Published in final edited form as:

J Child Psychol Psychiatry. 2018 October ; 59(10): 1083–1093. doi:10.1111/jcpp.12977.

Mediating pathways from childhood ADHD to adolescent tobacco and marijuana problems: roles of peer impairment, internalizing, adolescent ADHD symptoms, and gender

Irene J. Elkins¹, Gretchen R. B. Saunders¹, Stephen M. Malone¹, Sylia Wilson, Matt McGue¹, and William G. Iacono¹

¹Department of Psychology, University of Minnesota

Abstract

Background: We examined whether increased risk for adolescent tobacco and marijuana problems associated with childhood ADHD is explained by key intermediary influences during adolescence and differs by gender.

Methods: Longitudinal structural equation models examined mediating effects on problems with both substances (or each substance separately) through age-14 peer impairment, internalizing, and adolescent ADHD symptoms in two twin samples, prospectively assessed since age 11 (N=2,164). Whether these mediators contributed beyond mediating effects of early-adolescent substance use was also considered. Twin difference analyses further illuminated which mediators might be potentially causal.

Results: Direct effects of childhood ADHD on age-17 tobacco and marijuana problems (i.e., independent of included mediators), as well as effects of adolescent ADHD symptoms, were significant only for females. By contrast, mediation by peer impairment, evident particularly for marijuana, was relatively stronger for males than females. Depression and anxiety were not prospectively associated with age-17 substance problems when earlier substance problems were considered. Consistent with causal influence of early substance use on later problems, monozygotic twins with more severe tobacco or marijuana problems at age 14 than their co-twins were also more likely to have substance problems later in adolescence.

Conclusions: Mediation through peer impairment, continued presence of ADHD symptoms, and early substance use may alter development so that childhood ADHD indirectly contributes to problems with tobacco and marijuana. Targeting gender-sensitive interventions prior to mid-adolescence, before these patterns become established, is essential.

Keywords

ADHD; Gender Difference; Substance Use; Longitudinal Studies; Twins

---

Correspondence: Irene Elkins, Department of Psychology, University of Minnesota, 75 E. River Rd., Minneapolis, MN 55455, USA. ielkins@umn.edu.

Conflict of interest statement: No conflicts declared.

Supporting information.

Additional supporting information may be found online in the Supporting Information Section at the end of this article.

Introduction

The 2017 National Survey on Drug Use and Health reported that among adolescents ages 12–17, daily marijuana use occurred almost exclusively among current or previous tobacco smokers (Goodwin et al., 2018). Among other contributing factors, children with an ADHD diagnosis are more likely to initiate substance use early and escalate use during adolescence (e.g., Sibley et al., 2014). Recent findings that frequent tobacco and marijuana (but not alcohol) use become particularly associated with ADHD by adulthood (Molina et al., 2018) amplify the importance of an improved understanding of the mechanisms underlying these relationships.

The degree of risk associated with ADHD differs substantially depending on ADHD symptom subtype, co-morbidity, persistence, and gender (Looby, 2008; Rucklidge, 2010). For example, although hyperactive-impulsive ADHD symptoms and co-occurring conduct problems show the most consistent associations with substance use, inattentive symptoms may contribute uniquely to tobacco outcomes (Elkins, McGue, & Iacono, 2007; Pingault et al., 2013). Whether ADHD persists may affect risk for marijuana use disorder (Hechtman et al., 2016). Furthermore, ADHD may be associated with increased marijuana use for adolescent girls, relative to boys (Sihvola et al., 2011).

Recently, we found a stronger association between childhood ADHD and frequent cigarette smoking for adolescent females than males, attributable in part to potentially causal influences of inattention (Elkins, Saunders, Malone, Keyes, Samek, et al., 2018). In a related study, ADHD-marijuana associations, though relatively more similar across gender, were comparable in size to tobacco and less explained by conduct problems than were ADHD-alcohol associations (Elkins, Saunders, Malone, Keyes, McGue, et al., 2018). Distinguishing which factors mediate ADHD's associations with these substances, and whether they differ by gender, may be important for developing effective interventions. For example, although childhood ADHD increases the likelihood of related impairments for both genders, some problems may be more common among females, including peer impairment, internalizing (i.e., depression/anxiety), and self-harming (Swanson, Owens, & Hinshaw, 2014). Though few gender differences are found in co-morbidity with other externalizing disorders, girls with inattentive ADHD are more likely to have anxiety disorders (Bauermeister et al., 2007). Even when similarly likely to receive treatment, girls with ADHD have an increased likelihood of being unpopular, or bullied, compared to boys with ADHD (Elkins, Malone, Keyes, Iacono, & McGue, 2011). Due in part to lower ADHD prevalence among females (male/female ratio of 3:1; Erskine et al., 2013), however, many studies have too few affected females to examine gender differences.

Correspondingly, while the contributions of deviant peers and conduct problems to adolescent substance use among those with ADHD have been extensively documented, few studies have examined mediation by either peer impairment (Molina et al., 2012) or internalizing. Peer impairment, as manifested by low popularity and victimization by peers, increases risk for internalizing, whereas positive peer relations decrease risk (Kochel, Bagwell, Ladd, & Rudolph, 2017). Among children with ADHD, attentional impairments may cascade into problems with academics and peers (Campbell, Halperin, & Sonuga-

Barke, 2014), with peer impairments partially mediating the relationship of inattention to depression (Humphreys et al., 2013). In conjunction with internalizing, peer impairment may also lead to adolescent cigarette smoking (Vitulano et al., 2014).

