Title

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Authors

Howard, Andrea L
Kennedy, Traci M
Mitchell, John T
et al.

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Early substance use in the pathway from childhood ADHD to young adult substance use: Evidence of statistical mediation and substance specificity

Andrea L. Howard,
Carleton University

Traci M. Kennedy,
University of Pittsburgh

John T. Mitchell,
Duke University

Margaret H. Sibley,
University of Washington and Seattle Children's Hospital

Stephen P. Hinshaw,
University of California

Berkeley L. Eugene,
Arnold Ohio State University

Arunima Roy,
University of Ottawa

Annamarie Stehli,
University of California Irvine

James M. Swanson,
University of California Irvine

Brooke S. G. Molina
University of Pittsburgh

Abstract

Correspondence concerning this article should be addressed to Andrea L. Howard, Department of Psychology, Carleton University, Ottawa, ON, Canada K1S 5B6. andrea.howard@carleton.ca.

Collaborators formerly at NIMH: Benedetto Vitiello, (University of Turin); Joanne B. Severe; Peter S. Jensen (currently University of Arkansas); L. Eugene Arnold (currently Ohio State University); Kimberly Hoagwood, (currently Columbia); early-phase NIMH contributors: John Richters; Donald Vereen. Site PIs/Co-Is: University of California, Berkeley/San Francisco: Stephen P. Hinshaw (Berkeley), Glen R. Elliott (San Francisco); Duke University: Karen C. Wells; Jeffery N. Epstein (currently Cincinnati Children's Hospital); Desiree W. Murray (currently UNC Chapel Hill); early-phase Duke contributors: C. Keith Conners; John March; University of California, Irvine: James Swanson, Timothy Wigal; UCLA contributor: Dennis P. Cantwell; NYU School of Medicine: Howard B. Abikoff; Montreal Children's Hospital/McGill University: Lily Hechtman; NY State Psychiatric Institute/ Columbia University/Mount Sinai Medical Center: Laurence L. Greenhill; Jeffrey H. Newcorn; University of Pittsburgh: Brooke Molina; Betsy Hoza (University of Vermont); William E. Pelham (currently Florida International University). Follow-up statistical collaborators: Robert D. Gibbons (University of Illinois, Chicago); Sue Marcus (Mt. Sinai College of Medicine); Kwan Hur (University of Illinois, Chicago). Original study statistical/design consultant: Helena C. Kraemer (Stanford University). Collaborators from US Department of Education, Thomas Hanley and Karen Stern.

This study tested whether early and developmentally atypical substance use mediates risk for adult substance use among children with ADHD, and whether that risk is substance-specific. Participants were children with ADHD previously enrolled in a randomized controlled trial (RCT), and a demographically similar nonADHD group, assessed at 2 through 16 years after the original RCT baseline. Self-reports of heavy drinking, marijuana use, daily smoking, and other illicit drug use were collected at follow-ups to establish atypically early and frequent use. Models estimated statistically mediated effects of childhood ADHD on adult substance use via early substance involvement, with planned comparisons to evaluate substance specificity. Results supported the mediation hypothesis, showing that childhood ADHD was associated with more frequent adult substance use via early substance use for marijuana, cigarettes, illicit drugs, and to a lesser extent, alcohol. Mediation was not escalated by comorbid childhood conduct disorder or oppositional defiant disorder except for early use of non-marijuana illicit drugs. Substance-specificity in the mediational pathway was largely absent except for cigarette use, where ADHD-related early smoking most strongly predicted adult daily smoking. Findings from this study provide new evidence that atypically-early substance use associated with childhood ADHD signals important cross-drug vulnerability by early adulthood, but cigarette use at a young age is especially associated with increased risk for habitual (daily) smoking specifically. Efforts to prevent, delay, or reduce substance experimentation should occur early and focus on factors relevant to multiple drugs of abuse in this at-risk population.

Keywords

ADHD; adolescence; early substance use; mediation; smoking

Childhood attention-deficit/hyperactivity disorder (ADHD) has been extensively studied as a potential precursor to substance use and disorder in adolescence and young adulthood. Meta-analyses show that childhood ADHD predicts substance use and disorder (Charach, Yeung, Climans, & Lillie, 2011; Groenman, Janssen, & Oosterlaan, 2017; Lee, Humphreys, Flory, Liu, & Glass, 2011), but research is still needed to explain the development of substance use psychopathology in this population. Features of childhood ADHD such as behavioral disinhibition and academic impairment are known to increase risk for early substance use (Molina & Pelham, 2003; Molina et al., 2012). Recent findings from the Multimodal Treatment Study of ADHD (MTA; Molina et al., 2018) showed that adolescents with *and* without ADHD who were early substance users escalated more rapidly to heavy substance use in adulthood. What remains unclear is whether evidence supports a role for early substance use in the pathway from childhood ADHD to adult substance use. Direct tests of statistical mediation with prospective longitudinal data can help to clarify whether early substance use likely plays a contributing role in the pathway from childhood ADHD (and its associated impairments and vulnerabilities) to adult substance use (Rutter, Kim-Cohen, & Maughan, 2006). No studies have directly tested this pathway, crucial to establishing a need for future investigations of underlying causes of this pathway and for informing possible treatment-related efforts to prevent specific types of early substance use. Our primary aims were to test whether early substance use statistically mediates relations between childhood ADHD and frequent substance use in adulthood, and to examine whether such mediation is substance-specific.

Childhood ADHD and Substance Use Initiation

Substance use and disorder are developmental phenomena that steadily increase with age, beginning with substance experimentation in adolescence (Masten, Faden, Zucker, & Spear, 2008; Palmer et al., 2009). Conduct problems, social and academic impairments, negative affect, and neurocognitive deficits have all been implicated in ADHD-related substance pathways (Molina & Pelham, 2014). Heightened reward sensitivity in particular is thought to increase the likelihood that experimentation in adolescence will translate to regular, heavy use later on (Kollins & Adcock, 2014). Indeed, adolescents with ADHD are more likely than non-diagnosed peers to escalate from experimentation to regular substance use (Fuemmeler, Kollins, & McClernon, 2007; Sibley et al., 2014) and to escalate more rapidly (Molina et al., 2018). We previously found that 58% of children with ADHD (vs. 40% of non-ADHD) initiated substance use early (e.g., drinking alcohol at age 14) *and* engaged in repeated or heavy substance use early (e.g., binge drinking at age 15; Molina et al., 2018). Being an *early user* by this inclusive definition predicted faster increases in alcohol, marijuana, cigarettes, and other illicit drugs, and large differences in rates of use by age 25 for adolescents with and without childhood ADHD.

