



Prospective association of childhood attention-deficit/hyperactivity disorder (ADHD) and substance use and abuse/dependence: A meta-analytic review[☆]

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ABSTRACT

Given the clinical and public health significance of substance disorders and the need to identify their early risk factors, we examined the association of childhood attention-deficit/hyperactivity disorder (ADHD) with substance use (nicotine, alcohol, marijuana) and abuse/dependence outcomes (nicotine, alcohol, marijuana, cocaine, other). To strengthen a potential causal inference, we meta-analyzed longitudinal studies that prospectively followed children with and without ADHD into adolescence or adulthood. Children with ADHD were significantly more likely to have ever used nicotine and other substances, but not alcohol. Children with ADHD were also more likely to develop disorders of abuse/dependence for nicotine, alcohol, marijuana, cocaine, and other substances (i.e., unspecified). Sex, age, race, publication year, sample source, and version of the Diagnostic and Statistical Manual of Mental Disorders (DSM) used to diagnose ADHD did not significantly moderate the associations with substance outcomes that yielded heterogeneous effect sizes. These findings suggest that children with ADHD are significantly more likely to develop substance use disorders than children without ADHD and that this increased risk is robust to demographic and methodological differences that varied across the studies. Finally, few studies addressed ADHD and comorbid disruptive behavior disorders (DBD), thus preventing a formal meta-analytic review. However, we qualitatively summarize the results of these studies and conclude that comorbid DBD complicates inferences about the specificity of ADHD effects on substance use outcomes.

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1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is characterized by an early onset of persistent and impairing levels of inattention–disorganization and hyperactivity–impulsivity (American Psychiatric Association, 2000). ADHD occurs in 5–10% of school-age children (Scahill & Schwab-Stone, 2000) and represents one of the most common referrals for mental health and pediatric services in the U.S. (Barkley, 1998). ADHD is associated with comorbid mood (e.g., depression, anxiety) and disruptive behavior disorders (oppositional defiant disorder [ODD] and conduct disorder [CD]) (DBD), neuropsychological deficits (e.g., verbal working memory), family problems (e.g., negative parent–child interactions), poor academic achievement, and social dysfunction (e.g., peer rejection). These associations have been reported in boys and girls, including as young as preschool who have been followed prospectively into adolescence and young adulthood (Biederman et al., 2010; Lee, Lahey, Owens, & Hinshaw, 2008; Owens, Hinshaw, Lee, & Lahey, 2009). Thus, ADHD predicts a highly dispersed pattern of impairment across behavioral, academic, social, affective, and family domains (i.e., multifinality).

Substance use disorders (SUD) (i.e., abuse and dependence) also constitute a substantial clinical, public health, and economic concern in the United States and globally (Demyttenaere et al., 2004). In 2000, substance dependence was estimated to account for \$67 billion in economic loss due to crime, social problems, foster care, and other health services (McLellan, Lewis, O'Brien, & Kleber, 2000). Among 18–59 year-old individuals participating in the National Comorbidity Survey Replication, a nationally-representative study of English-speaking adults in the United States, lifetime prevalence estimates ranged from 14.0% to 16.3% and 6.0% to 6.4% for alcohol abuse and alcohol dependence disorders, respectively (Kessler et al., 2005). For SUD more broadly (i.e., combining abuse and dependence), the lifetime prevalence in the same age range varied from 15.3% to 18.0% (Kessler, Berglund, et al., 2005). Although the 12-month prevalence of SUD in the same sample was expectedly lower (0.4% for drug dependence to 3.1% for alcohol abuse disorder), the severity of the disorders, based on functional impairment (e.g., suicide attempts, work disability, poor social relationships), was moderate to severe for most individuals (Kessler, Chiu, Demler, & Walters, 2005). In terms of clinical significance, SUD are frequently comorbid with other disorders. Substance abuse and dependence was each uniquely associated with increased comorbidity with mood disorders across six countries, and with externalizing problems (e.g., CD, antisocial behavior [ASB]) in the U.S. and Canada specifically (Merikangas et al., 1998). Finally, in addition to comorbidity, substance problems (e.g., binge drinking) are often associated with violence, accidental injuries, risky behavior (e.g., sexually transmitted disease), and poor health outcomes (e.g., hypertension) (Courtney & Polich, 2009). Thus, SUD are highly prevalent, costly, impairing, and resistant to treatment (Goldstein et al., 2009). To facilitate the development of interventions, there is an urgent need to identify precursors of SUD, particularly early in development. Detection of individuals at risk for SUD may facilitate implementation of early, targeted interventions to prevent the onset of SUD or to minimize their negative sequelae.

There are several reasons that ADHD and substance problems may be related. First, dopamine (DA) neurotransmission is central to current models of ADHD and SUD (Bédard et al., 2010; Ray et al., 2010; Volkow, Fowler, Wang, Baler, & Telang, 2009; Volkow et al., 2009) and methylphenidate (MPH) is a highly efficacious treatment for the core symptoms of ADHD, although recent evidence suggests that therapeutic response may be time-limited (Molina et al., 2008). Positron emission tomography (PET) suggests that MPH enhances extracellular DA in the basal ganglia and anterior cingulate gyrus (Volkow, Fowler, Wang, Ding, & Gatley, 2002). MPH, by virtue of activating positive attention networks and distilling task-irrelevant stimuli, improves attention, vigilance, and motivation (Swanson, Baler, & Volkow,

2010). Second, a recent review of neuroimaging studies of humans with ADHD and SUD found replicated evidence of blunted striatal DA release and disrupted neural circuitry between the anterior cingulate cortex and striatum with prefrontal cortex (Frodl, 2010). Rodent and non-human primate models suggest the centrality of deficits in response inhibition, including dysfunctional circuitry in ventrolateral frontal, cingulate cortices, and basal ganglia regions, in both ADHD and SUD (Groman, James, & Jentsch, 2009). Third, offspring of adults with SUD are more likely to develop psychopathology, including ADHD (Clark et al., 1997; Schuckit & Smith, 1996). Elevated substance use problems have also been frequently reported in parents of children with ADHD (Chronis et al., 2003; Lahey, Piacentini, McBurnett, & Stone, 1988; Molina, Pelham, & Lang, 1997). Finally, the prevalence of psychopathology, including SUD, is higher in first-degree relatives of ADHD probands than in healthy controls (Biederman, Faraone, Keenan, & Benjamin, 1992). Therefore, ADHD and SUD may share common etiological influences, including similar genetic factors (Iacono, Malone, & McGue, 2008; Young et al., 2009; see Biederman et al., 2009, for an exception).

In fact, there is a sizable body of research suggesting that ADHD is associated with elevated substance use and related disorders (e.g., Boyle et al., 1993; Clure et al., 1999; Disney, Elkins, McGue, & Iacono, 1999; Katusic et al., 2005; Mannuzza, Klein, Bessler, Malloy, & LaPadula, 1998; Milberger, Biederman, Faraone, Chen, & Jones, 1997; Milberger, Biederman, Faraone, Wilens, & Chu, 1997; Whalen, Jamner, Henker, Delfino, & Lozano, 2002). In a large ($n = 240$) case-control study, children with ADHD were two times more likely to develop substance dependence disorders than matched controls (Biederman et al., 2006). ADHD was also robustly related (odds ratio >9) to the likelihood of having an SUD in a study of 968 male adolescents in Brazil (Szobot et al., 2007). Thompson, Riggs, Mikulich, and Crowley (1996) assessed 171 adolescents with CD in a residential treatment program and found that ADHD was significantly associated with severe CD and substance problems. Similarly, ADHD was associated with severe substance dependence in a sample of 367 clinic-referred male and female adolescents (Whitmore et al., 1997). However, null associations between ADHD and substance problems have also been reported. In a sample of 1302 12–16 year-old adolescents, ADHD was unrelated to substance use and related problems (Boyle & Offord, 1991). Similarly, in a prospective study of adolescents diagnosed with ADHD when they were 7–11 years old, maltreatment, but not childhood ADHD, independently predicted substance problems (De Sanctis et al., 2008). However, the inconsistent association between ADHD and SUD may also reflect methodological variability across studies including sample characteristics (e.g., sex, population-based vs. clinic-referred) and assessment methods (e.g., structured interviews, self-report, abuse/dependence vs. frequency). For example, in Biederman et al. (2010), girls were originally ascertained when they were 6–16 years old. Thus, developmentally-sensitive assessments of SUD must consider the censored nature of the age of participants at follow-up and the potential that substance patterns may reflect age-related differences in substance exposure and availability rather than diagnostic differences per se.