The current study utilized longitudinal structural equation modeling (SEM) to examine these potential mediators of the relationship of childhood ADHD to late-adolescent tobacco/marijuana problems. We investigated whether childhood ADHD symptoms predict tobacco/marijuana problems directly or indirectly, which mediators are involved, and whether they differ by gender. Because early-onset substance use also predicts later substance disorders (Brook, Brook, Zhang, Cohen, & Whiteman, 2002), whether mediators contribute beyond the effects of early adolescent use was considered. Two contrasting explanations may account for why childhood ADHD predicts substance outcomes. Both ADHD and substance problems may be manifestations of the same underlying risk (e.g., a genetic vulnerability). Alternatively, ADHD, along with its consequences, may alter the course of development such that it directly (or indirectly, through a mediator) causes these outcomes. Rather than relying only on temporal ordering to make causal assumptions, twin difference methods (McGue, Osler, & Christensen, 2010) were applied to significant mediating paths. Given that twin pairs share the same rearing environment and monozygotic pairs share all segregating genes, if differences within monozygotic pairs on a mediator account for differences in each twin's substance problems as well, this lends support to causal explanations beyond that contributed by mediator preceding outcome.

We hypothesized that increased risk for adolescent tobacco and marijuana problems associated with childhood ADHD may be mediated by peer impairment and/or internalizing, or conversely, that having prosocial peers would enhance resilience. We further expected that these mediators, along with continued presence of ADHD symptoms during adolescence, would be particularly key for females. Our large sample, including a cohort oversampling affected females, increased our ability to detect gender effects.

Methods

Participants

A total of 2,510 individual twins (52% female; 48% male) from 1,255 like-sex twin pairs (64% monozygotic; 36% dizygotic) visited at baseline. Participants were from two prospectively-assessed, community-ascertained cohorts from the Minnesota Twin Family Study, a longitudinal investigation of the development of substance abuse. For **Cohort 1**, twin pairs identified from Minnesota birth records (from 1977 to 1984) were eligible if they lived within a day's drive of University of Minnesota, with no physical/psychological disability that precluded assessment completion (Iacono, Carlson, Taylor, Elkins, & McGue, 1999). For **Cohort 2**, pairs from an additional birth cohort (1988 to 1994) were randomly allocated to screened (48%) or non-screened (52%) samples; higher allocation of female pairs to the screened sample ensured participation of more affected females. The non-screened sample was recruited using the same criteria as Cohort 1. To enrich the screened sample in Cohort 2 with twins exhibiting signs of ADHD, conduct problems, and academic disengagement, a parent was phone-interviewed and the family recruited if at least one twin exceeded an empirically-validated threshold, which maximized sensitivity and specificity for

identifying externalizing disorders (i.e., 52% of screened males and 41% of screened females met criteria for a diagnosis of ADHD or conduct/oppositional defiant disorder; Keyes et al., 2009). Comparisons of participants with non-participants suggested minimal bias on demographic variables; thus, both cohorts were representative of Minnesota for the birth years sampled (Iacono, et al., 1999; Keyes, et al., 2009).

Twins were assessed at ages 11–12 [Wave 1; 11.8 (0.4) years], with follow-up assessments at ages 14–15 [Wave 2; 14.9 (0.6) years] and 17–18 [Wave 3; 18.0 (.6) years]. Retention across follow-ups (completed by 2012) was excellent (93% at Wave 2; 89% at Wave 3). There was no evidence of selective attrition of those with more severe ADHD or externalizing behavior, though follow-up non-participants were slightly lower in parental socioeconomic status (SES; Cohen's $d = -.26$; $t = 6.46$, $p < .001$).¹ SEM models included 97% of Wave 3 participants ($N = 2,164$) with data from all waves (Cohort 1: $N = 1,283$; Cohort 2: $N = 881$).

Procedures and measures

The study received approval from University of Minnesota's Institutional Review Board. Written informed consent from parents and written assent from twins was obtained. Each parent and child was interviewed by a different interviewer. At Waves 1 and 2, interviews consisted of primary caregiver and adolescent reports on parallel versions of the Diagnostic Interview for Children and Adolescents-Revised (DICA-R; Reich, 2000), modified for DSM-IV. Childhood ADHD was assessed lifetime at Wave 1 with onset before age 12, consistent with DSM-5. At Wave 2, major depressive disorder (MDD), substance use disorders, and ADHD between ages 11–14 were assessed using the DICA-R. At Wave 3, parents reported on substance and MDD symptoms between ages 14–17 using the DICA-R; adolescents reported using age-appropriate interviews suitable for late adolescence [i.e., Substance Abuse Module (SAM) from the Composite International Diagnostic Interview (Robins et al., 1988); updated Structured Clinical Interview for DSM-III-R (SCID; Spitzer et al. 1987)]. Three recent teachers, nominated by adolescents and/or their parents as knowing the adolescent well, were contacted to provide ratings of age-14 peer functioning. At least one teacher rating was obtained for 92% of Wave 2 twins; responses were averaged across teachers.

Symptoms of all disorders were considered present if reported by parent or child, following review by two individuals with advanced clinical training. Symptoms were evaluated with guidelines including examples of frequency and severity (e.g., ADHD behavior resulting in teacher feedback) and were assigned if there was consensus that they constituted DSM-IV symptoms.²

¹Caregiver-reported ADHD is superior to adolescent- or teacher-reports for predicting ADHD diagnoses, particularly when checklists are used (Raiker et al., 2017). However, twin self-ratings are essential for detecting differences within pairs. An evaluation of the structured interview methods utilized here supported that ADHD symptoms endorsed by parents or 11-year-old twins provided unique predictive information when evaluated against teacher-reported behavior problems (Burt, McGue, Krueger, & Iacono, 2005)

²For males: Direct (.02) + Indirect (through Age-14 Tobacco/Marijuana Problems; .12 X.50) + Indirect (through Peer Impairment; .38 X.18) = .15. For females: Direct (.10) + Indirect (through Age-14 Problems; .10 X.51) + Indirect (through Peer Impairment; .33 X.09) = .18.

