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Attention Deficit-Hyperactivity Disorder in Adolescence Predicts Onset of Major Depressive Disorder through Early Adulthood

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Abstract

Background—The aim of this study was to examine the prospective relationship between a history of attention deficit/hyperactivity disorder (ADHD) assessed in mid-adolescence and the onset of major depressive disorder (MDD) through early adulthood in a large school-based sample. A secondary aim was to examine whether this relationship was robust after accounting for comorbid psychopathology and psychosocial impairment.

Method—1,507 participants from the Oregon Adolescent Depression Project completed rating scales in adolescence and structured diagnostic interviews up to four times from adolescence to age 30.

Results—Adolescents with a lifetime history of ADHD were at significantly higher risk of MDD through early adulthood relative to those with no history of ADHD. ADHD remained a significant predictor of MDD after controlling for gender, lifetime history of other psychiatric disorders in adolescence, social and academic impairment in adolescence, stress and coping in adolescence, and new onset of other psychiatric disorders through early adulthood (hazard ratio, 1.81; 95% confidence interval, 1.04, 3.06). Additional significant, robust predictors of MDD included female gender, a lifetime history of an anxiety disorder, and poor coping skills in mid-adolescence, as well as the onset of anxiety, oppositional defiant disorder, and substance use disorder after mid-adolescence.

Conclusions—A history of ADHD in adolescence was associated with elevated risk of MDD through early adulthood and this relationship remained significant after controlling for psychosocial impairment in adolescence and co-occurring psychiatric disorders. Additional work is needed to identify the mechanisms of risk and to inform depression prevention programs for adolescents with ADHD.

Keywords

Adolescence; ADHD; MDD

Attention-deficit/hyperactivity disorder (ADHD) affects up to 9% of children,[1] the majority (50–80%) of whom continue to display symptoms and psychosocial impairment in adolescence.[2–5] A growing body of evidence suggests that individuals with ADHD also

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experience unipolar depressive disorders at rates higher than would be expected by chance, even after accounting for overlapping diagnostic criteria.[6,7] Among youth with ADHD, reported rates of concurrent comorbid major depressive disorder (MDD) range from 12%–50%.[6,8–11] Similar findings have been reported among clinic-referred adults with ADHD.[12,13] Comorbid ADHD-MDD is associated with higher levels of substance use[14] and psychosocial impairment than either disorder in isolation.[6,8,9,12]

In addition to cross-sectional co-occurrence, a number of studies have examined the longitudinal relation between ADHD and MDD. Some investigations in referred, predominately male samples failed to find a significant association between ADHD and subsequent MDD.[15–17] Other studies from independent research groups, using male, female, and mixed gender referred samples, reported that youth with ADHD were at significantly elevated risk of MDD over follow-up periods ranging from 5–13 years.[8,12,18–20] To our knowledge, these findings have not yet been replicated in a non-referred sample. The purpose of the present study was to address this gap in the knowledge base by examining whether ADHD prospectively predicted MDD onset in a non-referred sample of adolescents.

The mixed pattern of longitudinal findings, as well as the high level of impairment seen among individuals with comorbid ADHD-MDD, highlights the need to examine whether an association between ADHD and MDD is robust or diminishes after controlling for potential confounding variables Determining whether an association between ADHD and MDD is robust after controlling for potential confounding variables may lay the groundwork for research into etiologic processes and suggest novel routes to prevention. Demoralization,[6] shared genetic diatheses,[21] shared psychological diatheses (e.g., impaired reward responsivity, emotion regulation)[22,23] and epiphenomenal comorbidity (i.e., the notion that ADHD-MDD comorbidity is explained by their co-occurrence with a third disorder),[24] represent potential explanations of ADHD-MDD comorbidity, although empirical findings do not support the demoralization model[6] and are mixed on epiphenomenal comorbidity.[8,24] In summary, research tends to suggest that youth with ADHD are at risk of developing MDD, but little work has examined whether this relationship remains significant when controlling for other psychiatric disorders and psychosocial risk factors. In addition, past work in this area has utilized referred samples in which individuals with comorbid presentations are likely to be overrepre-sented. As a result, comorbidity estimates between ADHD and MDD may be inflated and may not be representative of the general population. Finally, few studies have followed adolescents into adulthood. These limitations highlight the need for independent replication and extension of findings among non-referred youth.