Overall, the predictive validity of ADHD for SUD is unknown. Although future research on ADHD and substance outcomes must improve the methodological limitations described above, it is crucial to understand what the literature *currently* suggests. The goal of this meta-analysis was to characterize the most informative studies, which are likely to be *prospective* follow-up studies of children with and without ADHD into adolescence/adulthood. Prospective longitudinal studies significantly improve the empirical basis for determining direction of effects, evaluating mediational processes, and differentiating correlates, risk factors, and causal risk factors (Kraemer, Stice, Kazdin, Offord, & Kupfer, 2001). Indeed, temporal ordering of predictors and outcome is one of few methodological devices available to disentangle correlated constructs (Kraemer et al., 2001).

Second, meta-analysis rigorously evaluates associations from smaller studies, which is often the case for prospective longitudinal designs (Keenan & Shaw, 1997). To test the predictive validity of ADHD and SUD from methodologically diverse samples, a meta-analysis may provide superior traction relative to a single, larger study. Our aim was two-fold: (1) To meta-analyze the prospective contribution of childhood ADHD (vs. control) on dichotomized measures of lifetime substance use and abuse/dependence across nicotine, alcohol, marijuana, and cocaine; and (2) To test theoretically- and methodologically-relevant moderators (i.e., age, sex, race (percent Caucasian, DSM version, sample source) of these putative associations if and when significant heterogeneity in effect size was found.

2. Method

2.1. Study selection criteria

Each study satisfied the following inclusion criteria: (a) diagnostic ascertainment of ADHD with at least one control or non-ADHD group; (b) prospective longitudinal design (i.e., ADHD diagnosis preceded the measurement of SUD); (c) binary lifetime substance use and abuse/dependence measures; (d) available data to calculate proportions of children with and without ADHD with substance use, SUD, or odds ratios provided; (e) publication between 1980 and August 2009 in English; and (f) a non-intervention design. We prioritized case-control designs to improve the generalizability of the study to other children with ADHD (i.e., diagnostic criteria + impairment) and to specifically compare the likelihood of SUD in youth with and without ADHD. We also selected substance abuse/dependence outcomes to emphasize *clinical significance* (Kazdin, 1999). Given that experimentation with substances is often normative in adolescence (Moffitt, 1993), we chose outcomes that included impairment (i.e., failure to fulfill obligations, failed attempts to quit). Given that ADHD also predicts functional impairment, we cannot be certain that these clinically significant outcomes are attributable to substance patterns rather than the influence of ADHD (e.g., impulsivity). However, clinically significant dichotomous outcomes also resonate with person-centered research strategies that are central to developmental psychopathology (Bergman, von Eye, & Magnusson, 2006). Dichotomization does not significantly reduce statistical power and it yields meaningful effect sizes (i.e., odds ratios) (Farrington & Loeber, 2000). Finally, the intervention selection bias is a threat to internal validity in uncontrolled studies because treatment status is often positively correlated with negative outcomes (Larzelere, Kuhn, & Johnson, 2004). That is, severity of psychopathology may account for treatment status and outcome. To avoid misrepresenting the association of early ADHD and later SUD, we did not control for treatment status. We also excluded controlled intervention studies in an effort to focus on the naturalistic course of ADHD over time.

2.2. Search procedure

We employed several strategies to identify the 27 studies included in this meta-analysis. We conducted computer-based searches using the PsycInfo, PubMed, and Google Scholar databases. These inquiries entailed searching according to the following keywords (or stems when possible): alcohol, nicotine, smoking, tobacco, cigarette, marijuana, cannabis, cocaine, substance(s), drug(s), ADHD, ADD, attention-deficit, attention-deficit/hyperactivity disorder, hyperactivity, hyperactive, hyperkinetic, longitudinal, and prospective. Keywords were combined by using the Boolean operators “AND” and “OR.” Unpublished dissertations were also reviewed for potential inclusion. We also used the ancestry approach where potential studies were identified from the reference sections of existing reviews on the association of ADHD and SUD. Moreover, we thoroughly reviewed the bibliographies of identified studies for additional studies and used

both forward and backward searching. To combat the file drawer problem, we also attempted to locate unpublished studies (Rosenthal, 1979). Emails describing our study and its inclusion criteria were sent to membership listservs of research organizations including the International Society for Research in Child and Adolescent Psychopathology, Division 53 (Society for Clinical Child and Adolescent Psychology) of the American Psychological Association, and the Research Society on Alcoholism. However, all of the studies included in our meta-analysis were published in peer-reviewed journals. The majority of studies were excluded for the following reasons: (a) they were qualitative reviews, (b) ADHD and substance constructs were only measured using dimensional approaches (i.e., no formal diagnosis), or (c) ADHD designations did not precede the measurement of substance use. When multiple studies with the same substance outcome were derived from the same sample, the most recent publication was used (i.e., the longest follow-up period from baseline). Coding of individual studies was conducted by two intensively trained raters. We evaluated the reliability of all moderator codes (a total of 168) and the percentage agreement was very high (95.2%). In cases where raters provided contradictory judgments, disagreements were discussed and one of the authors (KLH) made a final determination. Studies that were included in our meta-analysis are denoted with an “*” in the reference section.

2.3. Moderator variables

We tested whether demographic/methodological factors across the studies moderated the association between childhood ADHD and SUD for studies with heterogeneous effect sizes as determined by Cochran's Q Test. The following demographic characteristics were coded: (a) average age of the sample at follow-up (in years); (b) gender composition (% male); and (c) racial diversity (% Caucasian). Methodological characteristics of each study were coded as follows: (a) sample source (clinic-referred vs. other), for both the ADHD and non-ADHD samples and (b) version of the Diagnostic and Statistical Manual of Mental Disorders (DSM) used to diagnose ADHD (i.e., DSM-III and DSM-III-R vs. DSM-IV). The final moderator was the average number of years between the initial assessment and follow-up (less than 5 years vs. 5 to 10 years vs. greater than 10 years).

2.4. Calculation of effect size

We calculated the odds ratio (OR) to estimate the effect size and significance of the association between diagnostic status (ADHD vs. control) and two separate substance measures: (a) use vs. no use and (b) abuse or dependence vs. non-abuse/dependence. The odds ratio was computed by the formula $(a + d)/(b + c)$, where *a* represented the number of individuals with ADHD who positively reported substance use or abuse/dependence; *b* represented the number of youth with ADHD who denied substance use or abuse/dependence; *c* represented the number of individuals in the control group who positively endorsed substance use or abuse/dependence; and *d* represented the number of control youth without substance use or abuse/dependence. When a cell had a value of 0, we followed expert recommendations and inserted .5 to all four cells to calculate the effect size (Lipsey & Wilson, 2001). An OR of 1 indicated that membership in the dichotomous substance outcome category was equivalent in children with and without ADHD whereas an OR greater than 1 indicated that the outcome was more likely in the ADHD group. An OR of less than 1 indicated that the outcome was less likely to occur in the ADHD group. The association of ADHD and substance outcome is statistically significant when the 95% confidence interval for the OR effect size does not include 1.0. If the 95% confidence interval included 1.0, the effect indicated statistical equivalence between the ADHD and control group. For each study, the OR was separately calculated for each available substance outcome measure. Thus, in the same study, as many as eight ORs could be derived that

corresponded to the three substance use outcomes (nicotine, alcohol, marijuana) and five abuse/dependence outcomes (nicotine dependence, alcohol abuse/dependence, marijuana abuse/dependence, cocaine abuse/dependence, and non-specified drug abuse/dependence). Using these procedures, a total 65 effect sizes were calculated from 27 eligible studies.