Childhood ADHD symptoms.

were defined as number of lifetime symptoms (ranging from 0 to 18) reported at Wave 1. *Adolescent ADHD symptoms*, assessed in Cohort 2 only, were represented by number of ADHD symptoms occurring between Waves 1 and 2. Given that 99.1% of those reporting ADHD symptoms at Wave 2 had reported onset of 1 symptoms prior to age 12, these primarily reflected continued presence of ADHD symptoms into adolescence, rather than new onsets. While all analyses utilized ADHD symptom counts, many individuals also had clinically-relevant ADHD [5 symptoms of either the predominantly inattentive or hyperactive-impulsive subtype, or 5 symptoms of each subtype (Combined)]: 417 adolescents (261 males; 156 females) at Wave 1; 42% of Cohort 2 cases continued to meet criteria at Wave 2.

Other observed indicators were used to form latent variables and are described below, under the corresponding latent variable. Internal consistency reliabilities for observed scales ranged from .78–.87.

Peer impairment at age 14.

The degree to which each adolescent had peers who were popular or good students (i.e., prosocial) was assessed via teacher ratings (5 items), provided relative to other students. Teachers who indicated they did not know the adolescent well enough to identify his/her friends did not provide ratings. Adolescents rated eight similar items. Adolescent-reported peer victimization (between ages 11–14) was assessed as “Have you been bullied or picked on a lot by other kids?”; relational/overt victimization (based on the Social Experience Questionnaire; Crick & Grotpeter, 1995) was assessed in Cohort 2 only (10 items, e.g., how often others “spread rumors to make others not like you”).

Tobacco/marijuana problems at ages 14 and 17.

Nicotine dependence and marijuana abuse/dependence symptom counts were assessed as described above. Composite measures of quantity and frequency of tobacco/marijuana use were derived from adolescent-reports via interview and self-administered computerized measures. These consisted of frequency of tobacco use since the previous wave (never to daily smoking), cigarettes per day in the past 12 months, and number of marijuana uses (lifetime, though uses prior to Wave 2 were minimal).

Depression/anxiety at ages 14 and 17.

was assessed with adolescent-reported Trait Anxiety (20 items, State-Trait Anxiety Inventory; Spielberger, 1983), Stress Reaction (18 items, Multidimensional Personality Questionnaire; tendency to be sensitive, easily upset; prone to worry/guilt; Tellegen & Waller, 2008), and a count of MDD symptoms.

Statistical analyses

We conducted SEM in Mplus 7.31 (Muthén & Muthén, 2015) to examine age-14 mediators of the relationship of childhood ADHD to age-17 tobacco/marijuana problems. Substance-specific models were also fit to separately examine latent tobacco or marijuana outcomes.

Full-information maximum likelihood produced unbiased estimates for data missing at random, permitting participants in all waves to be included even when missing data on a specific indicator. Substance indicators (and MDD symptoms) were log-transformed prior to analysis; a robust MLR estimator minimized effects of non-normality. The COMPLEX samples option accounted for correlated twin data via a sandwich estimator.

Age-11 ADHD symptom count was an exogenous predictor; latent variables representing each mediator and outcome were endogenous. Age at each wave, parental SES and cohort were included as covariates. Whether tobacco/marijuana problems and internalizing were predicted beyond their stability was evaluated with autoregressive and cross-lagged paths between substance problems and internalizing at ages 14 and 17. Correlated residuals between different latent variables assessed at the same age (and between the same indicators at different ages) were also included.

We fit a series of two-group, male/female models. Each baseline model included all possible paths, allowing paths and residual covariances to vary by gender. Whether a path could be dropped or constrained equal across gender groups was tested within a nested model, including the constraint on the path being tested, and prior, successively-imposed constraints. Each subsequent model was compared to the baseline, unconstrained model, using the Satorra-Bentler scaled chi-square test for nested models (Satorra & Bentler, 2010). Significance of indirect pathways between childhood ADHD and tobacco/marijuana problems for each final model was determined via bootstrapping, using the boot (Canty & Ripley, 2016) and Mplus Automation packages in R. The distribution of the product of standardized path coefficients was computed for 500 bootstrap samples of twin pairs; 95% confidence intervals were computed for these effects using bias-corrected and accelerated (BCa) intervals.

To determine which paths to age-17 outcomes were consistent with causality, factor scores for latent variables in each model (or ADHD symptom counts) were used to derive within-pair difference scores on the two variables constituting the path. Twin difference regressions were implemented as linear mixed models in SAS PROC MIXED. Differences within monozygotic pairs on a mediator that were significantly associated with twin differences in outcome were considered consistent with causality. Differences significant within all pairs (though not for monozygotic or dizygotic pairs separately) were considered partially consistent with causality, because within-pair differences in dizygotic pairs control only partially for genetic factors.

Results

Descriptive statistics for observed indicators and loadings on corresponding latent variables are in Table 1; correlations between indicators are in Appendix S1. Females were significantly less likely to lack prosocial peers than males, yet were higher in relational/overt victimization, stress reaction, anxiety, and depression. Males were higher on age-14 tobacco quantity/frequency and all age-17 substance indicators. Consequently, for SEM, means and thresholds were allowed to differ by gender, causing standardized path coefficients to vary slightly, even when unstandardized coefficients were constrained.

The prospective relationship between childhood ADHD and age-17 tobacco and marijuana problems was tested. Figure 1 displays significant paths and parameter estimates for final, two-group models of tobacco/marijuana problems combined (Figure 1a) and tobacco (Figure 1b) or marijuana (Figure 1c) separately; both cohorts were combined for these models. Because adolescent ADHD symptoms were only available for Cohort 2, however, the model in Figure 2 was fit in this cohort only. Standard errors are in Appendix S2. The smallest number of parameters necessary to explain the data was determined by sequentially constraining parameters to zero, or equal across genders. Degrees of freedom for chi-square tests below thus correspond to the difference in parameters between each model excluding or constraining a specific path (including all previously-applied constraints), compared to the baseline model (including all paths).

