intake or the presence or absence of a categorical diagnosis of ADHD and CD in predicting initiation of substance use by the age-14 follow-up. Comparison of the unadjusted and fully adjusted odds ratios (ORs) shows that, although IN significantly predicted tobacco, alcohol, and illicit drug use (ie, all unadjusted ORs had 95% confidence intervals not inclusive of 1.0), its contributions mostly overlapped those of HI and CD. Inattention still uniquely predicted alcohol use initiation, with a 1-SD increase in IN increasing the odds of having tried alcohol by 16% (OR, 1.16), after adjusting for HI and CD. However, HI significantly predicted initiation of tobacco, alcohol, and illicit drug use even when the significant contribution of CD was taken into account (eg, a 1-SD increase on the HI measure increased the odds of trying tobacco by 29%, even when adjusted for IN and CD). Finally, CD symptoms by 11 years of age significantly and uniquely predicted initiation of use of all 3 substances, especially illicit drugs, with a 1-SD increase in the CD measure increasing the odds of trying a drug by 60% (adjusted for HI and IN). A categorical diagnosis of ADHD significantly predicted initiation of tobacco and illicit drug use, even when significant contribution of CD by 11 years of age was taken into account, but did not significantly predict initiation of alcohol use even before adjusting for CD. A diagnosis of CD by 11 years of age significantly and uniquely predicted initiation of

use of all 3 substances, especially illicit drugs, when adjusting for ADHD diagnosis.

#### SUBSTANCE USE DISORDERS BY AGE-18 FOLLOW-UP

The lower half of Table 2 gives the results of the prospective regression analyses, including symptom dimensions of ADHD by 11 years of age and CD from ages 11 to 14 years or the presence or absence of a categorical diagnosis of ADHD by intake and CD by the age-14 follow-up, in predicting onset of DSM-IV nicotine, alcohol, and illicit drug use disorders by the age-18 follow-up. Because virtually all of the adolescents with an illicit drug diagnosis had cannabis abuse or dependence (sometimes accompanied by amphetamine or other drug diagnoses), we were unable to subdivide by drug type for outcome by 18 years of age. Inattention significantly predicted nicotine, alcohol, and cannabis use disorders, but its contributions mostly overlapped those of HI and CD by 14 years of age. For example, a 1-SD increase in the IN measure increased the odds of nicotine dependence by 43% but only by 10% when adjusted for HI and CD (Table 2, last footnote). Hyperactivity/impulsivity significantly predicted nicotine, alcohol, and cannabis use disorders (and remained significantly predictive except for alcohol use disorders) once CD by the age-14 follow-up was taken into account. Conduct disorder symptoms at intake, although significant predictors of all 3 substance disorders, were no longer significantly associated with any substance disorders once CD symptoms by the age-14 follow-up were included; thus, only ORs associated with CD by the age-14 follow-up are presented in Table 2. A diagnosis of ADHD significantly predicted nicotine dependence only when unadjusted for the effects of CD and did not predict alcohol or cannabis abuse/dependence even before adjusting for CD, whereas a diagnosis of CD between intake and the age-14 follow-up significantly predicted all 3 types of substance disorders. Even when adjusted for effects of diagnoses by 11 years of age, a diagnosis of CD by the age-14 follow-up quadrupled the odds of nicotine dependence (OR, 4.27) and quintupled the odds of alcohol (OR, 4.98) or can-

**Table 2. Risk of Initiating Substance Use by 14 Years of Age and Onset of Substance Use Disorders by 18 Years of Age<sup>a</sup>**

