


Risk Factors for Depression in Adolescents With ADHD: The Impact of Cognitive Biases and Stress

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Abstract

Objective: Youth diagnosed with ADHD are at heightened risk of depression. However, many do not develop depression. Individuals with specific cognitive biases are more likely to develop depression yet it remains untested whether these vulnerability-stress models apply to depression risk in youth with ADHD. **Method:** We examined whether interpretation and attention biases moderated the relation between stressful life events and depressive symptoms in a sample of adolescents ($M_{age} = 14.42$) with ADHD ($n = 59$) and without ADHD ($n = 36$). **Results:** Youth with ADHD experienced more stressful life events compared with those without ADHD. Interpretation biases moderated the association between stress and depressive symptoms in youth with and without ADHD. Attention biases moderated the association between stress and depressive symptoms in the non-ADHD youth only. **Conclusion:** These results enhance our understanding of vulnerability for depression in adolescence with ADHD and inform targeted prevention and treatment models during this critical developmental juncture. (*J. of Att. Dis.* XXXX; XX(X) XX-XX)

Keywords

ADHD, depression, stress, cognitive biases, adolescence, risk

Major depressive disorder (MDD) is one of the most common mental illnesses, with an estimated lifetime prevalence of roughly 16% (Kessler et al., 2005; Kessler et al., 2003). Research indicates that rates of depression are relatively low in childhood, but increase as much as sixfold from early to late adolescence (Hankin et al., 1998; Kessler, Avenevoli, & Merikangas, 2001). The early onset of depression during childhood and adolescence is associated with many psychosocial problems, including an increased risk of substance abuse and suicide (Hammen, Brennan, Keenan-Miller, & Herr, 2008).

One group that is at particularly high risk of developing depression is youth with Attention-deficit/hyperactivity disorder (ADHD). ADHD is one of the most commonly diagnosed disorders in childhood, with prevalence estimates ranging from 4% to 9% (Centers for Disease Control, 2010; Kessler et al., 2006; Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007; Wilens, Biederman, & Spencer, 2002). The co-occurrence of ADHD and MDD is well documented (Meinzer, Pettit, & Viswesvaran, 2014) and a recent meta-analysis indicates that children with ADHD are at significantly higher risk of developing depression in their lifetime (Meinzer et al., 2013). For example, Biederman et al. (2008) followed children and adolescents with and without ADHD for 5 years and

found that youth with ADHD were 2.5 times more likely to develop MDD by adolescence compared with those without ADHD. Similarly, Chronis-Tuscano et al. (2010) conducted a longitudinal study of 4- to 6-year-old children with and without ADHD and followed them until they turned 18 years. They found that youth with ADHD, compared with those without ADHD, were 4 times more likely to develop depression or dysthymia and 3 times more likely to attempt suicide (Chronis-Tuscano et al., 2010). In addition, children and adolescents with co-occurring ADHD and MDD have significantly more impairment in their social and academic functioning (Blackman, Ostrander, & Herman, 2005) and have more severe courses of psychopathology and higher rates of long-term impairment than youth with either disorder alone (Daviss, 2008; Miller, Nigg, & Faraone, 2007).

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Importantly, there is a window of opportunity to intervene and potentially prevent the development of MDD because ADHD is typically identified and diagnosed in childhood, before the dramatic increase in rates of depression that occurs during adolescence (Kessler, Berglund, Demler, & Wang, 2003). The majority of research to date that has examined the risk of depression among those with ADHD has focused on familial risk factors. Indeed, numerous studies have shown that offspring of depressed parents are at an increased risk of later depression (e.g., Hammen, Burge, Burney, & Adrian, 1990). Although there is likely a genetic contribution to the development of depression among these youth (Biederman et al., 2008; Chronis-Tuscano et al., 2010), there are a number of individual and environmental risk factors that can be identified and more readily modified (Meinzer et al., 2014). For example, peer problems or parent-child difficulties have been associated with depressive outcomes among youth with ADHD (Daviss, Diler, & Birmaher, 2009; Humphreys et al., 2013). In addition, perceptions of low self-competency have been associated with higher depressive symptoms in ADHD youth (McQuade, Hoza, Waschbusch, Murray-Close, & Owens, 2011; McQuade et al., 2014). However, further research is needed to understand specific risk factors that may be associated with an increased risk of depression in youth with ADHD.

One such risk factor that may help identify youth at risk of depression is information processing biases. According to cognitive models of depression risk (Abramson, Metalsky, & Alloy, 1989; Gotlib & Joorman, 2010; Mathews & MacLeod, 2005), information-processing biases, including biases in attention and interpretation, can increase risk of the development and maintenance of depression. One of the most common interpretation biases examined in relation to depression risk is an individual's inferential style. A negative inferential style, also called attributional style, describes the tendency to attribute negative life events to stable (persistent over time) and global (likely to affect many areas of life) factors and to infer negative self-implications and future consequences. Researchers have shown that individuals with a negative inferential style are more likely to become depressed when a negative event occurs (Abramson et al., 1989). There is evidence that these biases predict increases in depressive symptoms and the onset of major depressive episodes during adolescence and adulthood (Alloy et al., 2006; Jacobs, Reinecke, Gollan, & Kane, 2008; Scher, Ingram, & Segal, 2005; Shapero, McClung, Bangasser, Abramson, & Alloy, 2017). In addition, individuals at risk of depression show attentional biases to negatively valenced stimuli (e.g., sad faces; Clark, Beck, & Alford, 1999). Research highlights that individuals with depression, or those at familial risk of depression, have biased attention to sad faces (Gibb, Benas, Grassia, & McGeary, 2009; Gibb et al., 2016a; Harrison & Gibb, 2015;

Romens & Pollak, 2012). However, the direction of this bias in youth is unclear, with some research suggesting that depressed adolescents differentially attend toward sad faces (e.g., Duque & Vazquez, 2015; Hankin, Gibb, Abela, & Flory, 2010) whereas other studies find evidence of attentional avoidance of sad faces (e.g., Gibb et al., 2009; Gibb et al., 2016b; Harrison & Gibb, 2015). In addition, research suggests that attention away from negative emotions may be a risk factor for the development of depression during adolescence (Gibb et al., 2009; Price et al., 2016).