Direct and indirect effects of childhood ADHD symptoms on tobacco and marijuana problems

In Figure 1a, the direct path between childhood ADHD and age-17 tobacco/marijuana problems was significant. It could neither be dropped [$\chi^2_{\text{diff}}(2)=16.83, p<.001$] nor constrained equal across genders [$\chi^2_{\text{diff}}(1)=5.13, p<.05$] without a significant decrement in fit, as it was significant for females ($\beta=.10$) but not males ($\beta=.02$). As was true in all models, ADHD was highly related to all potential age-14 mediators, including increased tobacco/marijuana problems [$\chi^2_{\text{diff}}(4)=22.38, p<.001$], peer impairment [$\chi^2_{\text{diff}}(5)=85.30, p<.001$], and depression/anxiety [$\chi^2_{\text{diff}}(6)=57.62, p<.001$]. The hypothesized prospective path between peer impairment and age-17 tobacco/marijuana problems, though relatively larger for males ($\beta=.18$) than females [$\beta=.09$; $\chi^2_{\text{diff}}(8)=18.57, p<.05$], was significant [$\chi^2_{\text{diff}}(9)=23.29, p=.01$]. Conversely, residual covariances between age-14 mediators were greater in magnitude for females, including that between peer impairment and concurrent tobacco/marijuana problems [$\chi^2_{\text{diff}}(10)=21.28, p<.05$]. The hypothesized path from age-14 depression/anxiety to age-17 substance problems was not significant in any model. Paths between substance problems at ages 14–17 (and internalizing at both ages) were large in all models (e.g., $\beta\text{s}=.50\text{--}.63$; Figure 1a), indicating considerable stability in adolescents' relative standings on these latent variables between ages 14–17, even as scores on specific substance and internalizing measures generally increased during this time (e.g., see means in Table 1).

While significance of individual paths is shown in each Figure, significant mediating pathways between childhood ADHD symptoms (ADHD11) and substance problems are provided in Table 2. Indirect effects corresponded to the product of individual path coefficients comprising the given pathway, derived through bootstrapping. Age-14 tobacco/marijuana problems mediated one pathway in Figure 1a (ADHD11→TOBMAR14→TOBMAR17); peer impairment mediated the other (ADHD11→PEER14→TOBMAR17). The total effect of childhood ADHD in Figure 1a, including both direct and mediated effects, corresponds to an increase of 1 SD in childhood symptoms being associated with an increase (in SD units) of .15 (males) or .18 (females) in age-17 tobacco/marijuana problems.³

³Due partly to the modest size of these paths, they could be constrained equal across genders without decreasing fit, as could paths from adolescent ADHD symptoms in Figure 2. Because all were significant for females only, however, they were dropped for males.

Effects specific to each substance

The hypothesized relationship with peers, though not significant for tobacco (Figure 1b), was for marijuana [see Figure 1c, Peer Impairment→Age-17 Marijuana Problems path; $\chi^2_{\text{diff}}(8)=22.71$, $p<.01$]. As in Figure 1a, this path could not be constrained [$\chi^2_{\text{diff}}(7)=16.16$, $p<.05$] and was relatively stronger for males ($\beta=.17$) than females ($\beta=.08$). Indeed, the corresponding pathway (ADHD11→PEER14→MAR17) was associated with the largest indirect effect for males (Table 2). Despite concurrent relationships between greater depression/anxiety and more substance problems at age 14 (significant for females only; $r=.27$ for tobacco; $r=.16$ for marijuana), females with greater age-14 tobacco use were unexpectedly less depressed/anxious at age 17 [$\beta=-.12$; $\chi^2_{\text{diff}}(14)=28.50$, $p=.01$]; the same was true for marijuana. As expected (Humphreys et al., 2013), peer impairment also mediated the relationship of ADHD to increased age-17 depression/anxiety (see ADHD11→PEER14→DEPANX17 pathway; Appendix S2).

Effects when considering adolescent ADHD symptoms

In Figure 2, unlike the comparable model without adolescent ADHD symptoms, the path between peers and age-17 tobacco/marijuana problems was no longer significant [$\chi^2_{\text{diff}}(10)=11.46$, $p=.32$], nor was the direct effect of childhood ADHD. Instead, effects on tobacco/marijuana problems were primarily mediated by adolescent ADHD symptoms or age-14 substance problems. Although the path between adolescent ADHD and age-17 tobacco/marijuana problems could be constrained across gender [$\chi^2_{\text{diff}}(15)=19.48$, $p=.19$] and was significant [$\chi^2_{\text{diff}}(16)=28.44$, $p<.05$], this was true for females only ($\beta=.14$; $p<.01$). Significance of the ADHD11→Adolescent ADHD→TOBMAR17 pathway for females is confirmed in Table 2; ADHD associations with depression/anxiety were also mediated by adolescent ADHD symptoms (Appendix S2).

Twin difference analyses

To explicate mediation mechanisms (Zhang, Zyphur, & Preacher, 2009), significant longitudinal paths between childhood ADHD and age-17 substance problems were subdivided into influences shared by twins in a pair (like parental substance use) and those non-shared, or different within pairs. Complete pairs for these analyses included 658 monozygotic and 394 dizygotic pairs. Almost all paths involved some shared influences; however, those marked with a “C” in the Figures were consistent with causal influences as well (i.e., significant within monozygotic pairs).

Monozygotic twins whose age-14 tobacco/marijuana factor scores were 1 SD higher than their co-twins were .62 SD higher on age-17 tobacco/marijuana problems ($p<.0001$; Figure 2), consistent with causal influence of early substance problems on those in later adolescence. The direct ADHD11→Age-17 tobacco problem path for females (Figure 1b) was also consistent with causal influence of the former on the latter (monozygotic within-pair effect: $p=.001$). Notably, the ADHD11→Peer Impairment path was consistent with causal influence in all models (monozygotic within-pair effects: $p<.0001$), while the Peer Impairment→Age-17 Marijuana path (Figure 1c) was partially consistent with causal influence for males only (“PC”; see Figure footnote ^b), when controlling for early adolescent use. Other paths towards substance problems were primarily or fully confounded by shared

factors. For example, the direct ADHD11→age-17 marijuana path (Figure 1c) was entirely due to shared familial factors.