Substance Use	Predictors of Initiation of Substance Use by Age 14 y, OR (95% CI)				
	Symptom Dimension at Intake <sup>b</sup>			DSM-III-R Diagnosis at Intake	
	Inattention	Hyperactivity-Impulsivity	Conduct (Age 11 y)	ADHD	CD (Age 11 y)
Tobacco <sup>c</sup>					
Unadjusted	<b>1.29</b> (1.15-1.43)	<b>1.46</b> (1.29-1.64)	<b>1.42</b> (1.25-1.60)	<b>2.12</b> (1.32-3.43)	<b>1.65</b> (1.18-2.30)
Fully adjusted	1.09 (0.96-1.24)	<b>1.29</b> (1.12-1.49)	<b>1.28</b> (1.12-1.46)	<b>2.01</b> (1.24-3.28)	<b>1.56</b> (1.12-2.18)
Alcohol <sup>d</sup>					
Unadjusted	<b>1.29</b> (1.15-1.45)	<b>1.33</b> (1.18-1.49)	<b>1.29</b> (1.14-1.46)	1.47 (0.92-2.33)	<b>1.54</b> (1.12-2.11)
Fully adjusted	<b>1.16</b> (1.02-1.33)	<b>1.16</b> (1.02-1.33)	<b>1.17</b> (1.03-1.34)	1.39 (0.88-2.21)	<b>1.49</b> (1.08-2.04)
Illicit drug					
Unadjusted	<b>1.42</b> (1.21-1.67)	<b>1.61</b> (1.39-1.89)	<b>1.78</b> (1.50-2.13)	<b>3.19</b> (1.95-5.24)	<b>2.59</b> (1.65-4.06)
Fully adjusted	1.11 (0.92-1.34)	<b>1.30</b> (1.10-1.52)	<b>1.60</b> (1.33-1.91)	<b>2.82</b> (1.70-4.69)	<b>2.34</b> (1.50-3.65)
Substance Use Disorder	Predictors of DSM-IV Substance Use Disorder by Age 18 y, OR (95% CI)				
	Inattention	Hyperactivity-Impulsivity	Conduct (Ages 11-14 y)	ADHD	CD (Ages 11-14 y)
Nicotine dependence					
Unadjusted	<b>1.43</b> (1.26-1.63)	<b>1.53</b> (1.34-1.76)	<b>2.10</b> (1.82-2.44)	<b>2.23</b> (1.30-3.81)	<b>4.75</b> (3.36-6.72)
Fully adjusted	1.10 (0.93-1.30) <sup>e</sup>	<b>1.27</b> (1.06-1.52)	<b>1.92</b> (1.63-2.25)	1.61 (0.89-2.91) <sup>e</sup>	<b>4.27</b> (3.00-6.09)
Alcohol abuse/dependence					
Unadjusted	<b>1.24</b> (1.08-1.43)	<b>1.35</b> (1.16-1.58)	<b>2.05</b> (1.78-2.37)	1.31 (0.74-2.32)	<b>5.10</b> (3.57-7.30)
Fully adjusted	0.98 (0.81-1.19)	1.18 (0.95-1.46) <sup>e</sup>	<b>2.02</b> (1.71-2.40)	0.82 (0.45-1.47)	<b>4.98</b> (3.45-7.20)
Cannabis abuse/dependence					
Unadjusted	<b>1.30</b> (1.11-1.51)	<b>1.53</b> (1.31-1.78)	<b>2.24</b> (1.91-2.63)	1.02 (0.52-2.00)	<b>5.43</b> (3.74-7.88)
Fully adjusted	0.91 (0.73-1.13)	<b>1.35</b> (1.07-1.68)	<b>2.10</b> (1.75-2.53)	0.58 (0.28-1.20)	<b>5.51</b> (3.75-8.10)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CD, conduct disorder; CI, confidence interval; OR, odds ratio.

<sup>a</sup>Unadjusted and fully adjusted ORs and 95% CIs are given for symptom dimension and categorical diagnostic predictors. The ORs reflect the increase in the odds of developing a specific substance-related outcome associated with a 1-SD increase in the indicated symptom dimension or with the presence of an ADHD or CD diagnosis. Only ORs associated with main effects are presented because no interactions with sex and the ADHD and CD dimensions or diagnoses were significant. Unadjusted ORs were adjusted for sex only. For logistic regression models involving symptom dimensions as predictors, fully adjusted ORs and significance tests were adjusted for the other ADHD symptom dimensions and CD symptoms. For models with categorical diagnoses of ADHD and CD as predictors, fully adjusted ORs were adjusted for the other diagnosis. The ORs associated with risk for substance use disorders at 18 years of age were adjusted for CD symptoms or diagnosis between 11 and 14 years of age; CD symptoms or diagnosis between 11 and 14 years of age were adjusted for ADHD and CD symptoms or diagnosis present by intake at 11 years of age. Significant ORs are given in boldface type.