A key feature of cognitive models of depression is their vulnerability-stress hypothesis. Specifically, these information-processing biases are hypothesized to moderate the impact of stressful life events on depression (Monroe & Simons, 1991). That is, according to these models, individuals with more biased information processing should be particularly vulnerable to depression following the occurrence of stressful life events. A large corpus of research has indicated that these negative interpretation biases interact with stressful life events to predict depression (Liu, Kleiman, Nestor, & Cheek, 2015; Morris, Ciesla, & Garber, 2008). In addition, research has begun to examine whether stress affects attentional biases (Beevers & Carver, 2003; Jenness, Hankin, Young, & Smolen, 2016), but research has yet to utilize a stress-vulnerability model to understand whether stress moderates the relationship between attention bias and depression in youth. Of note, this research typically focuses on accumulated stress and not experimental research that examines situational stress at the moment of testing. Taken together, stress, both directly and in combination with vulnerability models, affects the development of depression.

Despite the burgeoning of research on cognitive vulnerabilities and stress in youth at risk of depression in general, researchers have yet to apply the vulnerability-stress models of depression to adolescents with ADHD. The need to identify which youth with ADHD are at higher risk in developing depression is needed to inform preventive measures. There is reason to expect that cognitive vulnerability-stress models would hold in youth with ADHD and help to identify who is at greatest risk. Youth with ADHD experience more problems in academic, family, and peer domains than youth without ADHD. It has been well documented that ADHD is associated with academic problems and academic failures (Barbarelli, Katusic, Colligan, Weaver, & Jacobsen, 2007; Faraone et al., 1993), as well as peer relation problems, including social skill deficits and experiences of peer rejection (Hoza, 2007; Hoza et al., 2005; Murray-Close et al., 2010). Several recent investigations have shown that ADHD is associated with higher levels of parenting and family stress (Graziano, McNamara, Geffken, & Reid, 2011; Musser, Karalunas, Dieckmann, Peris, & Nigg, 2016). Therefore, these youth experience more stressors that may interact with underlying vulnerabilities to

increase risk of depression. Some investigations of adults with ADHD have found preliminary evidence that cognitive factors, such as dysfunctional attitudes or negative automatic thoughts, are associated with depressive symptoms (Knouse, Zvorsky, & Safren, 2013; Mitchell, Benson, Knouse, Kimbrel, & Anastopoulos, 2013). One study compared cognitive style differences in youth with ADHD versus those with ADHD and a comorbid mood disorder. This examination found that youth with a comorbid mood disorder had a more depressogenic attributional style (Schmidt, Stark, Carlson, & Anthony, 1998). These studies provide initial evidence that vulnerability stress models may apply to these youth and may, therefore, help explain the increased risk of depression. Alternatively, it could be the case that cognitive deficits, such as weaker working memory or attention regulation, associated with ADHD may limit the deleterious effects of these cognitive biases. Given this, research that directly examines the impact of stress on these underlying vulnerabilities is needed to determine if these cognitive risk factors affect the relationship between stress and depression among those with ADHD.

Therefore, the goal of this study was to provide a preliminary test of cognitive vulnerability-stress models of depression in a cross-sectional study of adolescents with and without ADHD. We hypothesized that youth with ADHD would have the same levels of cognitive biases (interpretation or attentional biases) as youth without ADHD, but would experience more stress than youth without ADHD. In addition, we hypothesized that stress would amplify the relation between these underlying cognitive biases and depressive symptoms in children with ADHD, just as it does in children without ADHD. Because youth with ADHD are hypothesized to experience increased stress, they would present with increased rates of depression. In addition, because we also collected data on psychopathology in both parents, we were able examine whether these risk factors were associated with adolescent depression over and above risk conferred by parental depression alone, which is a well-known risk factor for depression in youth (Weissman et al., 2006).

Method

Participants

The study conducted at the Massachusetts General Hospital (MGH) during a 1-year period. We recruited adolescents with ADHD and without ADHD. Participants with ADHD were recruited from several clinics at MGH including the Child and Adolescent Outpatient Department, the Child Cognitive and Behavioral Therapy Program, and the Learning and Education Assessment Program. In addition, some participants with ADHD were recruited from community clinics and through online advertisement to increase

ecological validity. A three-tiered system of recruitment was used to ensure recruitment of cases with and without ADHD. The first tier was the participant's family's self-identification as having been previously diagnosed (or not) with ADHD. The second tier consisted of the telephone screen, in which the parent reported (or not) that the child met criteria for at least six symptoms of inattention or hyperactivity. The third tier was to confirm these diagnoses with a structured diagnostic interviews, described below, during the assessment process, which was administered to both the child and parent once they came to the office.

Potential participants completed a screening by phone to determine eligibility, which required adolescents: be between 11 and 18 years old, have been diagnosed with ADHD by a mental health practitioner, and have a parent or primary caregiver willing to participate in the study. Parents also needed to endorse the presence of at least six of the nine symptoms of their child's inattention or hyperactivity. Parents reported that original diagnoses of ADHD was made by a diverse body of mental health practitioners including neuropsychological evaluations (42%), pediatricians (25%), psychiatrists (21%), psychologists (6%), other physicians (e.g., neurologist; 4%), and 2% by the school.

Comparison adolescents without ADHD were a subsample of participants in a prospective longitudinal study of children at high and low risk of mood disorders conducted at MGH. Children in this study had originally been recruited irrespective of child ADHD, and had been included in the original prospective study based either upon having a parent meeting criteria for MDD or based upon the absence of a mood disorder in either parent. The children had been followed up using the identical methods to those used with the participants with ADHD. The subsample of adolescents included as controls in the present study were between 11 and 18 years old and did not meet criteria for past or current symptoms of ADHD in diagnostic interviews, as described below.

Adolescents from both groups were not eligible for the study if there was no parent/primary caregiver available to participate; the adolescent had symptoms of psychosis, diagnosis of bipolar disorder, or were currently actively suicidal; had a severe developmental disorder; or the parent or adolescent was unable to read or speak English or could not complete assessments for any other reason. Adolescents were not excluded if they had any other comorbid diagnosis. We did not exclude probands based on any parental diagnosis; however, controls had been drawn from a sample where parents did not have a bipolar I disorder.