Discussion

We evaluated potential mediating pathways for the association of childhood ADHD to adolescent tobacco and marijuana problems in two large, prospectively-assessed twin samples. Direct effects of childhood ADHD on tobacco and marijuana problems in late adolescence (i.e., those independent of included mediators), as well as effects through presence of ADHD symptoms during adolescence, were significant for females only. Effects of childhood ADHD on substance problems were also mediated by peer impairment, although this was unexpectedly stronger for males than females. Yet effects of childhood ADHD on tobacco and marijuana problems in late adolescence were largely mediated through presence of early substance problems for both genders. Accordingly, when accounting for earlier substance use, effects of depression and anxiety were associated concurrently, but not prospectively, with tobacco/marijuana problems.

Our findings regarding the importance of early substance use for the development of later problems are consistent with recent findings in the MTA study (Molina, et al., 2018), which followed children with the Combined ADHD subtype to adulthood. Our findings extend theirs to a population-based sample, with greater representation of females and different ADHD subtypes. Moreover, the twin difference analyses highlight the urgency of intervening prior to mid-adolescence. Afterward, adolescents' relative substance problem severity was consistent with causal influences of early use on their later tobacco/marijuana problems, in addition to underlying familial risk. Direct effects of childhood ADHD on tobacco problems specifically (Figure 1b) were also consistent with causality, at least for females. Previous findings of potentially causal effects of inattention in females suggest these might increase their relative susceptibility to self-medicate attentional problems with nicotine (Elkins, Saunders, Malone, Keyes, Samek, et al., 2018), whereas direct effects of ADHD on marijuana were attributable to familial risk only.

Notably, mediating effects of peer impairment appeared partially consistent with causality, at least for males. Lack of prosocial peers may promote subsequent involvement with deviant peers (Fergusson, Woodward, & Horwood, 1999) and therefore greater substance use. Accordingly, peer impairment among adolescents with ADHD was previously associated with increased alcohol use only through delinquent behavior (Molina, et al., 2012). Because we found significant mediation by peer impairment for marijuana (Figure 1c), but not tobacco (Figure 1b), peer impairment might particularly impact illicit use, as recreational marijuana is illegal for Minnesota adults.

That prospective associations between peer impairment and substance problems in later adolescence were comparatively stronger for males, while concurrent associations were for females (Figure 1a), might be related to gender differences in pubertal timing or peer relationships. Relative to males, females have an increased likelihood of attaining pubertal status earlier, with earlier pubertal onset increasing risk for affiliating with deviant peers (Ge, Brody, Conger, Simons, & Murry, 2002) and substance problems (Dick, Rose, Viken, &

Kaprio, 2000). However, while these pubertal influences for females may be primarily confined to mid-adolescence (Copeland et al., 2010), male-linked peer relationship processes, which increase males' risk for behavioral problems relative to females (Rose & Rudolph, 2006), may explain greater prospective influences of peer impairment for males.

The greater salience of adolescent ADHD symptoms for substance problems in females may have contributed to lack of significant prospective peer influence when these symptoms were considered (Figure 2). While overall variance in age-17 tobacco/marijuana outcomes explained was substantial in all models [e.g., $R^2=.35$ (females) or $R^2=.37$ (males); Figure 1a], it was greatest for females when including adolescent ADHD ($R^2=.47$; Figure 2). Conflicting findings regarding significance of the prospective peer influence for males, however, may have been due to limited power (i.e., Figure 2 included only one cohort, whereas Figures 1a–1c included both), rather than to inclusion of adolescent ADHD per se. That the peer impairment path estimate in the baseline model for Figure 2 was substantial for males, yet not significant due to a large standard error (see Appendix S2), suggests sample size may have been a factor.

The unanticipated lack of significant prospective paths between internalizing and later tobacco/marijuana problems likely resulted from inclusion of paths between substance problems at ages 14–17. With these stability paths removed (Appendix S3), a significant relationship between age-14 depression/anxiety and age-17 tobacco/marijuana problems was evident ($\beta=.16$, $p<.01$). Although mediational models involving childhood ADHD typically include paths between ADHD, mediator, and outcome, stability is often not considered. Consequently, not taking early substance use into account may result in overestimating mediation of ADHD effects by other factors, such as internalizing. Even so, while depression/anxiety did not mediate childhood ADHD effects, they may predict substance use disorders during adolescence, especially alcohol (Wolitzky-Taylor, Bobova, Zinbarg, Mineka, & Craske, 2012).

Limitations

Because teacher-rated data was limited to checklists and less complete than symptoms derived from structured clinical interviews of parents and adolescents, we were unable to incorporate teacher-reported ADHD. Moreover, although combining prospective and twin designs controls for many confounding factors (e.g., order of effects; genetic/environmental influences the twins share), causality cannot be conclusively proven. Non-shared experiences (e.g., specific peers the twins do not have in common) might still partially account for twin differences in substance problems across adolescence. Additionally, power to detect mediation by depression/anxiety may have been curtailed by studying adolescents, prior to onset of heaviest substance use. Similarly, although adolescent ADHD symptoms predicted increased tobacco/marijuana problems, by adulthood, heavy substance use may exacerbate attentional problems as well (Sibley et al., 2017). Additional research on the developmental unfolding of ADHD and substance problems into adulthood, including females as well as males, is needed.