The primary aim of the current study was to examine the prospective relation between ADHD history assessed in mid-adolescence and MDD onset through early adulthood. If a significant relation was found, a secondary aim was to examine whether ADHD remained a significant predictor of MDD onset when controlling for other variables such as comorbid psychiatric disorders and psychosocial impairment. Several aspects of the present study extend existing research on ADHD-MDD comorbidity. First, participants were drawn from a large, non-referred school-based sample, the Oregon Adolescent Depression Project (OADP), rather than a referred sample. Second, an array of potential risk and protective factors were assessed in adolescence, which allowed us to examine whether ADHD was a robust predictor of MDD onset. Finally, participants were recruited in mid-adolescence and followed prospectively up to age 30. During the course of the study, up to four separate structured clinical interviews were completed to identify the onset and course of psychiatric disorders. This allowed us to examine whether a history of ADHD increased the risk of MDD through early adulthood (a key onset period for MDD).[25]

Based on past findings that ADHD predicts MDD onset,[8,12,18] we hypothesized that adolescents with ADHD would be at higher risk of later MDD as compared to adolescents without ADHD. Based on findings that a demoralization model did not account for a persistence of depressive symptoms[6] and comorbid psychopathology did not account for the elevated risk of depression,[8] we hypothesized that ADHD would remain a significant predictor of MDD onset even after controlling for indicators of demoralization (social and academic impairment), stressful events and coping, and co-occurring psychiatric disorders.

Method

Participants

OADP participants were randomly selected from nine high schools in western Oregon. After a description of the study, written informed consent was obtained. This research was conducted as approved by the Institutional Review Boards. A total of 1709 adolescents (mean age= 16.6 years, SD = 1.2 years; 53% women) completed an initial (T1) assessment. At T1, a subset of parents (n=281) were interviewed with the KSADS for the purpose of establishing agreement between parent report and adolescent report of psychiatric disorders, which allowed us to use parent report to validate adolescent report of ADHD. Approximately one year later, 1507 (88%) returned for a second evaluation (T2; mean age = 17.7 years, SD = 1.2 years; 54% women). Differences between the sample and the larger population from which it was selected, and between participants and those who declined to participate or dropped out of the study before T2, were small.[26] At age 24 (mean age= 24.6 years, SD=0.61 years), all participants with a history of Axis I psychiatric disorder (n = 644) by T2 and a random sample with no history of psychiatric disorder (n = 457) were invited to participate in a third (T3) evaluation. Of the 1101 participants selected for a T3 interview, 941 (85%; 57% women) completed T3. The T2 diagnostic groups did not differ on the rate of participation at T3. At age 30 (mean age= 30.1 years, SD=0.71 years), all T3 participants were invited to participate in a T4 evaluation. Of the 941 T3 participants, 816 (87%) completed the T4 diagnostic interview. The 816 T4 participants included 484 (59%) women. Among those invited to T3 and T4 assessments, women were more likely than men to complete evaluations, $X^2 > 5.99$, $p < .05$. Participation did not differ as a function of other demographic variables or previous diagnoses, including a diagnosis of ADHD at T1.

The reference sample for the current investigation included the 1507 participants (54% women, 92% non-Hispanic White) who completed T1 and at least one follow-up assessment. Of these, 1222 (81%) had no lifetime history of MDD at T1 and no lifetime history of bipolar disorder at any assessment wave. Four-hundred eighteen (34%) of the 1222 also completed a supplemental ADHD assessment via mail near the time of the T4 interview.