The sample consisted of 95 youth, 59 with ADHD and 36 without ADHD ($M_{age} = 14.42$, $SD = 1.83$, range = 11-18), of whom 64% were male and 65% were Caucasian. Twenty one percent of participants had family annual incomes falling below US\$50k, 27% between US\$50k-US\$100k, 20% between US\$100k-US\$150k, and 29% above US\$150k. Eighteen percent of participants were

eligible for free school lunch, a measure of financial need that accounts for the number of dependents being supported on the family's income. The final sample consisted of 62% that had a diagnosis of ADHD. Of these youth, 80% were currently prescribed stimulant medication, which did not differ based on any demographic factors. In addition, 60% of the total sample was classified as high risk based on a history of parental depression. Participants with ADHD did not differ from those without ADHD based on risk status ($\chi^2 = .16, p = .69$) or age ($t[93] = 1.29, p = .20$) but were more likely to qualify for free or reduced lunch, $t(93) = 3.72, p < .001$. In addition, participants with ADHD, compared with those without ADHD, were significantly more likely that to be male ($\chi^2 = 5.06, p = .02$).

Measures

Adolescent psychopathology. The Schedule for Affective Disorders and Schizophrenia for School-Aged Children (K-SADS-E; Orvaschel, Lewinsohn, & Seeley, 1995) is a semistructured diagnostic interview that assesses current and past *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.; *DSM-IV-TR*; American Psychiatric Association [APA], 2000) axis I psychopathology in youth. We administered the K-SADS-E to adolescents and their parents to assess the youth's lifetime history of all Axis I disorders and treatment history, as well as current diagnoses. The same interviewer administered the K-SADS-E first to the parent and then to the youth, and then created summary ratings (e.g., Braaten et al., 2001; Cantwell, Lewinsohn, Rohde, & Seeley, 1997; Martel, Markon, & Smith, 2017). To maintain fidelity to the K-SADS-E, we used the interviewer's summary ratings based on his or her "best-estimate" clinical judgment from interviewing both parent and child. This is consistent with recent findings from the Multimodal Treatment Study of Children with ADHD, which found that the combination of parent and self-reports using an "or" rule optimized the sensitivity and specificity of diagnosis (Sibley et al., 2017). The K-SADS-E diagnostic interviews have good interrater and retest reliability (Orvaschel et al., 1995). The interviewer (B.G.S) was an advanced postdoctoral psychology fellow who had experience interviewing adolescents and was trained to reliability on the K-SADS with a perfect diagnostic reliability ($K = 1.00, p < .001$) and high item-level correlation ($ICC = .88, p < .001$). In addition, all diagnostic decisions were reviewed with a senior child psychologist (D.H.B) with extensive experience conducting, training, and supervising raters on the K-SADS-E and the SCID (structured clinical interview for DSM).

Familial risk status. The structured clinical interview for *Diagnostic and Statistical Manual of Mental Disorders* (SCID; 4th ed.; *DSM-IV*; APA, 1994; First, Spitzer, Gibbon,

& Williams, 1995) is a semistructured clinical interview used to diagnose adult psychopathology. For the current project, we used only the depression module to identify the risk status based on parental depression of each adolescent. Therefore, the presenting parent was asked to report first on their own history of depression and then on the other biological parent of the adolescent. Adolescents who had at least one parent who met criteria for MDD in their life were classified as being at high risk of depression. This interview was administered after the KSADS-E, so that the interviewer would not know about parents' depression history during the KSADS-E.

Interpretation bias. The Adolescent Cognitive Style Questionnaire (ACSQ; Hankin & Abramson, 2002) presents the adolescent with 12 negative hypothetical events in achievement, interpersonal, and appearance domains, and asks the youth to make inferences about the causes (internal-external, stable-unstable, and global-specific), consequences, and self-worth implications of the hypothetical event. For each item, adolescents use 7-point Likert-type scales to rate the internality, stability, and globality of the cause of the event, the consequences of each event, and possible negative self-implications of the event. The ACSQ has demonstrated excellent internal consistency, good test-retest reliability and stability, a factor structure consistent with the hopelessness theory (Hankin & Abramson, 2002), and good validity (Alloy et al., 2012). Consistent with prior work, scores on each of the stability, globality, consequences, and self-domains within the ACSQ are summed and then averaged with higher scores indicating a more negative cognitive style (range = 10.14-46.14; $M = 24.68, SD = 7.97$). The overall ACSQ negative composite exhibited good internal consistency in this study ($\alpha = .96$).

Attention bias. We used a modified dot-probe task (MacLeod, Mathews, & Tata, 1986) to assess attention biases to facial displays of emotion. We administered this computerized task using E-Prime, and presented pairs of facial expressions (on youth) that contained one emotion (sad, happy, or angry) and one neutral photograph from the same actor taken from a standardized stimulus set (Tottenham et al., 2009). We used a photograph from each of the actors (16 male and 16 female) to create the sad-neutral, happy-neutral, and angry-neutral stimulus pairs (96 pairs total). We presented each stimulus pair in random order over the course of two blocks, with a rest in between blocks. Consistent with previous studies (Gibb et al., 2009; Gotlib, Kasch, et al., 2004; Gotlib, Krasnoperova, Yue, & Joormann, 2004), we presented stimuli for 1,000 milliseconds and then both pictures disappeared and a dot replaced one of the pictures (either emotional or neutral). We asked the participants to indicate as quickly as possible using a response box the location of the dot (left vs. right side of the screen). In each

pair, the emotional face was presented with equal frequency on the left and right side of the screen and the probe occurred with equal frequency in the location of the emotional and neutral faces. We excluded trials in which the participant incorrectly identified the side of the dot. In addition, to account for response time inconsistencies, we excluded trials with response times that were too fast (150 milliseconds) or too slow (1,500 milliseconds). We calculated average attention bias scores (Mogg, Bradley, & Williams, 1995) for each emotion type (sad, happy, angry) by subtracting the mean response time for trials in which the probe replaced the emotional face from mean response times for trials in which the probe replaced the neutral face. Positive bias scores represent preferential attention toward the emotional faces, whereas negative scores indicate attentional avoidance of the emotional faces. Based on the literature documenting attention bias to sad faces associated with depression, the current study focused on participants' attention biases to sad faces.

Stressful life events. The Adolescent Life Events Questionnaire (ALEQ; Hankin & Abramson, 2002), is designed to assess the occurrence of a broad range of negative or stressful events often reported by adolescents, including familial (e.g., "you fought with your parent[s] over personal goals, desires, or choice of friends/boyfriend/girlfriend"), peer (e.g., "you had an argument or fight with a friend[s]"), and school/achievement events (e.g., "you did poorly on or failed a test or school project"). Adolescents and their parents separately completed the 63-item ALEQ and indicated whether events occurred in the adolescent's life in the previous 6 months. That is, this measure assesses accumulated stress and not situational stress at the time of the assessment. Prior studies have supported the reliability and validity of the ALEQ (Hankin, 2008; Hankin & Abramson, 2002; Rudolph & Flynn, 2007). The parent and child reports of live stress were moderately correlated, $r(98) = .45, p < .001$, so we combined them to form an overall score, which is consistent with prior studies (Jenness et al., 2016). Thus, the sum of the number of types of events reported by adolescents and their parents was used with higher scores indicating more experiences of stressful life events (range = 2-67; $M = 30.20, SD = 12.82$).