Conclusion

Adolescent problems with tobacco and marijuana appeared consistent with causal influences of earlier use on subsequent progression. Correspondingly, because early use of tobacco is more common than that of marijuana, preventing adolescent smoking among those with more symptoms of ADHD should decrease problematic marijuana use (Lee, McClernon, Kollins, & Fuemmeler, 2017) and disorders (Biederman, Petty, Hammerness, Batchelder, & Faraone, 2012). Peer impairment may also mediate effects of childhood ADHD on substance problems during adolescence, especially marijuana. Efficacy of interventions among those with ADHD might be enhanced by targeted coping strategies for ADHD symptoms (particularly for females) and increasing opportunities to affiliate with prosocial peers, thereby lessening subsequent risk for substance problems.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Supported by National Institute on Drug Abuse grants R01DA038065 to IE, K01DA037280 to SW R37DA005147 and R01DA013240 to WI; and National Institute on Alcohol Abuse and Alcoholism grant R01AA009367 to MM. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors have declared that they have no competing or potential conflicts of interest.

References

- Bauermeister JJ, Shrout PE, Chavez L, Rubio-Stipec M, Ramirez R, Padilla L, et al. (2007). ADHD and gender: are risks and sequela of ADHD the same for boys and girls? *Journal of Child Psychology and Psychiatry*, 48, 831–839. [PubMed: 17683455]
- Biederman J, Petty CR, Hammerness P, Batchelder H, & Faraone SV (2012). Cigarette smoking as a risk factor for other substance misuse: 10-year study of individuals with and without attention-deficit hyperactivity disorder. *British Journal of Psychiatry*, 201, 207–214. [PubMed: 22844023]
- Brook DW, Brook JS, Zhang C, Cohen P, & Whiteman M (2002). Drug use and the risk of major depressive disorder, alcohol dependence, and substance use disorders. *Archives of General Psychiatry*, 59, 1039–1044. [PubMed: 12418937]
- Burt SA, McGue M, Krueger RF, & Iacono WG (2005). Sources of covariation among the child-externalizing disorders: informant effects and the shared environment. *Psychological Medicine*, 35, 1133–1144.
- Campbell SB, Halperin JM, & Sonuga-Barke EJS (2014). A developmental perspective on attention-deficit/hyperactivity disorder (ADHD) In Rudolph KD (Ed.), *Handbook of Developmental Psychology* (pp. 427–448). New York: Springer US.
- Canty A, & Ripley B (2016). *boot: Bootstrap functions (originally by angelo canty for s)*[Computer software manual].
- Copeland W, Shanahan L, Miller S, Costello EJ, Angold A, & Maughan B (2010). Outcomes of early pubertal timing in young women: a prospective population-based study. *American Journal of Psychiatry*, 167, 1218–1225.
- Crick NR, & Grotpeter JK (1995). Relational aggression, gender, and social-psychological adjustment. *Child Development*, 66, 710–722. [PubMed: 7789197]
- Dick DM, Rose RJ, Viken RJ, & Kaprio J (2000). Pubertal timing and substance use: associations between and within families across late adolescence. *Developmental Psychology*, 36, 180–189. [PubMed: 10749075]

- Elkins IJ, Malone S, Keyes M, Iacono WG, & McGue M (2011). The impact of attention-deficit/hyperactivity disorder on preadolescent adjustment may be greater for girls than for boys. *Journal of Clinical Child and Adolescent Psychology*, 40, 532–545. [PubMed: 21722026]
- Elkins IJ, McGue M, & Iacono WG (2007). Prospective effects of attention-deficit/hyperactivity disorder, conduct disorder, and sex on adolescent substance use and abuse. *Archives of General Psychiatry*, 64, 1145–1152. [PubMed: 17909126]
- Elkins IJ, Saunders GRB, Malone SM, Keyes MA, McGue M, & Iacono WG (2018). Associations between childhood ADHD, gender, and adolescent alcohol and marijuana involvement: A causally informative design. *Drug and Alcohol Dependence*, 184, 33–41. [PubMed: 29402677]
- Elkins IJ, Saunders GRB, Malone SM, Keyes MA, Samek DR, McGue M, et al. (2018). Increased risk of smoking in female adolescents who had childhood ADHD. *American Journal of Psychiatry*, 175, 63–70. [PubMed: 28838251]
- Erskine HE, Ferrari AJ, Nelson P, Polanczyk GV, Flaxman AD, Vos T, et al. (2013). Epidemiological modelling of attention-deficit/hyperactivity disorder and conduct disorder for the Global Burden of Disease Study 2010. *Journal of Child Psychology and Psychiatry*, 54, 1263–1274. [PubMed: 24117530]
- Fergusson DM, Woodward LJ, & Horwood LJ (1999). Childhood peer relationship problems and young people's involvement with deviant peers in adolescence. *Journal of Abnormal Child Psychology*, 27, 357–369. [PubMed: 10582837]
- Ge X, Brody GH, Conger RD, Simons RL, & Murry VM (2002). Contextual amplification of pubertal transition effects on deviant peer affiliation and externalizing behavior among African American children. *Developmental Psychology*, 38, 42–54. [PubMed: 11806701]
- Goodwin RD, Pacek LR, Copeland J, Moeller SJ, Dierker L, Weinberger A, et al. (2018). Trends in Daily Cannabis Use Among Cigarette Smokers: United States, 2002–2014. *American Journal of Public Health*, 108, 137–142. [PubMed: 29161058]
- Hechtman L, Swanson JM, Sibley MH, Stehli A, Owens EB, Mitchell JT, et al. (2016). Functional Adult Outcomes 16 Years After Childhood Diagnosis of Attention-Deficit/Hyperactivity Disorder: MTA Results. *Journal of the American Academy of Child and Adolescent Psychiatry*, 55, 945–952. [PubMed: 27806862]
- Humphreys KL, Katz SJ, Lee SS, Hammen C, Brennan PA, & Najman JM (2013). The association of ADHD and depression: mediation by peer problems and parent-child difficulties in two complementary samples. *Journal of Abnormal Psychology*, 122, 854–867. [PubMed: 24016021]
- Iacono WG, Carlson SR, Taylor J, Elkins IJ, & McGue M (1999). Behavioral disinhibition and the development of substance-use disorders: findings from the Minnesota Twin Family Study. *Developmental Psychopathology*, 11, 869–900.
- Keyes MA, Malone SM, Elkins IJ, Leland LN, McGue M, & Iacono WG (2009). The enrichment study of the Minnesota twin family study: increasing the yield of twin families at high risk for externalizing psychopathology. *Twin Research and Human Genetics*, 12, 489–501. [PubMed: 19803776]
- Kochel KP, Bagwell CL, Ladd GW, & Rudolph KD (2017). Do positive peer relations mitigate transactions between depressive symptoms and peer victimization in adolescence? *Journal of Applied Developmental Psychology*, 51, 44–54. [PubMed: 29104337]
- Lee C-T, McClernon FJ, Kollins SH, & Fuemmeler BF (2017). Childhood ADHD Symptoms and Future Illicit Drug Use: The Role of Adolescent Cigarette Use. *Journal of Pediatric Psychology*, jsx098-jsx098. doi: 10.1093/jpepsy/jsx098
- Looby A (2008). Childhood attention deficit hyperactivity disorder and the development of substance use disorders: valid concern or exaggeration? *Addictive Behaviors*, 33, 451–463. [PubMed: 18037571]
- McGue M, Osler M, & Christensen K (2010). Causal inference and observational research: The utility of twins. *Perspectives on Psychological Science*, 5, 546–556. [PubMed: 21593989]
- Molina BSG, Howard AL, Swanson JM, Stehli A, Mitchell JT, Kennedy TM, et al. (2018). Substance use through adolescence into early adulthood after childhood-diagnosed ADHD: findings from the MTA longitudinal study. *Journal of Child Psychology and Psychiatry*. doi: 10.1111/jcpp.12855