<sup>b</sup>The CD symptoms were assessed at 11 years of age and between 11 and 14 years of age.

<sup>c</sup>Because some individuals had already tried tobacco by 11 years of age (5.8% of the sample, or 16.6% of those using tobacco by 14 years of age), analyses predicting tobacco initiation were repeated excluding these initiators at 11 years of age. However, this exclusion had no effect on the significance of any ORs presented in the table.

<sup>d</sup>Alcohol use was use without parental permission only.

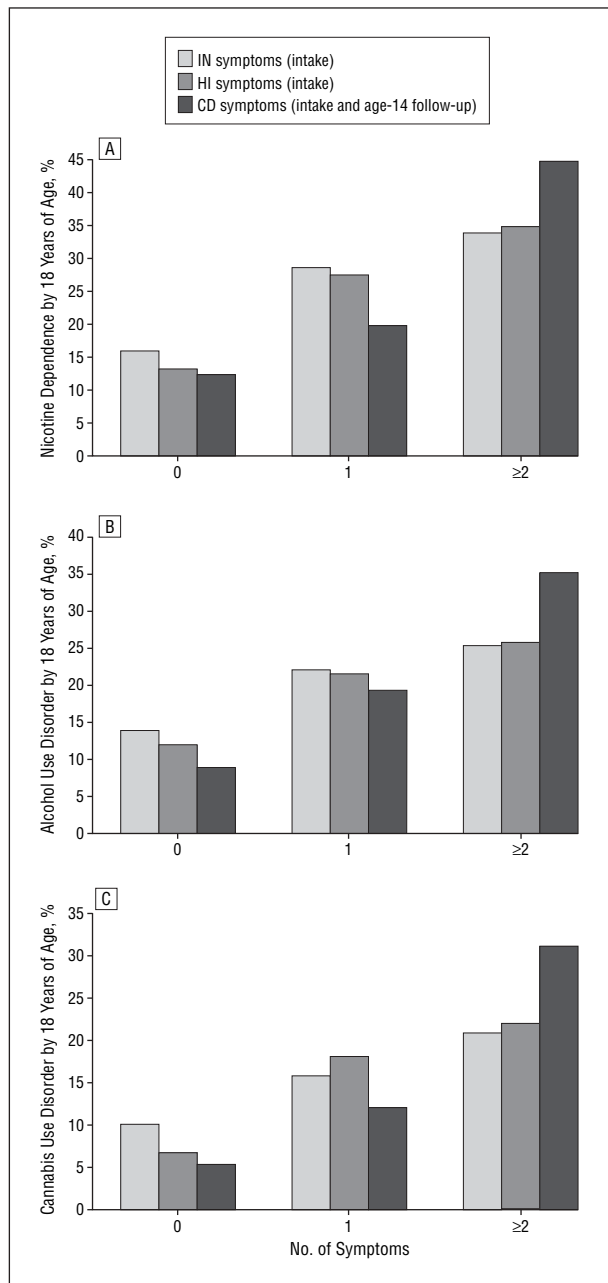
<sup>e</sup>The OR was significant when all predictors at 11 years of age were included but no longer significant when CD between 11 and 14 years of age was added.

nabis abuse or dependence (OR, 5.51) by the age-18 follow-up.

We wished to examine further the contribution of ADHD subtype dimensions at levels below clinical thresholds (similar to the approach of Kollins et al<sup>14</sup> with ADHD and smoking). Thus, rates of nicotine dependence, alcohol abuse/dependence, and cannabis abuse/dependence by the age-18 follow-up are presented in the Figure as functions of the number of best-estimate symptoms of ADHD and CD. Depending on the symptom category (IN, HI, or CD), the number of participants with no symptoms ranged from 648 to 743; with 1 symptom, from 256 to 292; and with 2 or more, from 324 to 424. Unlike the regression analyses, the Figure shows raw symptom counts only and does not control for the influence of co-occurring symptoms (ie, an adolescent with no CD symptoms might have 2 IN symptoms); nevertheless, it provides a useful picture of the data. As may be seen, there was a strong relationship between both types of ADHD symptoms (IN and HI present by intake) and CD symptoms (present by intake or between 11 and 14 years

of age) and all 3 types of substance use disorders, the strength of which increased as the number of symptoms increased.