Depressive symptoms. The Children's Depression Inventory (CDI; Kovacs, 1985) is a self-report questionnaire that contains 27 items to assess affective, behavioral, and cognitive symptoms of depression in youth aged 7 years to 17 years. Each item is rated on a scale from 0 to 2; items are summed for a total score (ranging from 0 to 54), with higher scores indicating more depressive symptoms (range = 0-33; $M = 9.61, SD = 7.23$). The CDI has good reliability and validity (Klein, Dougherty, & Olino, 2005). Internal consistency in the sample was $\alpha = .88$.

Procedure

After completing the telephone screen, adolescents, and their parents were invited into the lab. After signing informed consent/assent, adolescents completed self-report questionnaires evaluating current depressive symptoms, interpretation bias, and the occurrence of stressful life events. In addition, adolescents completed a computerized attention bias task that lasted roughly 10 min. Parents completed a questionnaire assessing the occurrence of stressful events that occurred to the adolescent. Both parents and adolescents completed a semistructured diagnostic interview to assess the history of psychopathology in the adolescent. In addition, the participating parent completed a semistructured diagnostic interview assessing their own history of depression and served as informant in a semistructured diagnostic interview assessing depression in the child's other parent. The entire visit lasted 2 to 3 hr, and adolescents were given breaks as needed.

Results

Descriptive Analyses

The final sample consisted of 95 participants, of whom 59 had a diagnosis of ADHD and 56 were classified as at high familial risk based on the presence of a lifetime history of MDD in at least one parent. Of those with ADHD, 56% were classified as primarily inattentive, 2% were classified as primarily hyperactive, and 42% were classified as a combined subtype. Chi-square analyses determined that sex was not significantly associated with a specific subtype ($\chi^2 = 0.00, p = .98$). A total of 27 participants met criteria for a lifetime major depression episode (MDD) with only five meeting criteria for a current episode. Chi-square analyses determined that ADHD group status was not significantly associated with a lifetime history of MDD ($\chi^2 = 1.09, p = .29$) but familial risk status was significantly associated with a lifetime history of MDD ($\chi^2 = 8.58, p = .003$). The average age of onset for ADHD was 6.42 years ($SD = 2.28$ years) and the diagnosis of ADHD predated that of MDD among those youth who met criteria. We used independent samples *t* tests, ANOVAs, or chi-square analyses to assess whether demographic variables were associated with depressive symptoms. These tests showed that there was no significant relation between participants' depressive symptoms and their sex ($t[93] = 0.53, p = .67$), race ($\chi^2 = 97.85, p = .43$), age, $F(93) = 1.81, p = .10$, or whether the family qualified for free or reduced lunch ($\chi^2 = 26.95, p = .31$). We calculated bivariate correlations among the main study variables (Table 1). As can be seen in the table, higher interpretation bias was associated with more depressive symptoms and higher levels of stress. In addition, higher levels of stress were associated with more depressive symptoms. Attention bias to sad faces was not significantly associated with interpretation bias or any other study variable.

Table 1. Correlation and Descriptive Statistics of Main Variables.

	1	2	3	4
1. ACSQ	—	-.12	.36***	.61***
2. Attention bias		—	-.05	-.20
3. ALEQ			—	.52***
4. CDI				—
<i>M</i>	17.45	-16.19	29.96	9.28
<i>SD</i>	6.79	53.11	12.81	6.97

Note. ACSQ = Adolescent Cognitive Style Questionnaire—negative composite score; attention bias = dot probe attention bias to sad faces; ALEQ = Adolescent Life Events Questionnaires—total combined; CDI = Children's Depression Inventory—self-report total.

* $p < .05$. ** $p < .01$. *** $p < .001$.

We conducted several independent sampled t tests to characterize the differences between the main study variables and the classification of adolescents with ADHD or being at high familial risk (Table 2). Adolescents who were classified at high familial risk had marginally higher negative interpretation biases. The majority of the youth with ADHD were currently prescribed stimulant medication (80%) and almost all of these youth had a history of treatment for ADHD (95%). Adolescents with ADHD had significantly higher levels of overall stress compared with youth without ADHD. Follow-up analyses were conducted to explore the domains of stress that differs between the groups (Table 3). Adolescents with ADHD had significantly higher family, academic, and peer stress than those without ADHD, with the highest effect in the academic domain. In addition, among those with ADHD, we explored whether the subtype was associated with the main study variables. Given the small number of individuals with the hyperactive subtype, we used independent sampled t tests to explore differences between those with primarily inattentive versus combined subtypes only. Adolescents with primarily the primarily inattentive subtype had significantly higher academic stress ($t = 2.22, p = .03$) but did not differ based on depressive symptoms, cognitive biases, or other types of stress.

Primary Analyses

Next, we used hierarchical regression analyses to determine whether information processing biases (interpretation or attention biases) moderated the relation between stressful life events and depressive symptoms, and whether this relation was further moderated by youth's ADHD status. Following the procedure outlined by Aiken and West (1991), we mean centered the predictor variables (cognitive biases and stressful life events) prior to analysis. In Step 1, we entered risk status and a lifetime history of MDD to account for variation based on a history of parental depression and a

history of depression. In Step 2, we entered main effects of cognitive bias, stressful life events, and ADHD status. In Step 3, we entered all two-way interaction terms between each of the predictors entered. In Step 4, the three-way interaction between ADHD status, stressful life events, and cognitive biases was entered. Separate models were run for interpretation and attention bias.