Evidence of a statistically mediating role of early substance use would suggest the possibility that ADHD-specific treatments to prevent or delay early substance involvement may play a critical role in decreasing long-term risk for heavy substance use. The present study is the first to our knowledge to directly test this pathway.

Substance Specificity

ADHD-related risk for adult substance use appears variable across substance classes (Charach et al., 2011). Cigarette smoking, for example, stands out as the most robust substance outcome associated with childhood ADHD (Kennedy, McKone, & Molina, in press; Lee et al., 2011). Like alcohol, cigarettes are legal and widely used by people at relatively low risk for behavioral problems, but they also mimic central nervous system stimulant properties of typical pharmacologic treatments for ADHD (Levin, McClernon, & Rezvani, 2005). Marijuana has historically been illegal and less widely available, but its legal status is changing and it currently ranks after alcohol as the second most commonly-used substance in adolescence (Johnston et al., 2018; SAMHSA, 2017). Moreover, it is increasingly perceived (not proven) as therapeutic for ADHD (Mitchell et al., 2016; 2018). Illicit drug use—including prescription misuse—is rare compared to other substances, although opportunities to experiment with illicit drugs predominantly through deviant peer affiliation may be particularly strong in adolescents with CD/ODD comorbidity (Marshal & Molina, 2006).

The meaningful differences across substance classes in ADHD-related risk for substance use and disorder (Sibley et al., 2014) provide good reasons to suspect that children with ADHD are at greater risk for use and abuse of some substances over others. At the same time, ADHD carries broad neurobiological risk for increased reward responsivity and deficits in inhibitory control (Sonuga-Barke, Sergeant, Nigg, & Willcutt, 2008) that could signal undifferentiated vulnerability to a wide range of problem behaviors, including substance use.

In the present study, we comprehensively examine whether a childhood ADHD diagnosis (with and without comorbid CD/ODD), assessed before substance use onset, leads to more frequent use of alcohol, marijuana, cigarettes, and other illicit drugs in adulthood by increasing risk for early-onset, developmentally atypical substance use in adolescence. To evaluate substance specificity, unexamined in the literature to date, we test whether early involvement with each substance mediates ADHD-related risk for more frequent continued use of the *same* substance versus frequent use of *other* substances in adulthood. We also test mediational chains through early involvement with each substance (versus early involvement with another substance) to its more frequent continued use in adulthood. Finally, we test whether same-substance mediated effects are stronger than other-substance mediated effects. Findings from these tests will help to clarify whether mediated ADHD-related risk for adult substance use differs across substance classes and reveal substance preferences that emerge at a young age and may ultimately be targets for additional research and treatment.

Contribution of childhood conduct problems to mediated risk

We also consider our proposed mediated pathways against a background of behavioral deviance. Conduct disorder (CD) or oppositional defiant disorder (ODD) are frequently comorbid with ADHD and frequently contribute to ADHD-related risk of adolescent substance use outcomes (Brook, Brook, Zhang, & Koppel, 2010; Bussing, Mason, Bell, Porter, & Garvan, 2010; Molina & Pelham, 2003; Sibley et al., 2014). Evidence is also available that ADHD is independently associated with substance risk in adolescence (Elkins, Iacono, & McGue, 2007; Groenman et al., 2013; Molina & Pelham, 2003) and adulthood (Flory, Milich, Lynam, Leukefeld, & Clayton, 2003; Wilens, Martleton, et al., 2011). Low academic achievement, impulsive decision-making, deviant peer relationships, and shared genetic liability are all possible mechanisms by which ADHD may specifically increase risk for early substance use (e.g., Serra-Pinheiro et al., 2013), leading in turn to heavier use in adulthood. CD/ODD comorbidity may thus represent an escalated form of ADHD, given their shared etiology (Patterson, DeGarmo, & Knutson, 2000), and the likelihood of early substance use following childhood ADHD may be especially high as a result of behavioral deviance.

Given the prominence of CD/ODD comorbidity with childhood ADHD, it is often standard practice to analytically adjust for CD/ODD symptoms or diagnosis in predicting substance use outcomes (Molina & Pelham, 2014). Indeed, there is ample evidence tying ADHD and conduct problems to substance use disorders later in life (see Groenman et al., 2017). What remains unclear is the extent to which the mediated risk for substance use in adulthood conferred by early substance use is *escalated* for children with comorbid CD/ODD beyond those with ADHD who do not exhibit similar disruptive behavior problems. Longitudinal studies that leverage a cumulative record of substance use with frequent, repeated assessments from early adolescence through early adulthood offer an important advantage over large-scale epidemiologic studies with smaller samples of childhood-diagnosed cases of ADHD with and without CD/ODD. In the present study, we consider this potential for escalated risk relative to children with ADHD alone.

Method

Sample

The MTA began as a 14-month randomized clinical trial of *n*=579 children aged 7–9.9 years diagnosed with DSM-IV ADHD Combined type and transitioned to an observational follow-up study 2 years after baseline, at which time 258 age- and sex-matched comparison children without ADHD were recruited as a local normative comparison group (LNCG). At each of six sites in the U.S. and Canada, between 95 and 98 children were randomly assigned to multicomponent behavioral treatment, systematic medication management, their combination, or referral to usual community care. Study eligibility was broad, and children with comorbid diagnoses participated. The complete MTA recruitment strategy, detailed inclusion/exclusion criteria, diagnostic procedures, treatment protocol, and sample demographics appear elsewhere (Arnold et al., 1997; MTA Cooperative Group, 1999).

Follow-up assessments of MTA probands (the ADHD group) and assessments of the LNCG took place at 2, 3, 6, 8, 10, 12, 14, and 16 years post-baseline, with *n*=547 of the ADHD group reassessed at least once. Retention at 16 years (M_{age} 25; range=21.7–28.6) was 75.1% (ADHD) and 84.9% (LNCG), though 81.3% of the ADHD group and 93% of the LNCG provided substance use data at one or more of the 12-, 14-, and 16-year assessments ("adulthood" in the MTA). Sample retention in the MTA is described in detail elsewhere (Swanson et al., 2017).