2.5. Statistical analysis

We employed a random-effects model where an OR for each substance outcome was weighted by the inverse variance of the OR. A random-effects model is more appropriate when the variability of findings is assumed to be attributed to other factors than subject-level sampling error (Lipsey & Wilson, 2001). In addition to calculating the mean effect size and its 95% confidence interval, we estimated heterogeneity of effects using the standard Cochran's Q Test and publication bias using Egger's (Egger, Smith, Schneider, & Minder, 1997) and Begg's tests (Begg & Mazumdar, 1994). We also calculated the Fail safe N to assess the potential for a file-drawer problem and evidence that any of the moderator variables predicted significant variance in the effect sizes where analyses resulted in significant heterogeneity. The meta-analysis was performed using STATA 11 with the meta, metareg, and metabias commands.

3. Results

To review, we evaluated the prospective contribution of childhood ADHD on measures of lifetime adolescent/adult substance use and abuse/dependence. We conducted separate meta-analyses across different substance types to examine the specificity of effects of early ADHD. We utilized random-effects models to estimate the mean effect size (and 95% confidence interval), statistical significance of the OR, and the χ^2 -based Q statistic for heterogeneity. The Q statistic approximates a chi-square distribution with $k - 1$ degrees of freedom, where k is the number of effect sizes, and it indicates the degree of consistency of findings across studies (Hedges & Olkin, 1985). Each of these parameters was estimated for the following dichotomous substance measures: (a) lifetime nicotine use, (b) nicotine dependence, (c) lifetime alcohol use, (d) alcohol abuse or dependence, (e) lifetime marijuana use, (f) marijuana abuse or dependence, (g) cocaine abuse or dependence, and (h) general illicit drug abuse or dependence (i.e., drug type not specified in the original study).

Although Table 1 summarizes the clinical, demographic, and methodological features of all 27 studies included in the meta-analysis, we note that there were 4142 to 4175 ADHD probands and 6835 to 6880 non-ADHD controls available for analysis (depending on the specific substance outcome analyzed). Based on studies that reported relevant data, the overall sample consisted mostly of Caucasian (88.9%; 15 studies) boys (74.2%; 26 studies). The average age at follow-up for participants was 18.9 years (24 studies). The sample size for ADHD probands and non-ADHD controls, respectively, was as follows: 1648 and 2323 for lifetime nicotine use; 2459 and 2950 for nicotine dependence; 872 and 597 for lifetime alcohol use; 1337 and 1195 for alcohol abuse or dependence; 600 and 2661 for lifetime marijuana use; 943 and 1885 for marijuana abuse or dependence (excluding Gignac et al. (2005)); 652 and 481 for cocaine abuse or dependence; and 542 and 637 for non-specific substance abuse or dependence.

3.1. Nicotine use and dependence

As shown in Fig. 1, children with ADHD were twice as likely to have a lifetime history of ever having used nicotine (OR = 2.08, CI = 1.66, 2.60, $p < .001$) compared to children without ADHD. The overall homogeneity statistic for nicotine use indicated that the effect sizes of the nine studies included in this analysis were comparable ($Q = 12.82$,

$p = 0.12$). A similar association was also observed for childhood ADHD and nicotine dependence. Children with ADHD were nearly three times more likely than children without ADHD to report nicotine dependence in adolescence/adulthood (OR = 2.82, CI = 2.41, 3.29, $p < .001$) (Fig. 2). The overall homogeneity statistic for nicotine dependence indicated that the twelve studies included in this analysis were largely uniform in their estimates ($Q = 5.92$, $p = .25$).

3.2. Alcohol use and abuse/dependence

Fig. 3 summarizes the individual effect sizes for each study and the aggregated estimate for lifetime history of ever having used alcohol for children with and without ADHD. Unlike nicotine use, children with ADHD were no more likely to have ever used alcohol than children without ADHD (OR = 1.27, CI = 0.85, 1.89, $p = .25$), as evidenced by the lower bound of the confidence interval falling below 1.0. The overall homogeneity statistic for alcohol use indicated that the five studies included in this analysis indicated a trend for effect size heterogeneity ($Q = 8.26$, $p = .08$). For alcohol abuse/dependence, childhood ADHD was significantly related to an increased risk for alcohol use disorder (OR = 1.74, CI = 1.38, 2.20, $p < .001$) (Fig. 4). Specifically, children with ADHD were 1.7 times more likely to meet diagnostic criteria for alcohol abuse or dependence than children without ADHD. The overall homogeneity statistic for alcohol dependence indicated no significant heterogeneity across the 11 studies ($Q = 13.20$, $p = .21$).

3.3. Marijuana use and abuse/dependence

Childhood ADHD was robustly related to an increased odds of lifetime marijuana use (OR = 2.78, CI = 1.64, 4.74, $p < .001$). Specifically, children with ADHD were nearly three times more likely to have reported ever having used marijuana than children without ADHD (Fig. 5). However, the overall homogeneity statistic for marijuana use indicated that the seven studies included in this analysis showed statistically significant variability in their effect size estimates ($Q = 20.38$, $p < .01$). This suggests that the overall effect size associating early ADHD with a higher likelihood of future adolescent/adult marijuana use should be interpreted cautiously. Results from our analysis of marijuana abuse or dependence revealed that children with ADHD were more than twice as likely to have met criteria for marijuana use disorder than children without ADHD (OR = 2.29, CI = 1.32, 3.99, $p = .003$). However, the overall homogeneity statistic for marijuana abuse/dependence indicated that the 10 studies included in this analysis showed significant variability in their effect sizes ($Q = 45.07$, $p < .001$). In particular, Gignac et al. (2005) reported an effect size that was more than two standard deviations above the grand mean. To assess the influence of this study, we removed it and re-analyzed the data. Without the Gignac et al. (2005) study, the homogeneity statistic was largely normalized ($Q = 11.81$, $p = .16$). The recalculated effect size (OR = 1.58, CI = 1.16, 2.14, $p = .003$) revealed that children with ADHD were approximately 1.5 times more likely than children without ADHD to develop marijuana abuse or dependence (Fig. 6).

3.4. Cocaine abuse or dependence

Children with ADHD were significantly more likely to develop cocaine abuse or dependence in adolescence/adulthood than children without ADHD (OR = 2.05, CI = 1.38, 3.04, $p < .001$) (Fig. 7). Children with ADHD were twice as likely to develop cocaine abuse or dependence than children without ADHD. The Q test indicated minimal heterogeneity in the five studies ($Q = 1.80$, $p = .77$), thus strengthening our inference that each study was relatively consistent in its estimation of the association between ADHD and cocaine abuse/dependence.

Table 1
Methodological features of studies included in meta-analysis.