First, we evaluated whether attention bias interacted with stress to predict depressive symptoms, and whether this effect differed based on ADHD status. A significant three-way interaction emerged between ADHD status, attention bias, and stress, controlling for family risk and depression history ($t = 2.31, p = .02$). Follow-up analysis examined the interaction between attention bias with regard to sad faces and stress in association with self-reported symptoms of depression among those with and without ADHD. As indicated in Table 4, attention bias moderated the relation between stress and depressive symptoms in youth without ADHD ($t = 2.43, p = .02$), but not among youth with ADHD ($t = 0.89, p = .37$). We present follow-up simple slope analyses in Figure 1. Among youth without ADHD, individuals who differentially attended away from sad faces had significantly more depressive symptoms when under higher than average stress compared with when they had lower than average stress ($t = 3.30, p = .002$). Among youth without ADHD and attention bias toward sad faces did not differ in depression symptoms when in high or low stress contexts ($t = 0.26, p = .79$). Although, as noted above, the attention bias by stress interaction among youth with ADHD was not significant, the main effects of attention bias ($t = 3.57, p = .001$), and stress ($t = 5.84, p = .000$), were significant indicating that greater attentional avoidance of sad faces and higher levels of stress were both uniquely related to higher levels of depressive symptoms in these youth.

Second, we evaluated whether interpretation bias interacted with stress to predict depressive symptoms, and whether this effect differed based on ADHD status. The three-way interaction between ADHD status, interpretation bias, and stress, controlling for family risk and depression history was marginally significant ($t = 1.85, p = .06$). Follow-up analysis examined the interaction between interpretation bias and stress with self-reported depression symptoms among those with and without ADHD. As indicated in bottom half of Table 4, interpretation bias moderated the relation between stress and depressive symptoms in both youth with ADHD ($t = 2.04, p < .05$) and without ADHD ($t = 2.12, p < .05$). Thus, the interpretation bias by stress interactions was relatively stronger for those without ADHD. We conducted follow-up simple slope analyses to characterize this interaction. As seen in Figure 2, the relation between stress and depressive symptoms was stronger for youth with high, compared with low, levels of interpretation bias among those with ADHD ($t = 5.73, p < .001$) and among those

Table 2. Independent Sample *t* Tests.

	ADHD		<i>t</i> test	Risk		<i>t</i> test
	ADHD	No ADHD		Risk	No risk	
	(<i>n</i> = 59)	(<i>n</i> = 36)		(<i>n</i> = 56)	(<i>n</i> = 36)	
ACSQ	17.69 (6.87)	17.06 (6.73)	0.44	18.38 (7.08)	15.67 (6.15)	1.94 [†]
Attention bias	-18.13 (56.98)	-12.97 (46.60)	0.47	-10.79 (52.27)	-22.80 (56.02)	1.02
ALEQ	34.00 (12.18)	23.14 (10.93)	4.46***	31.65 (11.62)	27.06 (14.53)	1.59
CDI	10.20 (6.29)	7.71 (7.84)	1.59	9.11 (7.07)	9.25 (7.12)	0.09

Note. Risk = family history of depression; ACSQ = Adolescent Cognitive Style Questionnaire—negative composite score; attention bias = dot probe attention bias to sad faces; ALEQ = Adolescent Life Events Questionnaires—total combined; CDI = Children's Depression Inventory—self-report total. [†]*p* < .08. **p* < .05. ***p* < .01. ****p* < .001.

Table 3. Independent Sample *t* Tests for ALEQ.

	ADHD	No ADHD	<i>t</i> test
	(<i>n</i> = 59)	(<i>n</i> = 36)	
Family	14.53 (5.65)	12.02 (5.90)	2.03*
Academic	9.31 (3.23)	5.55 (3.50)	5.22***
Peer	6.47 (4.56)	4.00 (3.16)	3.12**

Note. ALEQ = Adolescent Life Events Questionnaires—combined. **p* < .05. ***p* < .01. ****p* < .001.

without ADHD ($t = 4.32, p < .001$). Main effects indicate that interpretation bias was associated with depression symptoms among the whole sample. In contrast, higher levels of stress were significantly associated with depression symptoms only among participants with ADHD.^{1,2}

Discussion

Although there is ample evidence that youth diagnosed with ADHD are at significantly heightened risk to develop depression, less is known about which of these youth are at increased risk whereas others remain protected. The current study was the first to apply a vulnerability-stress model of cognitive biases and life stress in a sample of adolescents with ADHD. Consistent with our hypotheses, the results from this study support a direct relationship of cognitive biases and life stress with symptoms of depression in youth with ADHD. In addition, among youth with ADHD, as well as those without, interpretation biases moderated the relationship between life stress and depression symptoms such that those who had high negative interpretation biases exhibited the highest level of depressive symptoms when confronted with proximal life stress. In addition, findings held after taking into account family risk, suggesting that interpretation biases and life stress are important modifiable risk factors that may be amenable to change through treatment over and above familial risk for depression. These

findings were similar to those without ADHD, suggesting that interpretation bias-vulnerability models are an important indicator of risk in youth with and without ADHD.

Difficulties with attention are a central component of ADHD, however, no research to date has examined whether biases in attention to emotional stimuli are a risk factor for depression among these youth. When looking only at youth with ADHD, those who exhibited attentional avoidance of sad faces had higher levels of depression symptoms. These findings are consistent with some recent research suggesting that cognitive control deficits may be associated with depression symptoms through attention bias (Everaert, Grahek, & Koster, 2017) and provides additional evidence to the literature on biased attention to negative emotions in youth with psychopathology (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van Ijzendoorn, 2007; Pine et al., 2005). Although these findings are inconsistent with the adult literature in which depressed adults exhibit an attentional bias toward sad faces, it is consistent with a growing body of research suggesting that currently depressed youth and those at risk of depression due to a family history of MDD exhibit attentional avoidance of sad faces (Gibb et al., 2009; Gibb et al., 2016b; Harrison & Gibb, 2015; but see also Hankin et al., 2010). A similar pattern has been observed in infants of depressed mothers (Diego et al., 2004; Field, Pickens, Fox, Gonzalez, & Nawrocki, 1998; Striano, Brennan, & Vanman, 2002) in which this attentional avoidance has been interpreted as an emotion regulation strategy (Bistricky, Ingram, & Atchley, 2011; Termine & Izard, 1988). Specifically, consistent with Gross' (2014) model of emotion regulation in which attentional deployment is proposed as one of the earliest emotion regulation strategies to develop, attentional avoidance of sad faces may help reduce negative effect in the short term although there is evidence that it increases depression risk in the longer term (Gibb et al., 2009). Therefore, it could be the case that adolescents with ADHD who have higher depressive symptoms avoid negative emotional stimuli as a means of emotion regulation. However, we did not find this

Table 4. Main Effect and Interaction Models Between Cognitive Biases Life Stress, an Depressive Outcomes.