Measures

Substance use.—We used the self-report Substance Use Questionnaire (SUQ; Molina & Pelham, 2003), adapted for the MTA (Molina et al., 2013). Frequency of alcohol, marijuana, cigarette, and other illicit drug use was assessed in all follow-up years. As in our prior report (Molina et al., 2018), past-year *heavy drinking* was the higher score of two items assessing frequency of binge drinking and of drunkenness ("How many times did you drink five or more drinks when you were drinking?" "How many times have you gotten drunk or 'very, very high' on alcohol?"), and past-year *marijuana use* was one frequency of use question. Responses were recoded to a four-point scale: 0 (*none*), 1 (*less than once per month*), 2 (*at least monthly but less than weekly*), and 3 (*once per week or more*). Past-year *daily smoking* was coded as 0 (*no*) and 1 (*yes*) if participants reported smoking at least one cigarette per day or endorsed being a current daily smoker. Past-year *other illicit drug use* was coded by taking the maximum frequency of use across multiple drugs, including cocaine, heroin, inhalants, hallucinogens, and misused prescription drugs (stimulants, sedatives, and opioids), coded to a three-point scale: 0 (*none*), 1 (*less than once per month*), and 2 (*once per month or more often*). Base rates of use of all individual illicit substances were below 5% in adolescence (Molina et al., 2013), and below 3% in early adulthood (Molina et al., 2018), with no evidence of substance-specific ADHD-LNCG differences. In the present study, combining drug classes into a single variable offered higher-powered tests of illicit drug effects and low risk of obscuring effects specific to individual substances.

Early substance use.—In our prior report (Molina et al., 2018), we identified participants as *early substance users* in adolescence in relation to published norms

benchmarking developmentally atypical ages of onset and heavy use of each substance (e.g., Chassin, Pitts, & Prost, 2002; Chen, Storr, & Anthony, 2009; Nelson, van Ryzin, & Dishion, 2015; Palmer et al., 2009). Prospective reports and retrospective recall from the 2 through 16 year assessments informed our coding scheme. Participants were coded as early substance users if they initiated use of one or more substances early for their age (Criterion A) *and* used one or more substances heavily for their age (Criterion B). Criterion A for *alcohol* was consumption of a drink (i.e., 'not just a sip or taste of someone else's drink') before age 15; for *marijuana* was trying marijuana at least once before age 16; for *cigarette smoking* was smoking a cigarette before age 15. Criterion B for *alcohol* was any heavy drinking before age 16; for *marijuana* was using marijuana more than once before age 17; for *cigarette smoking* was smoking cigarettes 'more than a few times' before age 17. Criteria A and B were both deemed satisfied for *other illicit drugs* if participants endorsed any use before age 17.

Criteria could be met across different substances (317/547 ADHD and 108/258 LNCG met criteria for early use; Molina et al., 2018). For the present report, we further coded participants according to their early involvement with specific substances. Participants were classified as exhibiting *early alcohol use* if they met Criteria A and B *for alcohol*, regardless of their use of other substances. Participants were classified as exhibiting *early marijuana use*, *early cigarette use*, and *early illicit drug use* analogously.

Covariates.—Three baseline sociodemographic variables were primary covariates in our analyses, defined and used as in other reports (Mitchell et al., in press; Molina et al., 2018). *Sex* was coded as Male=0, Female=1. *Race/ethnicity* was coded using three weighted effects comparing each of Black, Hispanic, and Mixed/other racial/ethnic groups to the sample mean. *Household (dis)advantage* was coded similarly. Children from two-parent households with at least one college-educated parent ("household advantage") and children from single-parent households with no college-educated parents ("household disadvantage") were each compared to the sample mean. Effects codes are particularly suited to categorical variable coding when one group does not stand out as a meaningful "reference" category (see Cohen, Cohen, West, & Aiken, 2003; pp. 320–321). In adulthood, analyses adjusted for participants' nominal ages as well as their relative ages at each assessment point, defined as age relative to the mean age for that wave (e.g., a person aged 22 at a wave with mean age 21 has a *nominal* age of 22 but a *relative* age of 1 year older than average).

Within the ADHD group, our analyses also tested differences between participants with and without a childhood diagnosis of CD or ODD. Comorbid diagnoses were taken from the baseline assessment at which presence of ADHD was confirmed for study enrollment. Of 547 cases with childhood ADHD, 15.0% (n=82) also had CD and 39.7% (n=217) had ODD at baseline. Only 6 LNCG met criteria for CD or ODD at their initial assessment—mean age 10—precluding further comparisons within this group. We tested differences between LNCG and ADHD groups, and between cases with childhood ADHD plus CD/ODD versus ADHD-only using planned contrast codes (Cohen et al., 2003; pp. 332–335).

Missing data.—Comparisons between cases with complete versus incomplete substance use data are presented in our prior report (Molina et al., 2018). Cases with incomplete

data were not significantly different from cases with complete data on 76% of baseline sociodemographic variables assessed. ADHD and LNCG cases with incomplete data were more often male, racial or ethnic minority, and socioeconomically disadvantaged (e.g., lower-income, less-educated parents). As in prior reports (Mitchell et al., in press; Molina et al., 2018), we included sex, race/ethnicity, and household advantage/disadvantage to support the *missing at random* assumption (Schafer & Graham, 2002). Participants who responded to the SUQ at least once from age 17 and up were included in our mediation analyses (n=492/547 ADHD; n=246/258 LNCG).

Analysis strategy

We used the product-of-coefficients approach to estimate mediated (indirect) effects of childhood ADHD on adult substance use via early substance involvement. Temporal precedence was largely preserved in our analysis, though some children retrospectively reported substance use ages of onset equal to or younger than their ages at MTA baseline (61/547 ADHD; 21/258 LNCG). Early substance use preceded all measures of young adult substance use. Analyses were performed in M*plus* (v.8.0) using maximum likelihood estimation (adaptive quadrature for categorical outcomes). We obtained probit regression estimates of effects of childhood ADHD (vs. LNCG) and childhood ADHD plus CD/ODD (vs. ADHD-only) on early substance use (the “a” path coefficients), adjusting for covariates. We then obtained probit regression estimates of effects of early substance use (the “b” path coefficients) on repeated measures of substances used in adulthood (ages 17 and up) from ordinal mixed-effects (multilevel) models with random intercepts, adjusting for childhood ADHD, ADHD plus CD/ODD, covariates, nominal age, and relative age. In the case of substance-specific mediation, effects of early use in one substance class also adjusted for effects of substance use in the other three classes. Mediated effects were computed by taking products of “a” and “b” coefficients. Estimates of all individual path coefficients are presented in Supplement Tables S1 and S2. We used the Monte Carlo method (MacKinnon, Lockwood, & Williams, 2004) to construct confidence intervals for all mediated effects (Preacher & Selig, 2012) and differences between mediated effects. Monte Carlo sampling distributions were constructed in SAS (v.9.4; see Supplement for sample syntax). Analyses were performed separately for each adult substance outcome, and we adjusted for Type I error inflation within each set of planned comparisons using the Benjamini-Hochberg method (Benjamini & Hochberg, 1995).