It is particularly striking that going from no symptoms to 1 symptom is associated with a noticeable increase in risk. Compared with those with no symptoms, those with only 1 symptom of IN, HI, or CD were at significantly increased risk for subsequent development of all 3 types of substance use disorders by 18 years of age. For example, for cannabis use disorders (Figure, C), only 6.8% of those with no HI symptoms developed probable or definite cannabis abuse/dependence, whereas 18.1% of those with 1 HI symptom did ( $\chi^2=27.71$  [ $P<.001$ ]). Those with 1 HI symptom were also significantly more likely than those with none to develop nicotine dependence ( $\chi^2_1=27.46$  [ $P<.001$ ]) and alcohol abuse/dependence ( $\chi^2_1=14.15$  [ $P<.001$ ]). Similarly, compared with those with no symptoms, individuals with 1 symptom of IN also were significantly more likely to develop each type of substance use disorder (nicotine,



**Figure.** Percentage of adolescents (N=1359) with a specified number of inattentive (IN), hyperactive-impulsive (HI), and conduct disorder (CD) symptoms who develop nicotine dependence (A), alcohol use disorder (B), or cannabis use disorder (C) by 18 years of age. Intake refers to the initial assessment, which occurred when participants were 11 years of age. Age-14 follow-up indicates the first follow-up assessment, which occurred when participants were 14 years of age, on average.

$\chi^2=21.31$  [ $P<.001$ ]; alcohol,  $\chi^2=10.40$  [ $P=.001$ ]; and cannabis,  $\chi^2=6.82$  [ $P=.009$ ], as were those with 1 symptom of CD at intake or the age-14 follow-up (nicotine,  $\chi^2=8.73$  [ $P=.003$ ]; alcohol,  $\chi^2=20.20$  [ $P<.001$ ]; and cannabis,  $\chi^2=12.40$  [ $P<.001$ ]).

#### COMMENT

In a prospective design spanning 3 waves of assessment, we examined the relationship between ADHD and CD

at 11 years of age, initiation of substance use by 14 years of age, and development of nicotine, alcohol, and illicit drug use disorders by 18 years of age in a population-based sample of boys and girls. We found that HI symptoms uniquely contributed to subsequent initiation of all types of substance use and to nicotine dependence and cannabis abuse/dependence, even when controlling for CD at 2 time points. By contrast, significant relationships between IN and substance use initiation and disorders disappeared when HI and CD were added to the model, with the possible exception of alcohol initiation and nicotine dependence, the latter of which remained significant until CD from 11 to 14 years of age was added. There were no sex differences in these relationships, indicating that HI and CD make unique, and partially separate, contributions to risk for early substance initiation and abuse for girls as well as boys.

In addition, we found dimensional predictors of IN and HI to be more informative than a categorical diagnosis of ADHD. For example, even before adjusting for CD from 11 to 14 years of age, a diagnosis of ADHD significantly predicted only 3 outcomes (initiation of tobacco or illicit drug use by 14 years of age or nicotine dependence by 18 years of age), whereas HI symptoms predicted all 6 substance outcomes. That nicotine dependence was the only substance disorder significantly predicted by an ADHD diagnosis is consistent with a previous cross-sectional study in our older cohort of adolescent twins,<sup>32</sup> as is our finding that CD symptoms between 11 and 14 years of age were very powerful predictors of substance use disorders by 18 years of age. However, in contrast to our previous work<sup>32</sup> and that of others,<sup>5</sup> finding no significant relationships between a categorical diagnosis of ADHD and substance initiation once we controlled for other externalizing behaviors (eg, CD), our prospective findings suggest that a diagnosis of ADHD plays a role in initiation of use at younger ages, albeit less of a role in whether use escalates into abuse.