Dependent variable = CDI							
Step	Variable	ADHD			No ADHD		
		B	t	ΔR^2	B	t	ΔR^2
1	Risk	-0.11	0.78	.112*	-0.16	0.89	.155
	MDD history	0.35	2.56*		0.41	2.37*	
2	Attention bias	-0.35	3.57**	.420***	0.06	0.38	.114
	ALEQ	0.58	5.84***		0.40	2.10*	
3	Attention bias \times ALEQ	-0.24	0.89	.007	-0.78	2.43*	.127*
Step	Variable	B	t	ΔR^2	B	t	ΔR^2
1	Risk	-0.11	0.83	.101	-0.16	0.93	.149
	MDD history	0.33	2.43*		0.41	2.36*	
2	ACSQ	0.51	5.34***	.587***	0.53	3.34**	.861**
	ALEQ	0.43	4.65***		0.17	1.04	
3	ACSQ \times ALEQ	0.75	2.04*	.031*	1.29	2.12*	.073*

Note. CDI = Children’s Depression Inventory—self-report total; risk = family history of depression; MDD history = lifetime history of MDD; attention bias = dot probe attention bias to sad faces; ALEQ = Adolescent Life Events Questionnaires—combined; ACSQ = Adolescent Cognitive Style Questionnaire—negative composite score; MDD = major depressive disorder.

* $p < .05$. ** $p < .01$. *** $p < .001$.

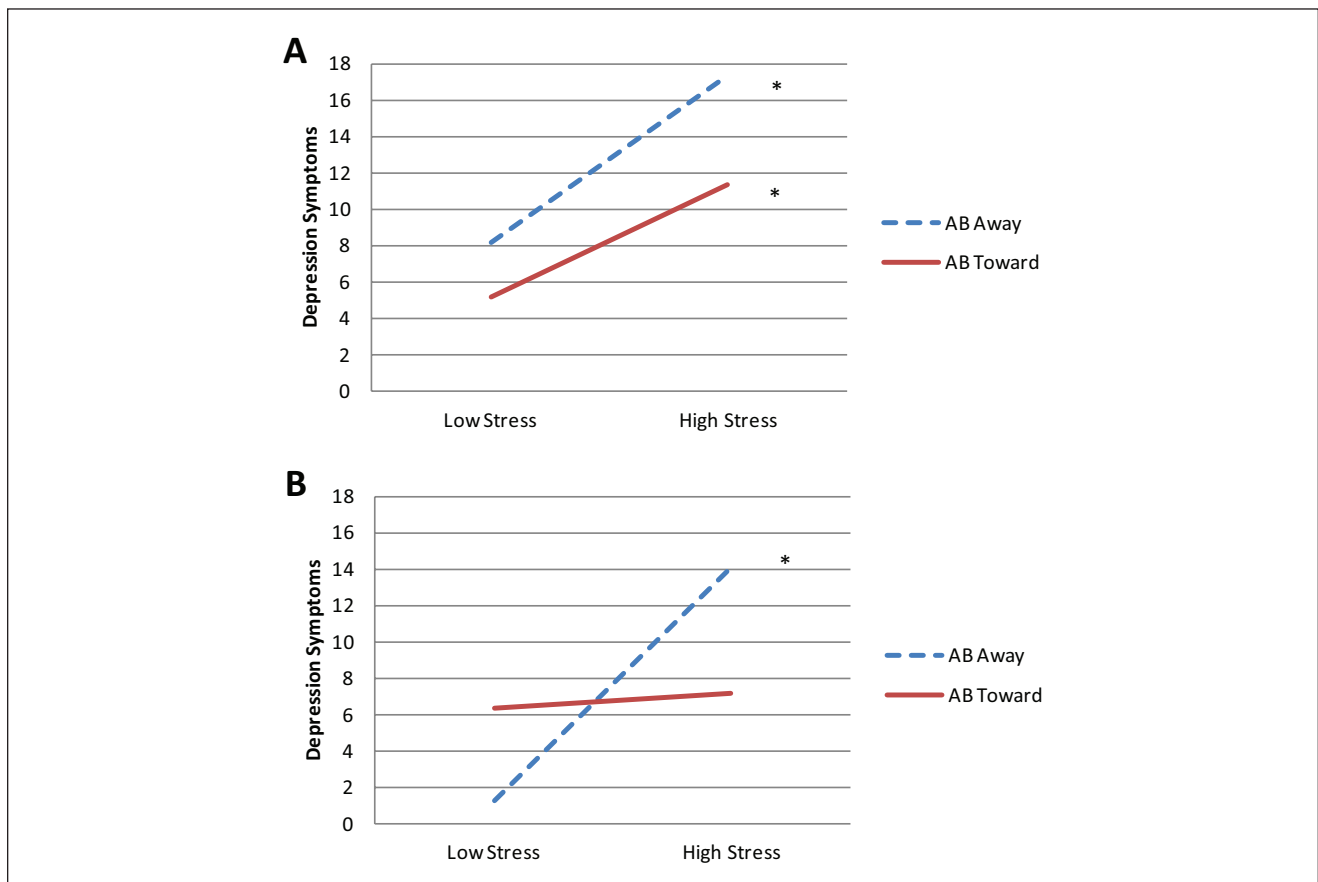


Figure 1. Interaction of attention bias and stress on depression symptoms.

Note. Figure 1A represents youth with ADHD and Figure 1B represents youth without ADHD. Figure presents independent variables at 1 standard deviation above (H) and below (L) the mean. Stress = Adolescent Life Events Questionnaire; AB = attention bias to sad faces.