- Molina BSG, Pelham WE, Cheong J, Marshal MP, Gnagy EM, & Curran PJ (2012). Childhood attention-deficit/hyperactivity disorder (ADHD) and growth in adolescent alcohol use: the roles of functional impairments, ADHD symptom persistence, and parental knowledge. *Journal of Abnormal Psychology*, 121, 922–935. [PubMed: 22845650]
- Muthén LK, & Muthén BO (2015). Mplus statistical software version 7.31. Los Angeles, CA: Author.
- Pingault JB, Cote SM, Galera C, Genolini C, Falissard B, Vitaro F, et al. (2013). Childhood trajectories of inattention, hyperactivity and oppositional behaviors and prediction of substance abuse/dependence: a 15-year longitudinal population-based study. *Molecular Psychiatry*, 18, 806–812. [PubMed: 22733124]
- Raiker JS, Freeman AJ, Perez-Algorta G, Frazier TW, Findling RL, & Youngstrom EA (2017). Accuracy of Achenbach Scales in the Screening of Attention-Deficit/Hyperactivity Disorder in a Community Mental Health Clinic. *Journal of the American Academy of Child and Adolescent Psychiatry*, 56, 401–409. [PubMed: 28433089]
- Reich W (2000). Diagnostic interview for children and adolescents (DICA). *Journal of the American Academy of Child & Adolescent Psychiatry*, 39, 59–66. [PubMed: 10638068]
- Robins LN, Wing J, Wittchen HU, Helzer JE, Babor TF, Burke J, et al. (1988). The Composite International Diagnostic Interview. An epidemiologic instrument suitable for use in conjunction with different diagnostic systems and in different cultures. *Archives of General Psychiatry*, 45, 1069–1077. [PubMed: 2848472]
- Rose AJ, & Rudolph KD (2006). A review of sex differences in peer relationship processes: potential trade-offs for the emotional and behavioral development of girls and boys. *Psychological Bulletin*, 132, 98–131. [PubMed: 16435959]
- Rucklidge JJ (2010). Gender differences in attention-deficit/hyperactivity disorder. *Psychiatric Clinics of North America*, 33, 357–373. [PubMed: 20385342]
- Satorra A, & Bentler PM (2010). Ensuring Positiveness of the Scaled Difference Chi-square Test Statistic. *Psychometrika*, 75, 243–248. [PubMed: 20640194]
- Sibley MH, Pelham WE, Molina BS, Coxe S, Kipp H, Gnagy EM, et al. (2014). The role of early childhood ADHD and subsequent CD in the initiation and escalation of adolescent cigarette, alcohol, and marijuana use. *Journal of Abnormal Psychology*, 123, 362–374. [PubMed: 24886010]
- Sibley MH, Rohde LA, Swanson JM, Hechtman LT, Molina BSG, Mitchell JT, et al. (2017). Late-onset ADHD reconsidered with comprehensive repeated assessments between ages 10 and 25. *American Journal of Psychiatry*, 175, 140–149. [PubMed: 29050505]
- Sihvola E, Rose RJ, Dick DM, Korhonen T, Pulkkinen L, Raevuori A, et al. (2011). Prospective relationships of ADHD symptoms with developing substance use in a population-derived sample. *Psychological Medicine*, 1–9.
- Swanson EN, Owens EB, & Hinshaw SP (2014). Pathways to self-harmful behaviors in young women with and without ADHD: a longitudinal examination of mediating factors. *Journal of Child Psychology and Psychiatry*, 55, 505–515. [PubMed: 25436256]
- Tellegen A, & Waller NG (2008). Exploring personality through test construction: Development of the Multidimensional Personality Questionnaire In Boyle GJ, Matthews G & Saklofske DH (Eds.), *The SAGE handbook of personality theory and assessment*, vol 2: Personality measurement and testing (pp. 261–292). Thousand Oaks, CA: Sage.
- Vitulano ML, Fite PJ, Hopko DR, Lochman J, Wells K, & Asif I (2014). Evaluation of underlying mechanisms in the link between childhood ADHD symptoms and risk for early initiation of substance use. *Psychology of Addictive Behaviors*, 28, 816–827. [PubMed: 25222174]
- Wolitzky-Taylor K, Bobova L, Zinbarg RE, Mineka S, & Craske MG (2012). Longitudinal investigation of the impact of anxiety and mood disorders in adolescence on subsequent substance use disorder onset and vice versa. *Addictive Behaviors*, 37, 982–985. [PubMed: 22503436]
- Zhang Z, Zyphur MJ, & Preacher KJ (2009). Testing Multilevel Mediation Using Hierarchical Linear Models Problems and Solutions. *Organizational Research Methods*, 12, 695–719.