Results

Table 1 shows numbers and percents of cases in each of the ADHD-only, ADHD plus CD/ODD, and LNCG groups meeting criteria for early substance use across any combination of substances (“any substance”) and for each specific substance. In the two ADHD groups, early involvement with more than one substance was common, reported by 68.8% of the ADHD-only early users and by 66.1% of the ADHD+CD/ODD early users. In contrast, just over half of LNCG early users (51%) reported early involvement with multiple substances. For descriptive purposes, we include pairwise contrasts that show where differences between groups in rates of early and adult substance use were statistically significant.

Figure 1 shows results of our first set of analyses testing whether early substance use in general mediates childhood ADHD-related risk for frequent heavy drinking, marijuana use, daily smoking, and other illicit drug use in adulthood (8 planned comparisons). For all substances, a childhood ADHD diagnosis predicted increased risk of early substance use, which in turn predicted more frequent use of every substance after age 17. Each coefficient (e.g., a_1b_1) is the *probit* of the difference in adult substance use between groups (ADHD vs. LNCG; ADHD plus CD/ODD vs. ADHD-only) that is statistically mediated by early substance use. To capture effect size, we also express each difference in terms of *relative risk* (*RR*), referenced against the base rates of adult substance use given in Table 1 for each diagnostic group. For example, the risk of weekly or greater marijuana use in adulthood is 1.74 *times as large* for people with versus without childhood ADHD, given their higher likelihood of early substance use. For each adult substance, *in addition* to ADHD-related risk via early substance use, risk of more frequent use via early substance use is even larger for people with childhood ADHD *plus* CD/ODD compared to ADHD alone. For example, the risk of more frequent marijuana use in adulthood is an *additional* 1.40 times as large for children with comorbid CD/ODD versus ADHD alone.

Same-substance pathways to adult substance use.

Our second set of analyses tested whether early use of each specific substance mediated ADHD-related risk for frequent adult use of the *same* substance (8 planned comparisons). The grey-shaded diagonal elements of Table 2 show that childhood ADHD predicted more frequent use in adulthood of every substance via early use of the same substance (e.g., adult heavy drinking via early alcohol use), controlling for early use of all other substances. However, we observed additional risk for people with ADHD plus CD/ODD only for adult illicit drug use via early illicit drug use, over and above risk associated with ADHD alone. All other same-substance mediated paths involving CD/ODD comorbidity were not statistically significant.

Other-substance pathways to adult substance use.

Our third set of analyses tested whether early use of each specific substance mediated ADHD-related risk for more frequent adult use of *other* substances (e.g., adult heavy drinking via early cigarette use; 24 planned comparisons). The off-diagonal elements of Table 2 show that childhood ADHD did not predict more frequent use in adulthood of any substance via early use of any other-substance class, controlling for early use of each of the other substance classes in adolescence. For example, the risk of more frequent marijuana use in adulthood is just 1.14 times as large (and not statistically significant) for people with versus without childhood ADHD through early cigarette use, after accounting for effects of early alcohol, marijuana, and illicit drug use. We also observed no additional risk for people with ADHD plus CD/ODD over and above risk associated with ADHD alone.

Pathways through early involvement with same versus other substances.

Our fourth set of analyses tested *differences* between same- and other-substance pathways (24 planned comparisons). We tested whether ADHD-related risk for frequent adult use of each substance was *greater* via early involvement with the same-substance class versus early involvement with other-substance classes. These comparisons pit the grey-shaded

diagonal elements of Table 2 against other effects within the same *column*. For example, we tested whether the statistically mediated effect of ADHD-related early cigarette use on adult daily smoking (*RR*=3.04; same-substance) was significantly larger than the statistically mediated effect of ADHD-related early alcohol use on adult daily smoking (*RR*=1.11; other-substance). Of 24 comparisons tested, 3 were statistically significant after correction for multiple testing, and two pathways reflected strong continuity of early cigarette use to adult daily smoking. Specifically, early cigarette use mediated ADHD-related risk for daily smoking in adulthood more strongly than early use of alcohol (*Diff*[1] = −1.06, *SE*=.30, *RR*=.43, *p*=.0004) and illicit drugs (*Diff* = −.98, *SE*=.31, *RR*=.47, *p*=.0018). Risk ratios indicate that the ADHD-LNCG *differences* in adult daily smoking risk via early alcohol and via early illicit drugs were just 43% and 47% the size, respectively, of the (same-substance) ADHD-LNCG difference in adult daily smoking risk via early cigarette use. Early marijuana use also mediated ADHD-related risk for adult marijuana use more strongly than early alcohol use (*Diff* = −.438, *SE*=.15, *RR*=.68 *p*=.004). There were no statistically significant differences in adult substance use risk via same- versus other-substance early use pathways for children with ADHD plus CD/ODD compared to ADHD alone.

Pathways to adult use of same versus other substances.

Our fifth set of analyses also tested differences between same- and other-substance pathways (24 planned comparisons). In this case, we tested whether ADHD-related risk for adult substance use via early use in each substance class was *greater* for frequent adult use of the same substance versus adult use of other substances. These comparisons pit the grey-shaded diagonal elements of Table 2 against other effects within the same *row*. For example, we tested whether the statistically mediated effect of ADHD-related early cigarette use on adult daily smoking (*RR*=3.04; same-substance) was significantly larger than the statistically mediated effect of ADHD-related early cigarette use on adult heavy drinking (*RR*=1.00; other-substance).

Difference tests from this fifth set of analyses are summarized in Table 3, and Figure 2 highlights mediated effects through early cigarette involvement. The ADHD-LNCG difference in adult heavy drinking risk via early cigarette (other-substance) was just 37% the size (*RR*=.37) of the ADHD-LNCG difference in adult daily smoking risk via early cigarette (same-substance). ADHD-LNCG differences in risk were also less than half as large for adult marijuana use (*RR*=.45) and for adult illicit drug use (*RR*=.42) compared to ADHD-related risk via early cigarette involvement for adult daily smoking. The ADHD-LNCG difference in adult heavy drinking risk via early marijuana involvement was also slightly less (*RR*=.78) than the ADHD-LNCG difference in adult marijuana use risk via early marijuana involvement. There were no same- versus other-substance differences across adult substances via common mediators for children with ADHD plus CD/ODD compared to ADHD alone.

[1]Diff = Difference between the mediated effects of same- versus early-substance mediation within the same column of Table 2 (e.g., Diff −1.06 = 1.196 − .135). SE is the standard error of the difference.