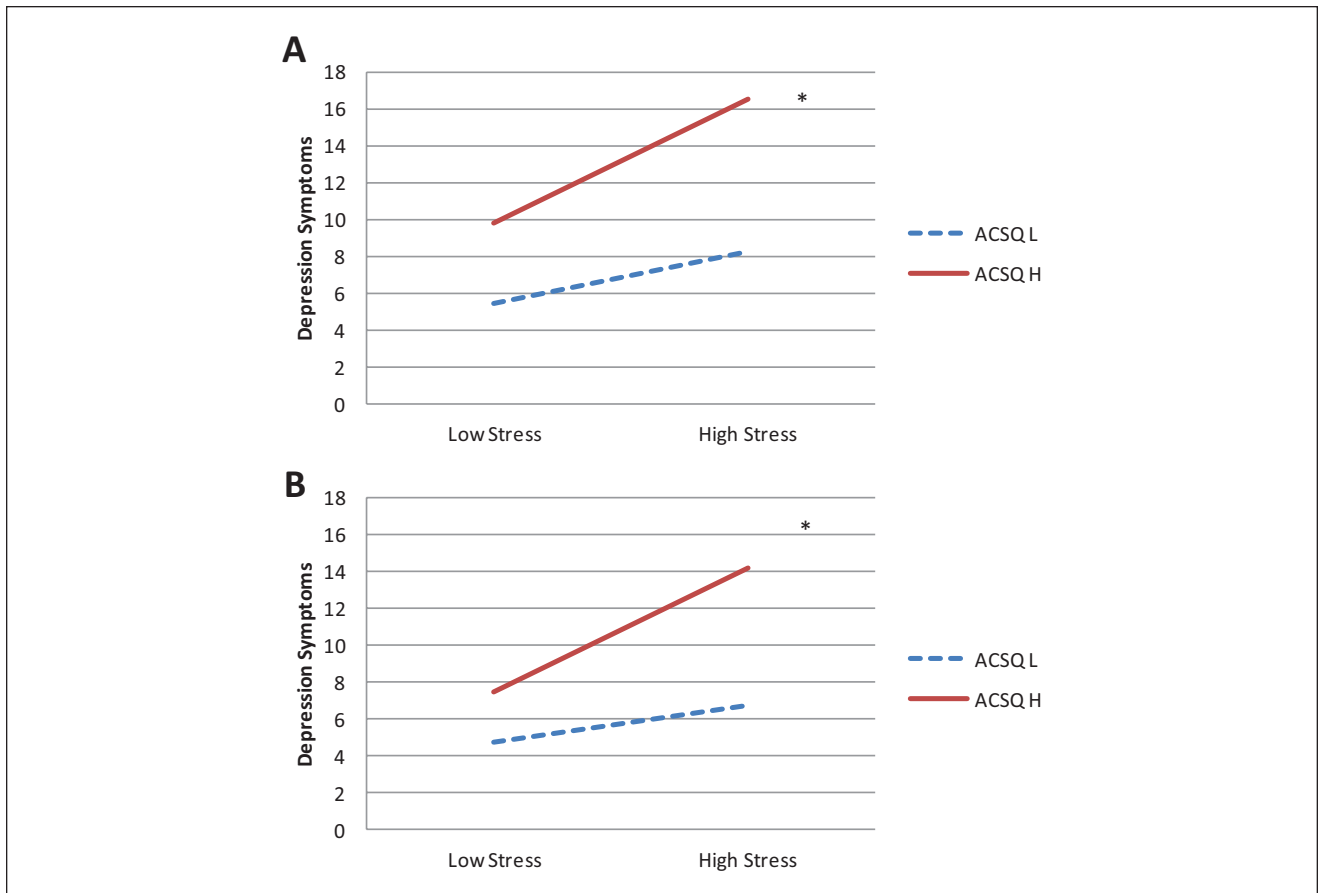


Figure 2. Interaction of interpretation biases and stress on depression symptoms.

Note. Figure 2A represents youth with ADHD and Figure 2B represents youth without ADHD. Figure presents independent variables at 1 standard deviation above (H) and below (L) the mean. Stress = Adolescent Life Events Questionnaire; ACSQ = Adolescent Cognitive Style Questionnaire.

same pattern in youth without ADHD. In the youth without ADHD, we found an attention bias by stress interaction. Further research is needed to provide strong evidence that indeed, ADHD-related attentional biases confer a risk to the development of depression.

In addition, few researchers have applied an attention bias-stress model to understanding risk of depressive symptoms (Beevers & Carver, 2003). We found that differential attention away from sad faces moderated the relationship between stress and depression symptoms among youth without ADHD. To our knowledge, this study was the first to apply the vulnerability-stress model of attention bias in adolescents. These findings suggest that attention bias away from sad faces amplifies the relation between life stress and depression symptoms among those with high levels of stress. However, this interaction appears to have a cross-over effect, such that those with a bias away from sad faces had the lowest symptoms when they were under low stress. This may suggest that youth who attend away from sad faces are more influenced by their stressful context. Interestingly, attention bias was not directly associated with

depressive symptoms in youth without ADHD, yet was associated with depressive symptoms among those with high stress. Although speculative, attention biases to emotional stimuli may be a dormant vulnerability to psychopathology that may need to be activated by increases in stress. Indeed, research to date has provided mixed results on whether attention bias toward or away from sad faces is associated with depression symptoms among youth. There may indeed be a nonlinear relationship between biased attention such that too much attention toward or away from sad faces is associated with symptoms of depression or it may be that stress activates these underlying biases to produce maladaptive outcomes. Among youth with ADHD, although there was no stress by attention bias interaction, life stress and attention bias away from sad faces were uniquely associated with depressive symptoms. Further research is needed to identify whether stress is an integral component of this information processing bias in relation to depression.

Previous research has documented that youth with ADHD experience heightened stress. However, a dearth of

research directly assesses the experiences of stressful life events compared with youth without ADHD. As expected, youth with ADHD in our sample had significantly more stressful life events than those without ADHD, whether relying on reports by the adolescents themselves or their parents. In addition, when examined more specifically, adolescents with ADHD had more family, academic, and peer stressors than those without ADHD. Furthermore, it appears that the largest difference between these groups was in experiences of academic stress. These findings are consistent with previous research documenting an association between ADHD and academic problems and academic failures (Barbatesi et al., 2007; Faraone et al., 1993), which is expected given the executive functioning and cognitive difficulties associated with ADHD (Frazier, Demaree, & Youngstrom, 2004; Wilcutt, Doyle, Nigg, Faraone, & Pennington, 2005). As hypothesized, youth with ADHD did not differ in cognitive biases from youth without ADHD. However, they did experience significantly more stress, and these experiences of stress were directly associated with symptoms of depression. Therefore, one interpretation of our findings is that one possible reason youth with ADHD are at elevated risk of depression is not that they have higher negative cognitive biases, but that they experience more stress. This stress activates these vulnerabilities, which is associated with depression symptoms. This highlights two important pathways for preventive intervention: acting at the level of stressors to reduce experiences of stress or to develop better ways to manage them, or acting at the level of vulnerabilities to reduce cognitive biases, either through cognitive-behavioral therapy or cognitive bias modification (Micco, Henin, & Hirshfeld-Becker, 2014).