Authors	N at follow-up	Average age at follow-up	% Male	% White	Sample source	Length of follow-up	DSM version for ADHD	Outcomes
August et al. (2006)	ADHD: 109 Control: 91	18.3	74.58	89.55	ADHD and Controls: School-based	6–12 years	DSM-III-R	Marijuana & alcohol abuse & dep.; nicotine use & dep.
Barkley et al. (1990)	ADHD: 123 Control: 66	14.55	91.53	Not provided	ADHD: clinical (psychological); Control: referrals from ADHD group	8 years	Not provided	Marijuana, alcohol, & nicotine use
Barman, Pulkkinen, Kaprio, and Rose (2004) ^a	ADHD: 672/705 Control: 1324/1369	14.04	50.09	Not provided	ADHD, Control: population-based (Finnish registry)	2–3 years	DSM-IV	Nicotine use & dep.
Biederman et al. (2006)	ADHD: 112 Control: 105	22	100	100	ADHD: clinical (psychiatric, medical); Control: clinical (medical)	10 years	DSM-III-R	Non-specific abuse & dep.; alcohol abuse & dep.; nicotine dep.
Biederman et al. (1997)	ADHD: 128 Control: 109	14.77	100	100	ADHD, Control: "psychiatric and nonpsychiatric settings"	4 years	DSM-III-R	Marijuana & cocaine abuse & dep.
Brook, Duan, Zhang, Cohen, and Brook (2008)	ADHD: 52 Control: 589	32	46.02	91	ADHD, Control: Subset of nationally representative sample of northeastern U.S.	19–22 years	DSM-IV	Nicotine dep.
Burke et al. (2001)	ADHD: 108 Control: 96	Not provided	100	70	ADHD, Control: clinical	3 years	DSM-III-R	Nicotine dep.
Claude and Firestone (1995)	ADHD: 52 Control: 52	19.7	100	Not provided	ADHD: "clinical group;" Control: schools, community	14.4 to 24.9 years for ADHD group	DSM-III-R	Non-specific abuse & dep.; alcohol abuse & dep.
Elkins et al. (2007) ^b	ADHD: Not provided Control: Not provided	18.15	49.74	97.9	ADHD, Control: population-based (Minnesota Twins)	6–8 years	DSM-III-R, supplemented with DSM-IV	Marijuana & alcohol abuse & dep.; nicotine dep.
Ernst et al. (2006)	ADHD: 50 Control: 28	16.0	69.23	Not provided	ADHD, Control: clinical, newspapers	3.8 years on average	DSM-IV	Marijuana, alcohol, & nicotine use
Fergusson and Horwood (1995)	ADHD: 24 Control: 912	16	Not provided	Not provided	ADHD, Control: Birth cohort	Approximately 1 year	DSM-III-R	Marijuana use & nicotine dep.
Fischer, Barkley, Smallish, and Fletcher (2002)	ADHD: 147 Control: 73	20.5	91	94	ADHD: clinical; Control: matched community	13.8 years on average	Not provided	Marijuana, cocaine, & alcohol abuse & dep.; non-specific abuse & dep.
Gignac et al. (2005)	ADHD: 28 Control: 179	20	47.83	Not provided	ADHD, Control: psychiatric and nonpsychiatric settings	6–17 years at baseline, 20 years on average at follow-up	DSM-III-R	Marijuana abuse & dep.; marijuana use
Hechtman, Weiss, and Perlman (1984)	ADHD: 75 Control: 44	19	90	Not provided	ADHD: clinical; Control: schools	10 years	Not provided	Marijuana, cocaine, & alcohol abuse & dep.
King, Iacono, and McGue (2004) ^c	ADHD: 193 Control: 163	14.8	48.75	Not provided	ADHD, Control: community-based sample of twins	10–12 years-old at baseline; Average age at follow-up was 14.8 years	DSM-III-R	Alcohol, nicotine, & marijuana use
Lambert (2005)	ADHD: 217 Control: 182	26	78.05	76.83	ADHD, Control: community-based	28 years	DSM-IV	Marijuana, cocaine, & alcohol abuse & dep.; nicotine dep.
Lambert and Hartsough (1998)	ADHD: 218 Control: 182	Not provided	78.05	77	ADHD, Control: community-based	School-age to adult	DSM-III-R	Nicotine use
Mannuzza et al. (1998)	ADHD: 85 Control: 73	24.1	100	100	ADHD: clinical; Control: clinical and community	15–21 years	Not provided	Marijuana, cocaine, & alcohol abuse & dep.
Mannuzza et al. (1991)	ADHD: 94 Control: 78	18.64	100	Not provided	ADHD: clinical; Control: clinical, phone-dialing	5–16 years	Not provided	Non-specific abuse & dep.
Milberger, Biederman, Faraone, Chen, and Jones (1997)	ADHD: 28 Control: 238	15	100	100	ADHD and Control: clinical	4 years	DSM-III-R	Nicotine use
Milberger, Biederman, Faraone, Wilens, and Chu (1997)	ADHD: 34 Control: 235	17.34	49.44	100	ADHD, Control: sibling referral	4 years	DSM-III-R	Alcohol abuse & dep.; non-specific abuse & dep.

(continued on next page)

Table 1 (continued)

Authors	N at follow-up	Average age at follow-up	% Male	% White	Sample source	Length of follow-up	DSM version for ADHD	Outcomes
Pelham (2003)	Control: 100				schools, newspapers	average		abuse & dep.; marijuana, alcohol, & nicotine use; nicotine dep.
Molina et al. (2007)	ADHD: 364 Control: 240	17.51	89.24	82.8	ADHD: clinical; Control: clinical, schools, newspapers	Average of 8 years	DSM-IV	Alcohol use, abuse, & dep.
Monuteaux et al. (2008)	ADHD: 139 Control: 122	Not provided	0	Not provided	ADHD and Control: clinical	5 years	DSM-III-R, supplemented with DSM-IV	Nicotine dep.
Reynolds and Kirisci (2001)	ADHD: 28 Control: 180	16	85.6	68.3	Not provided	4–6 years	Not provided	Nicotine dep.
Wilens et al. (2008)	ADHD: 80 Control: 86	19.2	48.01	Not provided	ADHD, Control: referrals from 2 previous studies	5 years for girls and 10 years for boys	DSM-III-R	Nicotine use & dep.
Wittchen et al. (2007)	ADHD: 40 Control: 1213	24	49.94	Not provided	ADHD, Control: government registries	10 years	DSM-IV	Marijuana abuse & dep.; marijuana use

Note. ADHD = attention-deficit/hyperactivity disorder (ADHD); DSM = Diagnostic and Statistical Manual; Dep. = Dependence.

^a Sample size differed by specific outcome measure.

^b Sample size not provided; odds ratio provided by authors.

^c Sample size provided for only one outcome (which is reported here).

3.5. General illicit drug abuse/dependence

The overall effect for drug abuse/dependence, defined by studies that did not explicitly specify the substance, also revealed higher rates abuse/dependence among children with ADHD (OR = 2.64, CI = 1.77, 3.94, $p < .001$; Fig. 8). Specifically, individuals with ADHD were more than two and half times as likely as controls to develop general illicit substance abuse/dependence. The overall homogeneity statistic indicated that the effect size of the six studies included in the analysis were not heterogeneous ($Q = 5.64, p = .34$).

3.6. Publication bias

We conducted the Egger's publication bias test and all tests were non-significant. The Begg's funnel plots also suggested no evidence of publication bias. We also used Orwin's (1983) formula for the fail-safe N to determine the number of studies that would be needed to reduce the findings to non-significance. Using an OR of 1 as the critical effect size value, for each outcome in which a significant group difference in

substance use outcomes was found, we determined the number of additional studies with an effect size showing equivalence between groups (i.e., OR = 1) that would have needed to be included in our meta-analysis to alter the effect of ADHD status. The following number of studies was indicated: 9 for lifetime nicotine use, 25 for nicotine dependence, 11 for alcohol abuse/dependence, 18 for lifetime marijuana use, 12 for marijuana abuse/dependence (excluding Gignac et al., 2005), 4 for cocaine abuse/dependence, 17 for general drug abuse/dependence. These numbers suggest that it is relatively unlikely that unpublished studies would change the significant contribution of ADHD to substance problems.