Supplementary analysis

The mediated effects we report here reflect planned contrasts testing differences between the LNCG and ADHD groups, and between cases with childhood ADHD plus CD/ODD versus ADHD-only. As a supplementary analysis, we repeated all tests of mediation for the contrast of LNCG versus ADHD-only. Findings are summarized in Supplement Tables S3 and S4, and Supplement Figures S1 and S2. We found that nearly all significant mediated effects that we reported for the general ADHD versus LNCG contrasts were also present after restricting the contrast to ADHD-only versus LNCG. Two exceptions occurred in our second set of analyses, testing whether early use of each specific substance mediated ADHD-related risk for frequent adult use of the *same* substance. Table S3 shows that childhood ADHD without CD/ODD predicted more frequent marijuana use in adulthood via early marijuana use, and predicted daily smoking in adulthood via early cigarette use. Same-substance pathways from early alcohol use to adult heavy drinking and from early illicit drug use to adult illicit drug use were not statistically significant. These findings align with simple group differences in rates of early and adult substance use we report in Table 1. Crucially, we replicated our difference test findings (the fourth and fifth sets of analyses) that suggest strong substance-specific continuity from childhood ADHD through early cigarette use to adult daily smoking.

Discussion

Using prospective longitudinal data from childhood through mean age 25, we comprehensively tested whether early-onset, developmentally atypical substance use in adolescence statistically mediates the prospective link to frequent substance use in adulthood from childhood ADHD. We found this to be true when use was atypically early and heavy across any combination of one or more substances in adolescence. In models that tested mediating effects of early use of individual substances, controlling for early use in every other substance class, we found evidence for mediation via same-substance pathways (e.g., from ADHD to early marijuana use to adult marijuana use, controlling for early alcohol, cigarette, and illicit drug use). Our evidence was weaker for early alcohol use as a mediating path to adult heavy drinking, given the small risk ratio for this mediated effect and lack of replication in a supplementary analysis restricted to children with ADHD and no CD/ODD comorbidity. Table 1 similarly showed that the ADHD-only and LNCG groups were not significantly different in early alcohol use or adult heavy drinking.

Our comparisons that tested substance specificity (the fourth and fifth sets of analyses) clarified that early cigarette use to adult daily smoking was the only pathway that showed consistently *stronger* mediated risk over other substances. Mediated pathways from childhood ADHD through early cigarette use to other adult substances *and* pathways through other (non-cigarette) early substances to adult daily smoking were generally weaker than the same-substance smoking pathway.

With the possible exception of cigarette use, substance opportunity and availability may be the dominant force in early adolescents' experimentation with one substance over another. Indeed, two-thirds of childhood-ADHD early users and 43.9% of LNCG early users met our criteria for early use across multiple substance classes. Expectations or preference for

the pharmacologic effects of specific drugs are likely more typical of later adolescent and adult substance use, after experience with drugs and alcohol accumulates (Katz, Fromme, & D'Amico, 2000). Our findings suggest that childhood ADHD is associated with a general propensity toward early substance involvement that leads to continued, heavy substance use in adulthood, a prototypical example of heterotypic continuity in substance-related psychopathology across development (Sroufe & Rutter, 1984). Childhood ADHD may act as a causal precursor to early substance involvement, it may manifest prior to early substance involvement as a result of their shared etiology such as shared genetic liability (e.g., Quinn et al., 2016), or some combination of these processes. Both interpretations suggest that a childhood ADHD diagnosis also represents early identification of eventual risk for heavy substance use. Although subject to experimental testing, delaying substance experimentation in this population may help to steer these adolescents off a developmental course of heavy substance involvement. Interventions targeting substance use psychopathology may also be improved by considering antecedent or co-occurring risk arising from ADHD symptoms and their associated impairments.

ADHD-related risk for adult daily smoking is most potent via early cigarette involvement

We found that early cigarette involvement statistically mediated ADHD-related risk of adult daily smoking more strongly than to any other substance in adulthood, and more strongly than any other substance used atypically early in adolescence. This is consistent with our prior report showing that by mean age 25, twice as many young adults with childhood ADHD were daily smokers compared to their non-ADHD counterparts (38% vs. 19%; Molina et al., 2018). A meta-analysis of longitudinal studies similarly showed that the odds of later developing nicotine dependence were three times as high in children with versus without ADHD (Lee et al., 2011). Given that children with ADHD are likely to exhibit dopamine-related disruption in reward and reinforcement processes, one interpretation is that their reactions to initial cigarette use may sensitize them more strongly to the effects of nicotine compared to non-ADHD peers (Kollins & Adcock, 2014). From the perspective of incentive sensitization (Robinson & Berridge, 1993), early cigarette use may translate more readily to nicotine craving in adolescents with ADHD. Indeed, we separately found that MTA children in the LNCG and ADHD groups first smoked at comparable ages, but children with ADHD initiated *daily* smoking earlier and progressed to daily smoking more quickly (Mitchell et al., 2019). Sensitization to stimulant effects, and possible contributions of ADHD stimulant medication on substance use risk, is a topic of ongoing debate (see Chang et al., in press; Humphreys, Eng, & Lee, 2013; Schoenfelder, Faraone, & Kollins, 2014). In the MTA, participants' complex profiles of medication continuation, discontinuation, and initiation following the initial RCT phase are the focus of ongoing work.

ADHD with CD/ODD comorbidity signals stronger risk for frequent adult illicit drug use via early involvement with illicit drugs

We also considered whether statistical mediation of ADHD-related risk for adult substance use through early substance use is *stronger* for children whose ADHD is comorbid with CD/ODD at baseline. Compared to children with ADHD and no CD/ODD, children with ADHD and comorbid CD/ODD were at additional risk only for more frequent adult illicit

drug use, and only through early involvement with illicit drugs, not other substances. Non-marijuana illicit drugs differed from other substance classes in the MTA by their comparatively low rates of use in ADHD and non-ADHD youth alike (rates of monthly or greater use of any illicit substance in adulthood were 5.1% and 4.2% respectively; Molina et al., 2018). Our supplementary analysis also showed no substance-specific mediation to adult illicit drug use when we restricted our sample of children with ADHD to only those *without* comorbid CD/ODD, emphasizing the importance of conduct problems in illicit drug experimentation. Illicit drug use is likely a distinct deviant behavior more often observed in tandem with conduct problems. Traits such as susceptibility to boredom and novelty-seeking that correlate with conduct problems are also associated with a preference for illicit drugs over alcohol and marijuana (Adams et al., 2003; O'Connor, Berry, Morrison, & Brown, 1995).