The current study had several strengths. We utilized a clinically referred and verified sample of youth with ADHD. Furthermore, instead of comparing youth with ADHD to supranormal individuals, we compared them to a sample enriched with youths at risk of depression based upon familial vulnerability (having a parent with depression). High familial risk was associated with a lifetime history of a depressive episode and was not differentially present among those with and without ADHD in our sample. Thus familial risk did not confound our findings, and matching the level of risk between samples allowed us to examine whether the risk factors associated with the development of depression differed between the two groups. Furthermore, results from the current study remained after taking into account this risk status as well as a lifetime history of depression. In addition, we assessed cognitive biases using multiple methods. Much of the prior literature either examines interpretation or attention biases separately with many fewer studies incorporating an assessment of both cognitive biases. Indeed, limited research has identified an association with self-reported and behaviorally assessed information processing biases (e.g., White, Suway, Pine, Bar-Haim,

& Fox, 2011). We did not find an association between attention and interpretation biases, yet both conferred additional risk of symptoms of depression. Finally, we utilized multiple informants to gather information about stress. Although prior research has found support for the differential reporting of adolescent stress (Daryanani et al., 2015), both parents and adolescents with ADHD reported higher levels of stress than those without ADHD. Further research utilizing larger clinical samples of patients with ADHD and utilizing multimethod and multi-informant designs can be useful in furthering our understanding of the various risk factors for the development of depression.

Findings from the current study should take into account several limitations. First, this was a cross-sectional study that assessed the association between cognitive biases, life stress, and symptoms of depression. Importantly, all diagnoses of ADHD predated enrollment in the study and the onset of MDD. Although reporting of life stress was retrospective in nature and cognitive biases are theorized to be relatively stable by this point, and covarying presence of earlier (lifetime) major depressive episodes did not affect our results, further prospective studies are needed to identify whether these vulnerability-stress models are temporally predictive of depressive symptoms in youth with ADHD. In addition, prospective longitudinal studies can assess whether cognitive biases are a risk factor for the onset of major depression. The current study examined risk factors by assessing who is at the highest risk of depression utilizing a moderation analysis based on the vulnerability-stress model. Longitudinal research may examine whether cognitive biases mediate the relationship between ADHD and MDD, which this study was unable to examine given the cross-sectional study design. This could help clarify the mechanism by which youth with ADHD go on to develop MDD. It is important to examine risk utilizing both moderator and mediator factors, to increase our understanding of how risk factors work together or offer independent information to identify high-risk individuals (Kraemer, Stice, Kazdin, Offord, & Kupfer, 2001).

Second, although the overall sample size was adequate, replication using a larger sample is needed to confirm these findings and further examine more fine-grained research questions. For example, we found that youth with ADHD had significantly more academic, family, and peer stress than youth without ADHD. However, an examination of whether the vulnerability-stress models were specific to particular types of stressors or particular aspects of vulnerability was precluded by the sample size. Third, sample characteristics may influence findings. Although research has found support that stimulants may be protective against the development of depression (Biederman, Monuteaux, Spencer, Wilens, & Faraone, 2009; Chang, D'Onofrio, Quinn, Lichtenstein, & Larsson, 2016; Daviss, Birmaher, Diler, & Mintz, 2008), the majority of the current sample

with ADHD (80%) was taking stimulant medication, and these vulnerability-stress models continued to provide support for this risk model. Indeed, findings may be different for adolescents with ADHD that are not treated with medication. That is, given the possible protective effects of stimulants against depression, outcomes may be pronounced with an untreated sample. However, it is unclear whether the association between cognitive biases and depression would be consistent. Therefore, results may generalize largely to treated samples with further research needed to understand how cognitive biases are associated with depressive symptoms among nonmedicated youth. The current study did not utilize teacher report in the diagnostic process nor obtained cognitive abilities testing. Teacher report would increase the confidence in the diagnoses of ADHD, however, original diagnoses were made by an outside practitioner that was confirmed by study staff and the majority of youth with ADHD were under the care of a mental health provider to treat symptoms. Cognitive abilities may differentially affect the relationship between biases and symptoms. Thus, future research could incorporate measures of working memory, attentional control, and overall IQ to understand whether these factors mitigate the impact of cognitive biases.

Finally, several recent investigations have expressed concern over the assessment of attention biases and their association with psychopathology (Brown et al., 2014; Gibb, McGeary, & Beevers, 2016a; Stevens, Rist, & Gerlach, 2011; Waechter, Nelson, Wright, Hyatt, & Oakman, 2014). These studies note that there may be limited reliability in assessing attentional biases using reaction time indices of bias, and that the use of eye-tracking equipment increases the utility of this measurement. This concern over reliability may be increased among a sample of participants who have attention deficits. To reduce assessment error we accounted for variation in responses that were too fast or too slow. However, further studies should employ more advanced designs that incorporate eye-tracking to capture a more fine-grained understanding of attention deployment and biases.

Taken together, the current study confirms that cognitive biases and stress are associated with depression symptoms in youth with ADHD. The risk factors for the development of depression found in the general population are also of substantive risk in those with ADHD. In addition, these youth experience more stress that activates these vulnerabilities. This suggests that it may be important clinically to assess cognitive biases in adolescents with ADHD to determine which youth may differentially be affected by life stress that is likely to increase as they progress through adolescence (Ge, Lorenz, Conger, Elder, & Simons, 1994). Identifying and intervening with these modifiable vulnerability factors may reduce the adolescent's risk of developing MDD during these pivotal developmental years. If confirmed, our results suggest that preventative care to reduce cognitive biases could be a part of the standard of

treatment for youth with ADHD that have high cognitive biases, as they are more likely to experience stressful life events than youth with high biases without ADHD. Alternatively, another aim of intervention could be to preemptively anticipate and reduce the likelihood of stressful life events or to increase coping skills to manage stressful events in these youth. More research is needed to identify modifiable risk factors in these youth and to develop effective interventions to both prevent and treat depression in adolescents with ADHD.

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Notes

1. Given the association between behavioral disorders, ADHD, and subsequent depression (Loeber, Burke, Lahey, Winters, & Zera, 2000), we conducted a sensitivity analysis to determine if controlling for a lifetime history of oppositional defiant and conduct disorder influenced the outcomes presented. The addition of these two diagnoses did not change the outcomes presented as all significant and nonsignificant findings remained.
2. We also ran sensitivity analysis in the ADHD sample to determine if medication status influenced the outcomes presented. The additional covariate of medication status did not change the outcomes presented.

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