3.7. Moderators

To further explore the nature of the association between ADHD and future substance patterns in those effect sizes with heterogeneity (i.e., alcohol use, marijuana use), we examined potential moderators using the metareg command for simple regressions. We separately tested the following variables as potential moderators: sex, average age at follow-

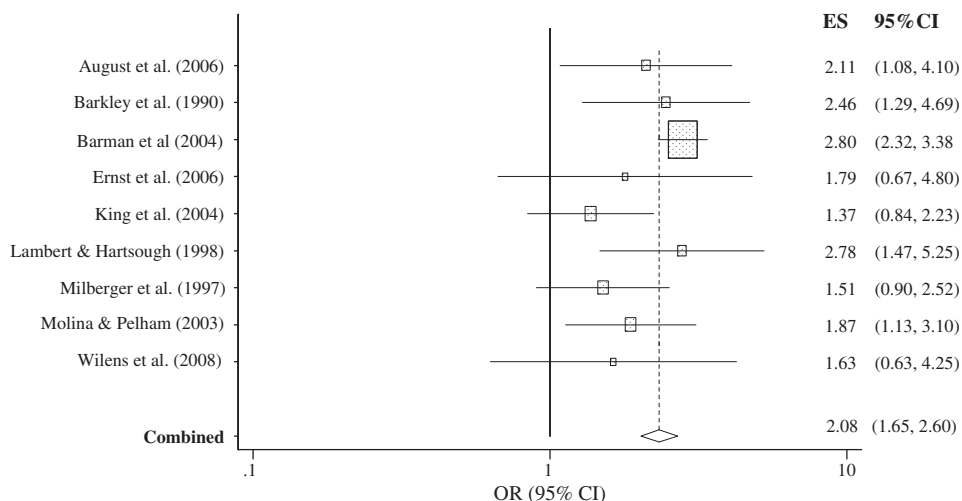


Fig. 1. Lifetime nicotine use predicted from childhood ADHD.

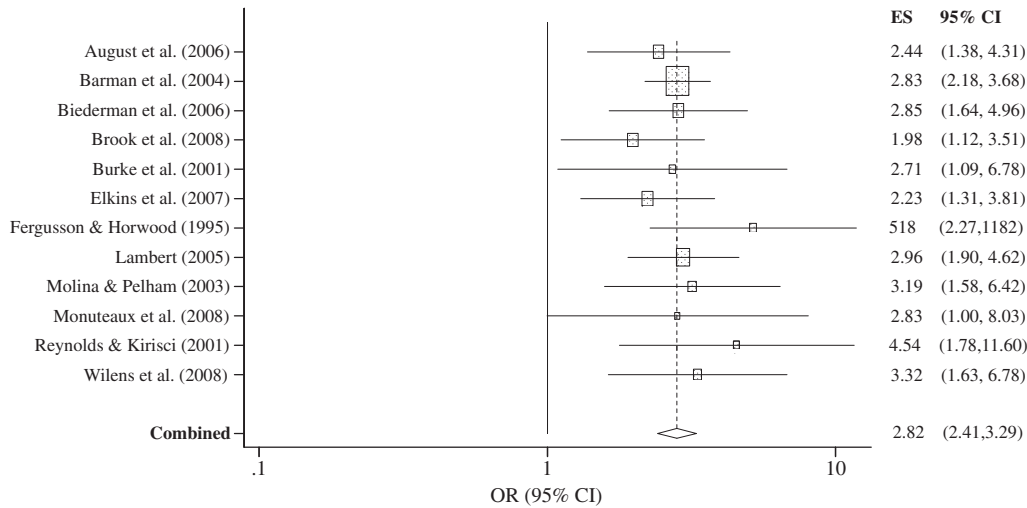


Fig. 2. Nicotine dependence predicted from childhood ADHD.

up, race (i.e., percent Caucasian), sample source for both the ADHD and non-ADHD groups, version of the DSM used to ascertain ADHD, and average length of time between initial assessment and follow-up. For substance outcomes with heterogeneous effect size estimates, none of the demographic or methodological variables significantly moderated the associations between childhood ADHD and adolescent/adult SUD.

3.8. Comorbid disruptive behavior disorders (DBD)

Given the substantial comorbidity between ADHD and disruptive behavior disorders (DBD), including ODD and CD (Barkley, 2006), as well as the robust relations between ODD/CD and substance outcomes (see Flory & Lynam, 2003 for a review), the conclusions suggested from this meta-analysis must be interpreted cautiously. We had initially intended to include comorbid ODD/CD as a moderator of ADHD predictions of substance outcomes in our meta-analysis. However, a careful review of the existing literature revealed surprisingly few studies that adequately addressed this comorbidity and that satisfied our inclusion criteria. For example, there was little consistency in the measurement of ODD/CD, particularly with respect to temporal factors (i.e., some studies measured CD during childhood, some concurrently during adolescence, and some used a combination). Therefore, this significant variability prevented our ability to formally examine ODD/CD comorbidity in the meta-analysis. Never-

theless, we strongly contend that DBD should be addressed, even if informally. Thus, we review existing findings here so that they can be interpreted concurrently with the results of the meta-analysis.

A thorough search of the literature identified 10 longitudinal studies of substance outcomes that measured ODD/CD and ADHD. For the present summary, we included only prospective longitudinal studies that utilized dichotomous measurement of all variables to enhance comparability with the studies in the meta-analysis. All 10 studies prospectively followed clinical or community samples of children with ADHD into adolescence or young adulthood where group differences (e.g., ADHD alone vs. ADHD + ODD/CD vs. controls) in substance outcomes were examined. Overall, our review suggests that comorbid ADHD + ODD/CD children may demonstrate significantly greater substance problems than children with ADHD only and controls (when included).

For instance, in a 10-year prospective study of youth with ADHD ($n=27$), ADHD + ODD/CD ($n=82$), and controls ($n=91$), children with ADHD + ODD/CD group had significantly higher rates of regular tobacco use and alcohol and marijuana SUD than either the ADHD only or control groups (August et al., 2006). Similarly, in a longitudinal study of 364 adolescents and young adults diagnosed with ADHD in childhood and 240 matched controls, Molina, Pelham, Gnagy, Thompson, and Marshal (2007) found that adolescents with concurrent ADHD and CD were more likely to have an alcohol use disorder

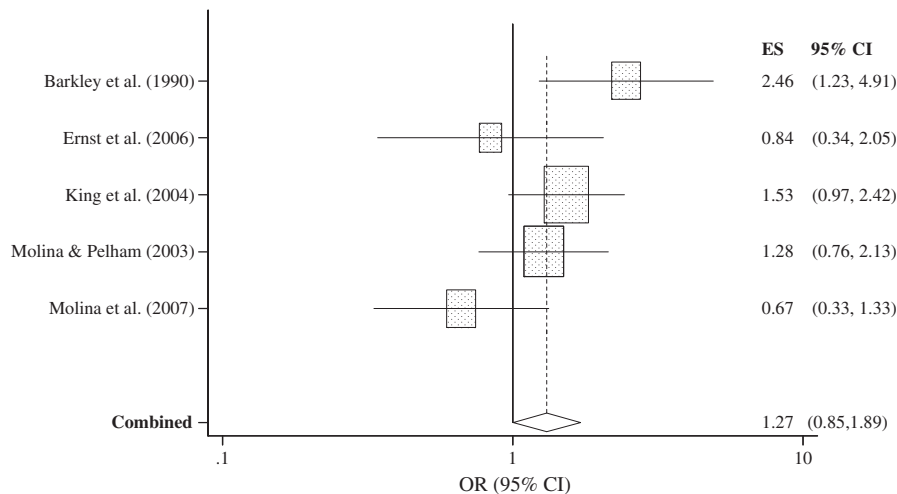


Fig. 3. Lifetime alcohol use predicted from childhood ADHD.