Key points:

- Despite established relationships of childhood ADHD with peer impairment, internalizing, and tobacco/marijuana use, few studies have examined mediation of ADHD effects on later substance problems by these factors.
- Direct effects of childhood ADHD on tobacco/marijuana problems in late adolescence, or indirect, through adolescent ADHD symptoms, were significant for female adolescents only.
- Peer impairment mediated ADHD effects on marijuana problems, particularly for males; depression and anxiety did not, when effects of earlier use were considered.
- Early substance problems, which prospectively mediated relationships of ADHD with later problems in both genders, were consistent with causal effects of early use.
- Targeting gender-sensitive interventions prior to mid-adolescence is warranted.

Figure 1a:
Mediation of Childhood ADHD Effects on Tobacco and Marijuana Problems (N=2,164)

Figure 1b:
Mediation of Childhood ADHD Effects on Tobacco Problems (N=2,164)

Figure 2:
Mediation of Childhood ADHD Effects on Tobacco and Marijuana Problems, Including Adolescent ADHD (N=881)

Table 1:

Descriptive Statistics For Observed Indicators of Latent Variables

Latent/Observed Variable	Source	Loading on Latent Variable ^a		Age 14		Age 14		Age 17	
		Age 14	Age 17	Mean (SD) or %		Gender Difference ^b		Mean (SD) or %	
				Males	Females			Males	Females
<i>Peer Impairment</i>									
Lack of Prosocial Peers	T	.61		50.0 (10.0)	48.4 (9.3)	F<M		—	—
Lack of Prosocial Peers	A	.48		50.0 (10.0)	47.3 (9.7)	F<M		—	—
Bullied by peers (combined sample) ^c	A	.38		13.9%	12.7%	ns		—	—
Victimized by peers (cohort 2 only) ^c	A	.56		50.0 (10.0)	51.5 (10.0)	F>M		—	—
<i>Depression/Anxiety</i>									
Trait Anxiety	A	.83	.89	50.0 (10.0)	53.2 (11.7)	F>M		55.9 (12.9)	57.4 (14.2)
Stress Reaction	A	.78	.75	50.0 (10.0)	53.2 (11.6)	F>M		49.9 (10.5)	54.0 (11.3)
Major Depression symptoms	P, A	.34	.38	0.4 (1.3)	0.7 (1.9)	F>M		0.6 (1.7)	1.3 (2.5)
<i>Tobacco/Marijuana Problems^d</i>									
1 Cigarette in Past 12 Months (%)	A	.88	.98	19.7%	15.3%	M>F		56.9%	39.8%
Tobacco Frequency (% weekly/daily use)	A	.82	.89	12.2%	9.7%	M>F		44.8%	29.5%
Nicotine Dependence symptoms	P, A	.76	.80	0.3 (1.0)	0.3 (1.1)	ns		0.8 (1.5)	0.5 (1.2)
1 Use of Marijuana (%)	A	.76	.71	11.3%	8.0%	ns		39.2%	30.5%
Marijuana Abuse/Dependence symptoms	P, A	.51	.52	0.1 (0.7)	0.1 (0.5)	ns		0.9 (2.1)	0.3 (1.2)

A=adolescent; P=parent; T=teacher; M=male; F=female; ns=not significant. Dashes indicate variables not included at age 17.

^aStandardized latent variable loadings are based on the model in Figure 1a, averaged across gender. Given the episodic nature of Major Depression symptoms, their lower loading compared to more stable internalizing indicators was expected.^bGender differences significant at $p<.05$ are indicated, based on t-tests (or χ^2) conducted on raw scores. Scale scores are presented as T-scores (mean=50; SD=10 for 14-year-old males), to facilitate interpretation (e.g., a 2-point difference between males and females corresponds to .2 SD).^cOnly one measure of being bullied or victimized was included in each model.^dQuantity/frequency variables are shown as categories; continuous measures were used in analyses.

Table 2:

Significant^a Mediation Pathways From Childhood ADHD Symptoms (ADHD11) to Tobacco and Marijuana Problems at Ages 17–18

Model	Indirect Pathway to Substance Problems	Females		Males	
		Indirect Effect	95% CI	Indirect Effect	95% CI
Figure 1a <i>Childhood ADHD to Age 17 Tobacco/Marijuana</i>	ADHD11 → TOBMAR14 → TOBMAR17 ^b	.05	(.04, .07)	.06	(.05, .08)
Figure 1c <i>Childhood ADHD to Age 17 Marijuana Only</i>	ADHD11 → PEER14 → TOBMAR17	.03	(.01, .05)	.07	(.04, .10)
Figure 2 <i>Childhood ADHD to Age 17 Tobacco/Marijuana, Including Adolescent ADHD Symptoms</i>	ADHD11 → PEER14 → MAR17	.04	(.01, .07)	.11	(.07, .14)
	ADHD11 → TOBMAR14 → TOBMAR17	.07	(.05, .10)	.07	(.05, .10)
	ADHD11 → Adolescent ADHD → TOBMAR17	.08	(.04, .12)	— ^c	—

TOB=Tobacco Problems; MAR=Marijuana Problems; PEER=Peer Impairment; CI = Confidence Interval.

^aIndirect effects shown above were significant because CIs do not include zero.

^bIndirect effects through age-14 tobacco and marijuana problems separately were similar to those for both substances combined.

^cBecause the Adolescent ADHD→TOBMAR17 path was not significant for males; the associated pathway does not apply.