Overall, our findings suggest that an ADHD diagnosis, irrespective of conduct problems, may be an important childhood indicator of risk for early and developmentally-atypical substance involvement that, in turn, confers risk for heavy substance use in adulthood (see Elkins et al., 2007; Groenman et al., 2013; Flory et al., 2003; Wilens, Martleton et al., 2011). Evidence for this interpretation was strongest for marijuana and cigarette use. At the same time, we do not discount the important role of conduct problems in the constellation of substance-related risk, and risks are at least somewhat lower for children with ADHD who exhibit no conduct comorbidity, particularly with respect to illicit drug use. As shown in Table 1, early use of every substance occurred at higher rates, though not significantly so, in the group of children with ADHD and comorbid CD or ODD compared to ADHD alone. This upward-marching pattern of risk is similar to one shown in an earlier Pittsburgh sample (Molina & Pelham, 2003) that concluded ADHD-related risk for substance use to be further elevated when conduct problems are also present. Importantly, CD/ODD symptoms are not necessarily absent in the ADHD-only group—subclinical symptoms and diagnoses emerge for some later in childhood.

Our findings also do not preclude the possibility that mediated paths from childhood ADHD to adult substance use also include a causal influence of childhood ADHD on later conduct problems or delinquent behavior (Brook et al., 2010; Bussing et al., 2010; Molina & Pelham, 2003; Sibley et al., 2014). In the present sample, hyperactive-impulsive symptoms were more severe for children with ADHD and CD/ODD comorbidity into mid-adolescence (mean differences in hyperactivity-impulsivity symptoms were significantly higher in the ADHD+CD/ODD group vs. ADHD-only at the 2, 3, and 6 year assessments; Cohen's d values ranged from .21 to .33, all $p<.025$). Mediated effects that appear to be driven by CD/ODD comorbidity thus also reflect greater ADHD symptom severity. This interconnectivity invites further tests of ways that time-varying relations between ADHD and CD/ODD symptoms through adolescence jointly contribute to emerging substance use risk. However, the modest escalated risk associated with childhood CD/ODD in the present study, relative to the overall ADHD versus LNCG mediated effects, suggest that vulnerabilities other than early behavioral deviance likely contribute to increased risk for early substance use that we observe in children with ADHD (see also Chang et al., 2012).

Limitations.—In addition to those noted above, childhood diagnoses of ADHD in the MTA were limited to Combined subtype. Some shifted to Inattentive subtype in adolescence (Molina et al., 2009), and half exhibited persistent ADHD symptoms into adulthood (Hechtman et al., 2016). We thus urge caution in generalizing findings from this study to the broader population of children with ADHD. Similarly, other childhood comorbidities beyond CD/ODD were present in this sample (e.g., anxiety) and possible contributions of other disorders to early substance involvement and preference were not explored here. In adulthood, our analyses are also restricted to substance use frequency and not disorder. The mediated paths we identified in the present study align with risk pathways that we expect may lead to eventual substance use disorder, but our frequency measures offer a higher-powered, dimensional measure from which to capture substance-specific versus non-specific associations with ADHD. Indeed, we reported elsewhere (Molina et al., 2018) that only half of the weekly marijuana users in the present sample met criteria for cannabis use disorder in adulthood.

We also note that our findings are based on a largely U.S. sample, limiting generalizability to countries in which legal drinking ages are lower, and in which other substances (notably marijuana) are broadly legal or non-criminal and more widely available. We further acknowledge that our ADHD sample comprises children and families who were willing and able to participate in an intensive randomized controlled trial, raising the possibility that self-selection bias shaped the sample. Finally, we also acknowledge important limitations to causal inference. The timing of our constructs (ADHD, early substance use, adult substance use) coincide well with distinct developmental periods, and measures in the mediational chain preceded each other in time, but alternative models that include additional behavioral and contextual factors as confounds or additional mediators remain plausible.

Conclusion.—We established that early and developmentally atypical adolescent involvement with marijuana, cigarettes, illicit drugs, and to a lesser extent alcohol, statistically mediated the prospective link to frequent continued use of the same substances in adulthood by children with ADHD. In line with our prior conclusions (Molina et al., 2018), these findings underscore the importance of increasing public awareness of potential long-term substance use risks associated with childhood ADHD and the need for early screening before substance experience accumulates. Our findings also invite further examination of the role of ADHD-related neurocognitive deficits in addiction, given that early cigarette involvement was a more potent mediator of ADHD-related daily smoking than ADHD-related use of any other substance. This is particularly relevant given the rise of e-cigarette use by adolescents and its potential to promote cigarette use (Schneider & Diehl, 2016). Future research that replicates and extends these findings to recent substance trends not captured in the MTA—such as e-cigarettes and opioid drugs—would be welcome. Overall, our mediational findings provide strong support for ADHD-related pathways to adult substance use that have roots in adolescence, including escalated risk for children with comorbid CD/ODD through early illicit drug use. Many causal factors are likely at play, and these pathways may ultimately be visible manifestations of neurobiological and genetic vulnerability. Our findings nonetheless suggest that we consider the real possibility, through experimental study, that preventing atypically-early substance use in adolescents