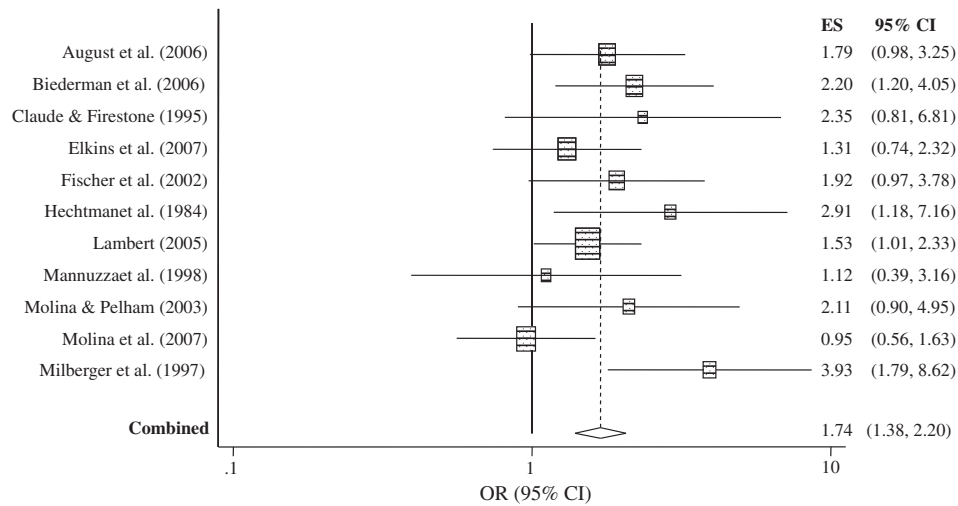


Fig. 4. Alcohol abuse or dependence predicted from childhood ADHD.

than controls. In this study, a direct comparison was not made between adolescents with ADHD + CD and those with ADHD alone; however, results indicated that those with ADHD + CD reported nearly five times the rate of alcohol use disorders than did youth with ADHD alone. In another prospective study of 177 clinic-referred boys, a significant bivariate relation between childhood ADHD and adolescent tobacco use was reduced to nonsignificance once childhood CD was included in the model (Burke, Loeber, & Lahey, 2001).

In an effort to further explore how the course of CD over time impacts the relation between ADHD and substance outcomes, Biederman and colleagues conducted two studies of 140 boys diagnosed with ADHD. At the 4-year follow-up, cigarette smoking, drug and alcohol dependence, and SUD in general were significantly elevated among participants with persisting symptoms of CD ($N=24$) vs. those with desisting symptoms of CD ($N=18$), and those without CD ($N=73$) (Biederman, Mick, Faraone, & Burbach, 2001). Similarly, at the 10-year follow-up of the same sample, the presence of CD along with ADHD was significantly associated with increased risk for psychoactive substance use disorders (defined as alcohol or drug abuse or dependence) compared to ADHD alone (Biederman et al., 2008). Loeber, Stouthamer-Loeber, and White

(1999) also examined the effects of persistent delinquency and ADHD on substance use among a large longitudinal sample of approximately 500 boys. Results revealed that ADHD did not predict substance use, once persistent delinquency and internalizing problems were controlled.

Two older studies which did not use current DSM ADHD diagnostic criteria also found results consistent with the six studies previously reviewed. August, Stewart, and Holmes (1983) followed 22 purely hyperactive (later classified as meeting DSM-III ADD criteria) and 30 hyperactive/unsocialized-aggressive boys for 4 years, examining alcohol and/or drug abuse (broadly measured) at follow-up. Results revealed that no purely hyperactive boys endorsed substance abuse, whereas a statistically significant 30% of the hyperactive/unsocialized-aggressive boys did endorse substance abuse at follow-up. Similarly, in an 8-year follow-up of 158 hyperactive children (later characterized as likely to meet DSM-III-R ADHD criteria) and 81 controls, Barkley and colleagues found that purely hyperactive children had no greater use of cigarettes and marijuana than controls whereas a comorbid hyperactive/CD group had 2–5 times the use of these substances compared to purely hyperactive or control youth (Barkley, Fischer, Edelbrock, & Smallish, 1990).

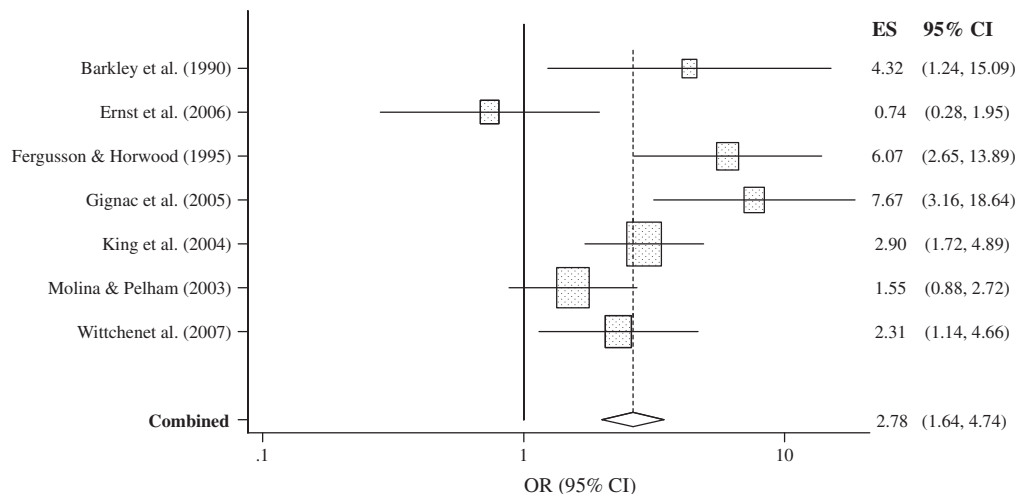


Fig. 5. Lifetime marijuana use predicted from childhood ADHD.

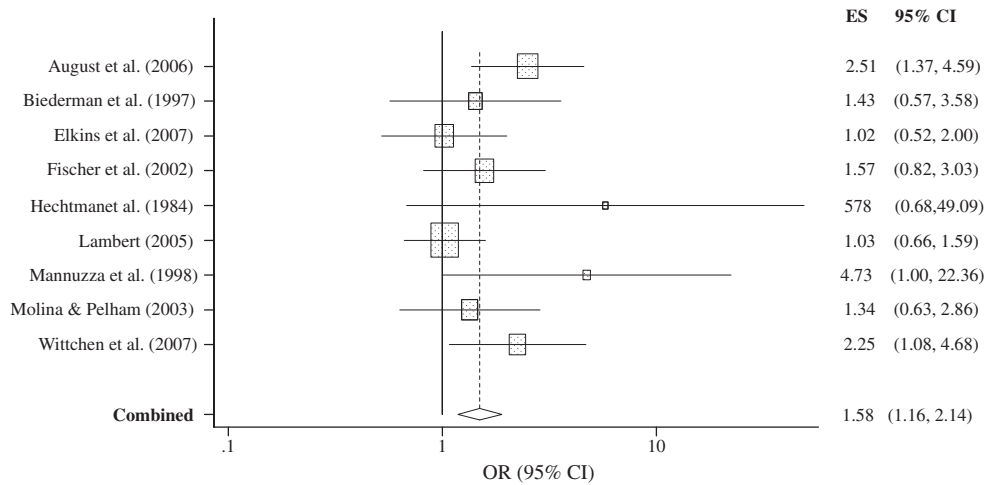


Fig. 6. Marijuana abuse or dependence predicted from childhood ADHD (excluding Gignac et al. (2005)).

Interestingly, two studies found that ADHD was independently associated with substance outcomes. In a 28-year prospective study of 492 children with ADHD and age-matched controls, Lambert (2005) found that ADHD increased the odds of tobacco, cocaine, and amphetamine dependence whereas child conduct problems did not increase these odds after other variables were controlled. Similarly, among a very large sample of twins followed from ages 11 to 18, Elkins, McGue, and Iacono (2007) found that, at the age 14 follow-up, ADHD significantly predicted tobacco and illicit drug use initiation even when childhood CD was taken into account. However, at the age 18 follow-up, ADHD did not predict any substance outcomes independent of CD. One final study which was identified in our literature search (Ernst et al., 2006) only included one participant with ADHD + CD. Thus, their results are not generalizable.