Our prospective results regarding the relative importance of HI and IN to nicotine dependence are consistent with the retrospective findings of Kollins et al,<sup>14</sup> who found that, although IN and HI symptoms predicted regular smoking, when controlling for the other dimension and for CD, only HI remained significant. In our study, IN was still a significant predictor of nicotine dependence even with symptoms of HI and CD by 11 years of age in the model, but it was no longer significant when CD symptoms between 11 and 14 years of age were added (OR, 1.10; 95% confidence interval, 0.93-1.30). Although this stands in contrast to other research finding a greater role for IN than HI in smoking<sup>11,33</sup> and other substance use,<sup>13</sup> the mean age at outcome in those studies was about 15 years. Thus, they are primarily relevant in predicting substance initiation and use but not abuse, and whether the independent effect of HI was significant was not consistently examined.<sup>11</sup> Furthermore, the rarity of childhood CD could account for discrepancies between our findings and those of another study<sup>13</sup> that included childhood CD as a prospective predictor and found it less important than ADHD. Because our sample was assessed through late adolescence, we were able to assess the influence of the substantial growth of adolescent CD on the later development of substance disorders.

To put the relative contributions of ADHD and CD to substance use disorders into perspective, the magnitude of influence of a CD diagnosis between 11 and 14 years of age on the later development of nicotine dependence was nearly double the odds associated with having an ADHD diagnosis by 11 years of age (OR of 4.27 adjusted for all variables at intake, compared with an OR of 2.08 for ADHD before adjusting for CD by the age-14 follow-up, or an OR of 1.61 after this adjustment). Previous twin research has provided evidence of common genetic<sup>34</sup> and shared environmental (partly via parent-child conflict<sup>35</sup>) risk for the comorbidity of ADHD and CD, and the combination of ADHD and CD is characterized by a more pathological personality profile than either disorder alone.<sup>36</sup> Thus, adolescent CD might reflect further progression down a developmental pathway of externalizing psychopathology, including substance abuse. It is also possible that ADHD measured at 11 years of age was a weaker predictor of substance disorders at 18 years of age because it was more distal in time from the outcome (eg, CD at 11 years of age also did not predict substance use disorders as well as CD between 11 and 14 years of age did; ie, all ORs, <2.0). Indeed, ADHD was still significant in predicting nicotine dependence with only predictors for 11 years of age in the model (Table 2, last footnote); however, ADHD was not a significant predictor of alcohol or cannabis abuse/dependence, even before adjusting for CD by the age-14 follow-up.

One advantage of the present study is the extremely high (approximately 90%) retention rate across follow-up assessments, which warrants confidence in its results. There are several limitations, however, that we hope to address in future research. For example, although our sample of 1512 twins was large, because ADHD and CD are considerably rarer among girls than boys, more affected girls may be needed to fully evaluate the effect of sex. Although we found no sex differences in the present study, sex-specific factors such as an early onset of menses in girls have been shown to be important in increasing environmental influence on the growth of CD<sup>37</sup> and thus important to consider in timing intervention efforts. Finally, although we reassessed CD at 14 years of age in the present prospective study, we did not assess persistence of ADHD symptoms between intake and the age-14 follow-up. Given that persistence of ADHD symptoms into adolescence may be substantial<sup>16</sup> and may affect the likelihood of substance use,<sup>13</sup> we are now investigating the roles of ADHD persistence and sex within another cohort of female and male twins aged 11 years who were selected for ADHD and CD symptoms. Thus, it is possible that persistence of IN symptoms into adolescence or sex may play more of a role in substance abuse than our present results suggest.

## CONCLUSIONS

The significance of HI may be that it is one of the earliest manifestations of externalizing behavior and continues to show unique predictive effects even after the subsequent growth in other, later emerging externalizing conditions

(ie, CD) are taken into account. Furthermore, the increase in risk for substance use disorders conferred by even a single symptom of HI or IN in our data was not negligible. Dimensional approaches to psychopathology have gained substantial acceptance among psychologists,<sup>38</sup> although concerns from the psychiatric community have been raised about their clinical utility.<sup>39</sup> However, a dimensional approach was useful in our study for clarifying the roles of ADHD and CD in the risk for substance use and has recently received substantial support in medical journals.<sup>14,40</sup> Dimensional approaches may be more sensitive in identifying those children who are at heightened risk for later substance use disorders and may be helpful in broad-based preventative intervention efforts.

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**Correspondence:** Irene J. Elkins, PhD, Department of Psychology, University of Minnesota, 75 E River Rd, Minneapolis, MN 55455 (ielkins@tfs.psych.umn.edu).

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