with childhood ADHD may contribute to long-term reductions in frequent and heavy substance use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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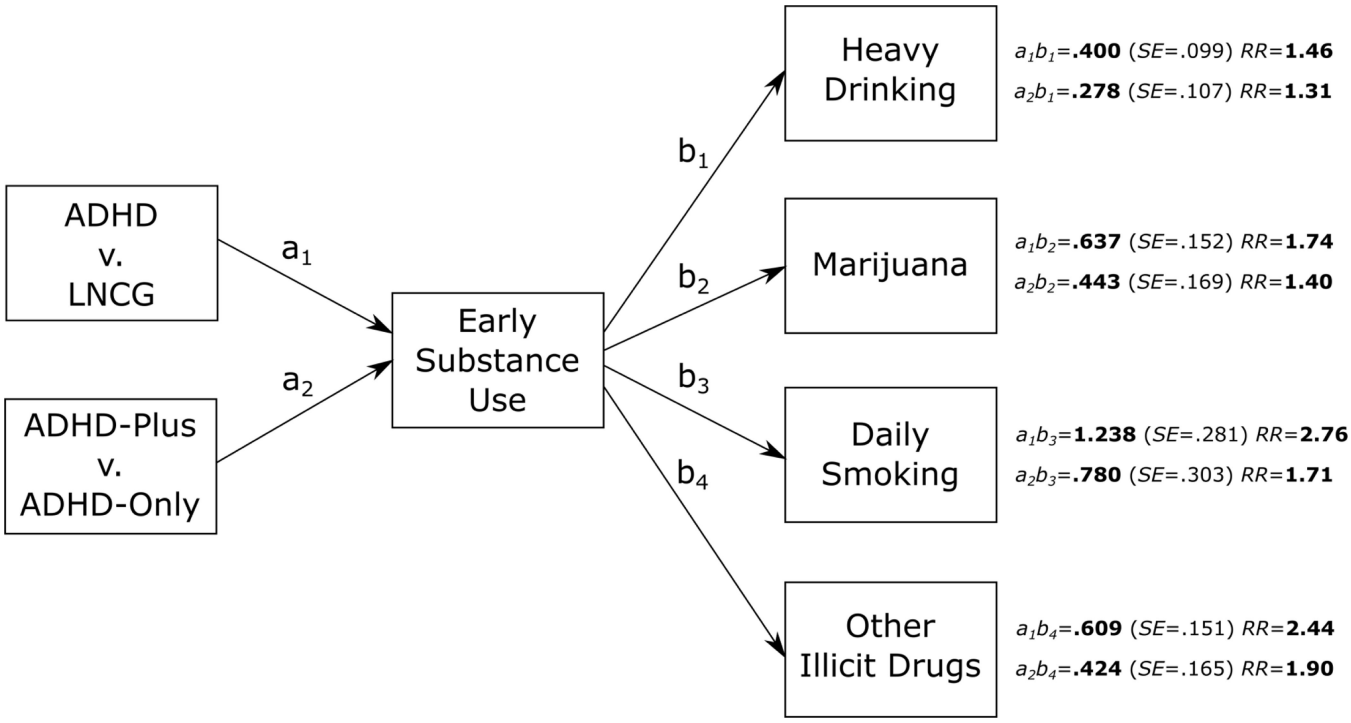

Figure 1.

Mediated effects of childhood ADHD (vs. LNCG) and ADHD plus CD/ODD (vs. ADHD-only), established prior to age 10, through early substance use (established prior to age 17) to adult substance use frequency (repeated measures at ages 17 and older). Labeled paths refer to direct regression relations between variables (e.g., a_1, a_2, b_1; see Tables S1 and S2 for estimates of individual paths). Mediated (indirect) effects are the products of pairs of paths (e.g., a_1b_1, a_2b_1). All indirect effects (shown in **bold**) were statistically significant after correction for multiple testing using the Benjamini-Hochberg method (all $p<.02$). *SE*=standard error. *RR*=relative risk ratio.

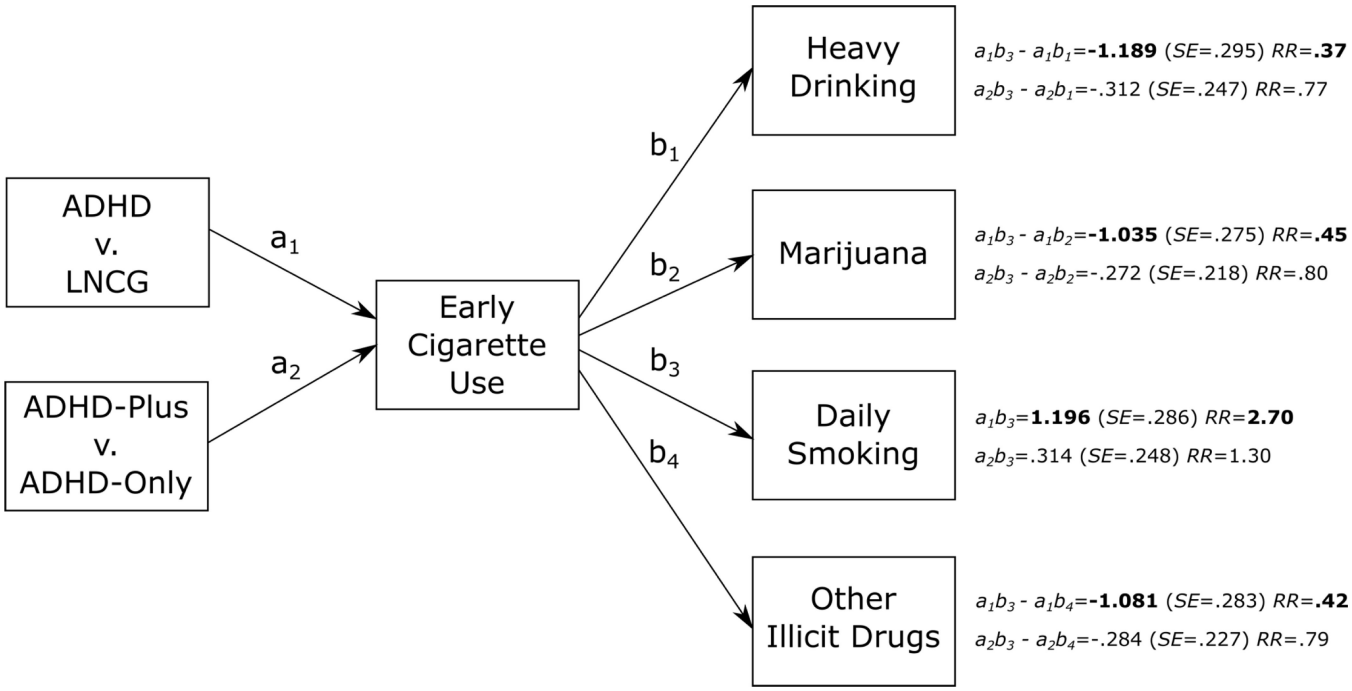

Figure 2.

Comparisons of mediated effects of childhood ADHD (vs. LNCG) and ADHD plus CD/ODD (vs. ADHD-only), established prior to age 10, through early cigarette use (established prior to age 17; controlling for concurrently influences of all other mediators) to adult daily smoking versus adult heavy drinking, daily smoking, and illicit drug use (repeated measures at ages 17 and older). Labeled paths refer to direct regression relations between variables (e.g., a_1, a_2, b_1; see Tables S1 and S2 for estimates of individual paths). Mediated (indirect) effects through early cigarette involvement are the products of two pairs of paths (i.e., a_1b_2, a_2b_2). Comparisons of mediated effects through early cigarette use to adult daily smoking versus adult use of other substances are shown as the *differences* between mediated effects (e.g., a_1b_3 - a_1b_1). Effects and differences are **bolded** if statistically significant after correction for multiple testing using the Benjamini-Hochberg method (here, all significant p<.005). *SE*=standard error of the difference. *RR*=relative risk ratio of the difference.