4. Discussion

Childhood ADHD is a reliable predictor of negative outcomes across academic, social, neuropsychological, and affective domains. Hence, multifinality, where multiple negative outcomes share a

common developmental origin, is a defining feature of ADHD (Cicchetti, 2006). However, far less is known about the prospective contribution of childhood ADHD to subsequent substance use and related disorders (abuse/dependence) than these other domains. To quantitatively characterize the association of ADHD on SUD and to strengthen a potential causal inference by establishing temporal ordering, we focused on prospective longitudinal studies (Kraemer et al., 2001). Our meta-analysis provides persuasive evidence of three key findings: (a) childhood ADHD conferred a significant increase in the odds of ever having used nicotine or illicit drugs, but not for alcohol; (b) childhood ADHD prospectively predicted the likelihood of developing adolescent/adult nicotine, alcohol, marijuana, and cocaine use disorders (i.e., abuse or dependence), as well as unspecified drug abuse/dependence; and (c) empirical tests of potential moderators for outcomes with heterogeneity in effect size estimates, consisting of demographic or methodological features that varied across studies, were not significant. That is, the reported effect sizes for ADHD and substance problems did not differ significantly by average age at follow-up, gender, race, sample source (clinic-referred vs. school/population-based), or DSM version used to determine ADHD. In

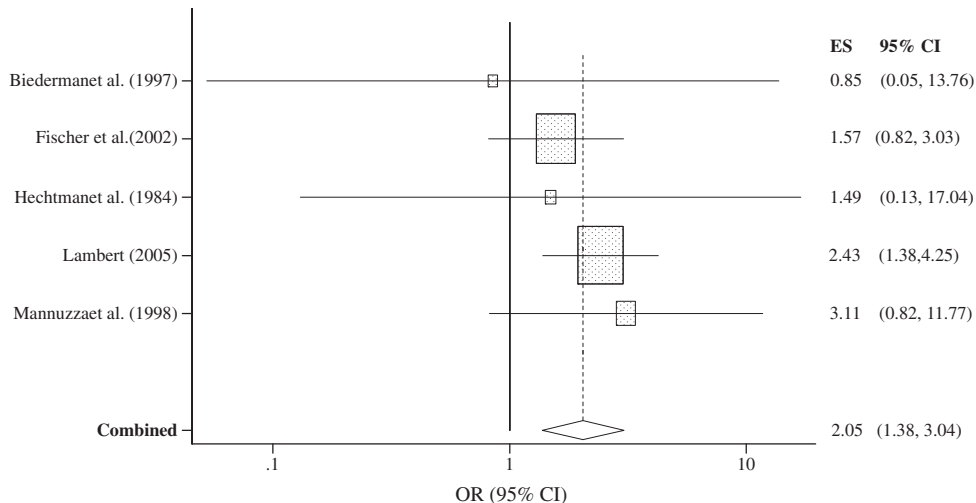


Fig. 7. Cocaine abuse or dependence predicted from childhood ADHD.

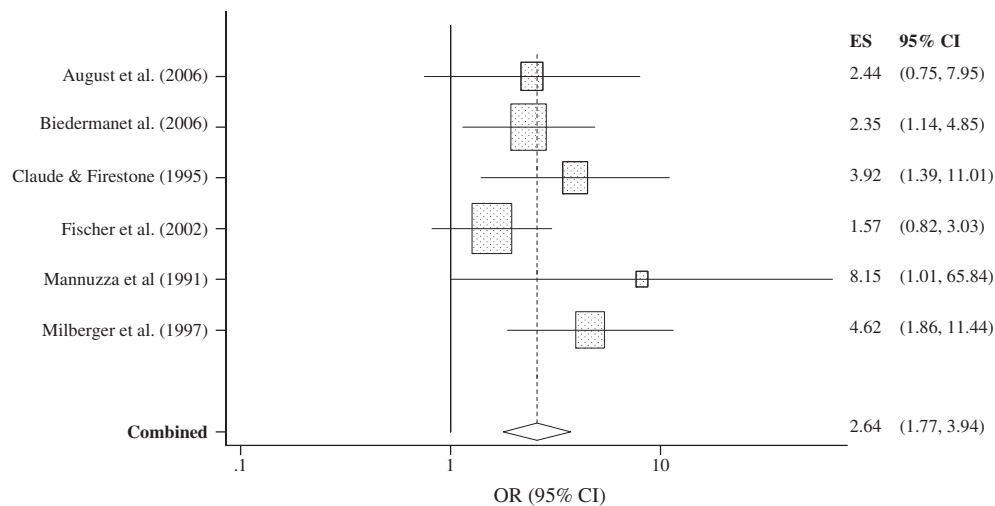


Fig. 8. Non-specific substance abuse or dependence predicted from childhood ADHD.

addition to the statistical significance of the association between ADHD and substance problems, we emphasize the size of the effects: children with ADHD were at least 1.5 times more likely to develop SUD across diverse forms of substances, including nearly 3 times higher for nicotine dependence. Considered together, our results suggest that early ADHD strongly predicts future substance abuse/dependence in adolescence/adulthood and that this association is largely impervious to demographic and methodological factors that varied across each study.

Overall, findings from previous studies of ADHD and comorbid ODD/CD predicting substance use outcomes are somewhat consistent, and they suggest that the relation between ADHD and substance outcomes in the literature (and potentially in our meta-analysis) may be partially or fully accounted for by the comorbidity between ADHD and ODD/CD, which is robustly related to substance outcomes. However, it is crucial to note that this characterization is based on only ten published studies and a literature with highly variable methods, including sample characteristics. For example, the study of Burke et al. (2001) was based exclusively on clinic-referred boys whereas the Loeber et al. (1999) study was based on a high-risk epidemiological sample. In fact, we were surprised at how infrequent comorbid ODD/CD was accounted for in the literature (either statistically controlled or explicit interactive effects between ADHD and ODD/CD). Thus, we echo the prescient review of Lilenfeld and Waldman (1990) who observed that prospective studies of ADHD and antisocial behavior (ASB) outcomes were likely contaminated by high rates of ODD/CD. That is, the association between ADHD and substance problems cannot be adequately discerned until its frequent comorbidity with ODD/CD is cogently addressed. Additionally, researchers must adopt greater consistency in how ODD/CD is measured and conceptualized. For instance, studies varied in their ascertainment of ODD/CD, ranging from adult retrospective recall of childhood CD, to concurrent assessment of adolescent CD, to measures of childhood ADHD and CD gathered concurrently in a prospective study, to some combination of these strategies. This variability may influence how or whether the relation between ADHD and substance outcomes is accounted for by comorbid ODD/CD. Moreover, equifinality suggests that there are multiple pathways to SUD that may involve ADHD and ODD/CD to varying degrees (Cicchetti, 2006).

4.1. Limitations and guidelines for future research

Although dimensional perspectives on psychopathology, including ADHD and SUD, have considerable empirical support (Barkley, 2003;

Helzer et al., 2006; Neuman et al., 1999), our meta-analysis was limited to dichotomous designations of ADHD and substance use and abuse/dependence disorders. Thus, *within* each diagnostic group, there is likely to be significant variability. For example, in two separate studies, children with ADHD varied dramatically with respect to the precise combination of functional impairments demonstrated in adolescence across affective, social, and behavioral domains, although ADHD probands were reliably more impaired than youth without ADHD (Lee et al., 2008; Owens et al., 2009). Similarly, the family context of ADHD is likely to contribute to the developmental course of ADHD (i.e., persistent vs. less severe) based on factors such as parenting and parent psychopathology (Chronis et al., 2007). An important question not addressed by this meta-analysis is if ADHD is associated with the *timing* of substance use disorders (e.g., earlier onset). Other studies (Odgers et al., 2008) suggest that age of onset of substance use is inversely related to negative outcomes and that this association is not exclusively explained by more conduct problems in early-onset substance users. If ADHD is related to an earlier onset of substance use/problems, this would suggest that preventive interventions must be implemented earlier in development for children with ADHD.

This meta-analysis also did not clarify potential differences among ADHD subtypes, an important consideration given that Combined-type ADHD is more strongly associated with externalizing disorders than other subtypes (Lahey, Applegate, McBurnett, & Biederman, 1994; Lahey et al., 2004). Moreover, even if all ADHD subtypes show significant associations with future SUD, one cannot assume that the mechanisms underlying those associations are identical (Hinshaw & Lee, 2003). For example, the association between Combined-type ADHD and SUD may be driven by comorbidity with ODD/CD whereas the association between Inattentive-type ADHD and SUD may be driven by the need to temporarily ameliorate neurocognitive deficits, including sluggish cognitive tempo (Milich, Balentine, & Lynam, 2001). Similarly, because of our dichotomous approach to ADHD, we were unable to examine the differential contribution of inattention-disorganization vs. hyperactivity-impulsivity symptoms to SUD. Previous evidence suggests that inattention and hyperactivity may be differentially related to substance outcomes, including some studies implicating a stronger contribution from inattention (Molina & Pelham, 2003) and others from hyperactivity (Lee & Hinshaw, 2006). Finally, the intervention selection bias (Larzelere et al., 2004) threatens the internal validity of uncontrolled studies because intervention status typically correlates positively with psychopathology and its severity. Although our meta-analysis excluded controlled

intervention studies, the precise contribution of treatment status to variability in substance outcomes was not definitively addressed.

Our preceding review of the potential importance of comorbid ODD/CD in studies of ADHD and substance outcomes necessitates a careful discussion of comorbidity more broadly, including ADHD and its frequent overlap with mood and anxiety disorders (Angold, Costello, & Erkanli, 1999). Unfortunately, our meta-analysis was unable to accommodate moderator analyses for disorders commonly comorbid with ADHD, including ODD/CD, depression, and anxiety. Although there may be differential patterns of prediction of SUD based on ADHD and its comorbidity (e.g., ADHD + ODD/CD), these groups may also represent a latent continuum characterized by heterotypic continuity rather than discrete disorders with separate etiologies (Patterson, DeGarmo, & Knutson, 2000; Shaw & Winslow, 1997). In fact, common influences across these phenotypes (e.g., disruptive parenting practices, deviant peer affiliation) may work synergistically with neurodevelopmental influences that are particularly salient in adolescence, including striatal dopamine and its influence on reward sensitivity and risk-taking (Galvan, 2010). Finally, some dimensions of anxiety may actually protect individuals with ADHD from risk-taking, externalizing behavior, or SUD (Levy, 2004). Thus, future research must consider comorbidity and the potential for interactive effects with ADHD, particularly across time.

Our meta-analysis provides further evidence that childhood ADHD is prospectively associated with a distressing array of negative outcomes, adding to previous studies that implicated ADHD with elevated rates of comorbid mood, anxiety, and externalizing problems (Biederman et al., 2010; Hinshaw, Owens, Sami, & Fargeon, 2006). In addition to conducting prospective longitudinal studies, future research must obtain greater traction on identifying the complex and potentially diverse mechanisms and pathways that lead from early ADHD to later SUD. There is evidence that academic problems and peer difficulties mediate the association between early behavior problems, including ADHD, and subsequent depression (i.e., dual failure model; Herman, Lambert, Jalongo, & Ostrander, 2007; Burke, Loeber, Lahey, & Rathouz, 2005; Capaldi & Stoolmiller, 1999). Previously identified mediators of ADHD and SUD also include deviant peer affiliation, coping, and parental support (Molina, Marshal, Pelham, & Wirth, 2005; Marshal, Molina, & Pelham, 2003). We propose that neuropsychological correlates of ADHD, including executive function (EF) deficits (e.g., response inhibition, planning, cognitive flexibility), should be tested as mediators given that EF is strongly associated with ADHD and independently predicts externalizing behavior and substance problems (Nigg et al., 2006). Given that mediators are targets for intervention, they offer the possibility to interrupt the cascade of negative sequelae associated with a predictor of negative outcomes. Thus, mediational analyses of ADHD–substance linkages must be prioritized in future studies. We also advocate that careful attention be paid to design features of existing studies and their potential influence on results. Wide age ranges in prospective studies of children with ADHD require extended follow-up to ensure that participants have equally entered periods of adolescent risk when substance experimentation often emerges (Moffitt, 1993).

Although meta-analyses support the efficacy of MPH in the treatment of ADHD (Faraone, Spencer, Aleardi, Pagano, & Biederman, 2004; Schachter, Pham, King, Langford, & Moher, 2001), there are unresolved questions about the development of future substance problems in children treated with stimulant medication (Kollins, 2008; Volkow, 2008). For example, Wilens, Faraone, Biederman, and Gunawardene (2003) reported that stimulant medication substantially reduced the risk for future substance problems, but two recent studies failed to replicate the protective effects of MPH (Biederman et al., 2008; Mannuzza et al., 2008). In one study, exposure to stimulant medication was positively associated with future substance use (Lambert & Hartsough, 1998). Given that MPH and amphetamines have similar neural reward properties and that repeated exposure to

stimulants alters the sensitivity of dopamine receptors in non-human animals, concerns have been raised about the relative safety of MPH and its potential to increase neural sensitivity to the reinforcing properties of stimulants (and to substances more broadly) (Vitiello, 2001; Kollins, 2003). Despite neurodevelopmental evidence that the timing of exposure to stimulants in non-human animals adversely affects outcomes (i.e., earlier exposure was associated with worse outcomes), a recent study found that children who received treatment with stimulants early in development (<8 years old) were less likely to develop substance problems than those treated with stimulants later in life (8–12 years). Specifically, children in the latter group were more likely to develop non-alcohol substance problems, and the association between age of stimulant treatment and substance problems was mediated by antisocial personality disorder (Mannuzza et al., 2008). Collectively, these studies underscore that treatment of ADHD with stimulant medication and its prospective contribution to substance use problems must be more precisely characterized in future studies.

Although the cost-effectiveness of interventions designed to reduce substance problems primarily through the prevention of mental disorders may be prohibitive, there is considerable interest in the potential contribution of childhood ADHD to the development of future SUD (Armstrong & Costello, 2002; Flory & Lynam, 2003; Molina et al., 2007; Molina & Pelham, 2003). If ADHD is causally related to SUD, then tailored prevention programs could be delivered to youth with ADHD prior to the developmental periods of greatest risk for substance initiation and progression to problem use. For example, parent- and family-based interventions for ADHD youth should emphasize the potential importance of parental monitoring (i.e., knowing the child's peers, recreational activities, and whereabouts after school), given its centrality to the onset of adolescent substance use and subsequent prevention of deviant peer affiliation (Steinberg, Fletcher, & Darling, 1994). In addition, interventions that reduce ADHD may also effectively reduce the risk of SUD and/or make substance problems more responsive to interventions. This is a crucial consideration given that psychopathology (e.g., ADHD, depression) and comorbid SUD are particularly resistant to intervention (Goldstein et al., 2009; Wilens, 2003) and that patients often delay treatment many years after the onset of the disorder (Kessler et al., 2001). We also emphasize that SUD must be thoughtfully assessed among adolescents and adults with a history of early ADHD. In particular, clinical ascertainment must differentiate experimentation from problematic substance use (e.g., functional impairment), given that children with ADHD were no more likely to have used alcohol than non-ADHD controls in our analysis. In other words, oversimplified designations of substance use are likely to betray important differences in underlying risk factors. For example, clinicians should separately consider positive vs. negative reinforcement processes underlying substance problems given their differential contribution to risk-taking behavior in adolescents, particularly as a function of individual differences in distress tolerance (MacPherson et al., 2010).

In sum, childhood ADHD is associated with a substantially higher risk of a lifetime history of nicotine and illicit substance use, in addition to nicotine dependence, alcohol, marijuana, cocaine, and illicit drug abuse/dependence. Although the mechanisms governing these associations are not yet fully understood, the findings from this meta-analysis underscore the clinical and public health significance of ADHD and its persistent effects into adolescence and adulthood (i.e., multifinality). To more rigorously evaluate a potential causal role of ADHD in the development of SUD, ongoing intervention studies of ADHD must concurrently assess substance problems and whether they respond favorably to standard ADHD intervention methods (e.g., methylphenidate, behavior management). Furthermore, more intensive neural (e.g., striatal, anterior cingulate cortex) and genetic (e.g., dopamine neurotransmission) assays of potential common etiological influences on ADHD and SUD should refine our understanding of their

comorbidity and may signal logical targets for pharmacological interventions.

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