Table 1

Observed numbers and rates of early substance use and adult substance use by diagnostic group (LNCG, ADHD-only, ADHD+CD/ODD)

	LNCG[1] N (%)	ADHD-only[2] N (%)	ADHD + CD/ODD[3] N (%)	Contrasts
Early substance use (age <17)				
Any substance	108 (41.9)	128 (48.5)	189 (60.0)	1, 2 < 3
Alcohol	73 (29.4)	83 (36.4)	115 (41.2)	1 < 3
Marijuana	63 (25.4)	84 (36.8)	126 (45.0)	1 < 2, 3
Cigarettes	34 (13.7)	64 (28.2)	93 (33.1)	1 < 2, 3
Illicit drugs	35 (14.2)	48 (21.7)	85 (30.9)	1 < 2 < 3
N	246–258	221–264	275–315	
Adult substance use (age 17+)				
Weekly or greater heavy drinking	83 (33.7)	75 (34.3)	101 (37.0)	1 = 2 = 3
Weekly or greater marijuana use	83 (33.7)	95 (43.4)	112 (41.0)	1 < 2, 3
Daily smoking	65 (26.4)	92 (42.0)	131 (48.0)	1 < 2, 3
Monthly or greater illicit drug use	27 (11.0)	25 (11.4)	39 (14.3)	1 = 2 = 3
N	246	219	273	

Note. Early substance use numbers shown for alcohol, marijuana, cigarettes, and illicit drugs reflect cases who met criteria ("A" and "B" as defined in the study Method) for each specific substance. Numbers shown for *any substance* reflect cases who met any combination of criteria A and B on one or more substances. Adult substance use numbers reflect cases who used each substance at the listed threshold *at least once* in adulthood (ages 17 and up). Substance use at less frequent thresholds (e.g., monthly, less than monthly) is not shown. These rates differ from substance use reported at the *last available* adult assessment point, in Molina et al. (2018). Pairwise contrasts (p<.05) are shown between LNCG (1), ADHD-only (2), and ADHD+CD/ODD (3) groups.

Table 2

Mediated effects of childhood ADHD (vs. LNCG), and childhood ADHD plus CD/ODD (vs. ADHD-only) on adult heavy drinking, marijuana use, daily smoking, and illicit drug use through early use of alcohol, marijuana, cigarettes, and illicit drugs.

		Adult Substance Use Outcome							
		Heavy Drinking		**Marijuana Use**		**Daily Smoking**		**Illicit Drug Use**	
Contrast	**Mediator**	***ab* (*SE*)**	***RR***	***ab* (*SE*)**	***RR***	***ab* (*SE*)**	***RR***	***ab* (*SE*)**	***RR***
ADHD vs. LNCG	Early alcohol	**.167 (.068)**	**1.19**	.053 (.048)	1.06	.135 (.088)	1.17	.132 (.066)	1.24
	Early marijuana	.157 (.064)	1.18	**.491 (.144)**	**1.57**	.370 (.140)	1.50	.234 (.088)	1.46
	Early cigarette	.006 (.072)	1.01	.161 (.095)	1.18	**1.196 (.286)**	**2.70**	.115 (.095)	1.21
	Early illicit drug	.174 (.074)	1.19	.217 (.092)	1.24	.215 (.129)	1.28	**.394 (.130)**	**1.84**
ADHD plus CD/ODD vs. ADHD-only	Early alcohol	.084 (.068)	1.09	.027 (.033)	1.02	.068 (.069)	1.06	.067 (.059)	1.12
	Early marijuana	.088 (.054)	1.10	.274 (.148)	1.25	.207 (.123)	1.20	.131 (.078)	1.24
	Early cigarette	.002 (.023)	1.00	.042 (.044)	1.04	.314 (.247)	1.30	.030 (.038)	1.05
	Early illicit drug	.137 (.067)	1.15	.171 (.084)	1.16	.169 (.110)	1.16	**.311 (.128)**	**1.63**

Note. *ab*=coefficient representing the probit of more frequent use of each substance due to group through its influence on the mediator, controlling for concurrent influences of all other mediators. *SE*=standard error. *RR*=relative risk ratio (calculated for each substance relative to base rates of use reported in Table 1). **Bolded**effects are statistically significant after correction for multiple testing using the Benjamini-Hochberg False Discovery Rate method (here, all significant $p<.015$). Grey shaded entries show same-substance mediation.

Table 3

Differences in mediated effects of childhood ADHD (vs. LNCG) and childhood ADHD plus CD/ODD (vs. ADHD-only) through early use of alcohol, marijuana, cigarettes, and illicit drugs on continued use of the same substance versus a different substance in adulthood.

		Adult Substance Use Outcome							
		Heavy Drinking		Marijuana		Daily Smoking		Illicit Drug Use	
Contrast	**Mediator**	***Diff* (*SE*)**	***RR***	***Diff* (*SE*)**	***RR***	***Diff* (*SE*)**	***RR***	***Diff* (*SE*)**	***RR***
ADHD vs. LNCG	Early alcohol	-	-	−.114 (.068)	.89	−.031 (.083)	.97	−.035 (.058)	.97
	Early marijuana	**−.333 (.117)**	**.75**	-	-	−.121 (.121)	.91	−.256 (.101)	.81
	Early cigarette	**−1.189 (.295)**	**.37**	**−1.035 (.275)**	**.45**	-	-	**−1.081 (.283)**	**.42**
	Early illicit drug	−.219 (.105)	.72	−.177 (.106)	.77	−.179 (.140)	.77	-	-
ADHD plus CD/ODD vs. ADHD-only	Early alcohol	-	-	−.057 (.055)	.94	−.016 (.050)	.98	−.018 (.037)	.98
	Early marijuana	−.186 (.108)	.86	-	-	−.068 (.079)	.95	−.143 (.091)	.89
	Early cigarette	−.312 (.247)	.77	−.272 (.217)	.80	-	-	−.284 (.226)	.79
	Early illicit drug	−.409 (.165)	.52	−.375 (.171)	.55	−.376 (.188)	.55	-	-

Note. For each contrast, *Diff*=coefficient representing the difference in the probit of more frequent continued use in adulthood of the same substance versus another substance, through the early substance mediator and controlling for concurrent influences of all other mediators. Negative sign indicates that the mediated effect predicting other-substance risk is *weaker* than the mediated effect predicting continued use of the same substance in adulthood. *SE*=standard error of the difference. *RR*=relative risk ratio of the difference. **Bolded**effects are statistically significant after correction for multiple testing using the Benjamini-Hochberg False Discovery Rate. For ADHD vs. LNCG mediated effects, all significant $p<.007$.