Diagnostic status

Participants were interviewed with a version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) at T1, T2, and T3 that combined features of the Present Episode and Epidemiologic versions.[27,28] In conjunction with the K-SADS, the Longitudinal Interval Follow-Up Evaluation (LIFE)[29] was used to evaluate the presence and course of disorders since the previous diagnostic interview at T2 and T3. T4 diagnostic assessments were based on the Structured Clinical Interview for Axis I DSM-IV Disorders–Non-Patient Edition (SCID-NP),[30] with the LIFE also used to evaluate disorder presence and course since T3. Symptom endorsements were evaluated in conjunction with DSM-III-R criteria[31] at T1 and T2 and DSM-IV criteria[32] at T3 and T4. Interviews at T3 and T4 were conducted by telephone, which provides comparable validity to face-to-face interviews.[33,34]

Dichotomously-coded variables were created to represent the lifetime presence of ADHD, MDD, any anxiety disorder (ANX), conduct disorder (CD), oppositional defiant disorder (ODD), and substance use disorder (SUD) at the T1 assessment, as well as the new onset of these disorders after the T1 assessment. Participants were coded as positive for a new onset disorder if they met lifetime diagnostic criteria for that disorder at any of the follow up assessment waves (i.e., T2, T3, or T4).

At T1, a subset of participants' parents (n=281) were interviewed with the K-SADS. There was moderate-good agreement between parent and adolescent report for ADHD (kappa = .51),[35] which lends support to the validity of adolescent-reported ADHD in the remainder of the sample.

T1 psychosocial measures

The following measures of psychosocial impairment were developed from items administered to adolescents at the T1 assessment: *Academic Impairment* (7 items, α= .68), *Family Social Impairment* (8 items, α= .77), and *Friend Social Impairment* (7 items, α= .72). Prior research in the OADP has supported the factor structure and internal consistency of the three measures.[36]

Loneliness—An 8-item version of the UCLA Loneliness Scale[37] was used to measure adolescents' feelings of solitude, disconnection, and lack of closeness. Internal consistency (α = .78) was adequate.

Coping—Coping skills assessed the ways in which adolescents coped with stressful situations, using 17 items originally selected from the Self-Control Scale,[38] the Antidepressive Activity Questionnaire,[39] modified by Parker and Brown,[40] and the Ways of Coping Questionnaire.[41] Internal consistency was adequate (α= .76).

Stress—This construct assessed the occurrence of 14 negative major life events to self in the year preceding T1 in adolescents. Events were selected from the Schedule of Recent Experiences[42] and the Life Events Schedule.[43]

T4 ADHD Assessment

A subset (n=418) of the 1222 participants with no T1 MDD completed the Conners' Adult ADHD Rating scale (CAARS)[44] near the time of the T4 interview. Research has supported the test-retest reliability and validity of the CAARS in distinguishing individuals with ADHD from healthy controls.[45] The DSM-IV total symptoms score from the CAARS was used (α= .97).

Analytic Strategy

Logistic regression was used to examine cross-sectional associations between lifetime ADHD and lifetime MDD at T1 in the full sample (n=1507). In prospective analyses, Cox proportional hazards models were used to examine T1 predictors of subsequent MDD onset among the 1222 participants (602 women) with no T1 history of MDD. Cox proportional hazard models take into account the length of follow-up and permit the inclusion of participants lost to attrition. The probability of developing MDD was expressed as a hazard ratio (HR) with a 95% confidence interval (CI). A HR of one indicates equivalence in the hazard rate of MDD onset across values of the predictor variable. A HR greater than one indicates the hazard rate of MDD onset increases as values of the predictor variable increase, whereas a HR of less than one indicates the hazard rate of MDD onset decreases as values of the predictor variable increase. The proportional hazards assumption was tested in each model by including a Time X Predictor interaction term. When the assumption was not met,

the predictor, time variable, and the Time X Predictor interaction term were retained in the model.[46]

A series of four Cox proportional hazards models was conducted with MDD onset as the dependent variable. The first model included T1 lifetime ADHD; the second model added gender and other lifetime psychiatric disorders at T1; the third model added T1 social and academic impairment; and the fourth model added new onset of psychiatric disorders after T1. New onset of psychiatric disorder was added to the model to determine whether an association between ADHD and subsequent MDD was robust after controlling for their association with a third disorder (epiphenomenal comorbidity). Ancillary analyses were conducted among the subset (n=418) of participants who completed the T4 ADHD assessment to examine whether an association between T1 ADHD and subsequent MDD onset was robust after controlling for the presence of continued ADHD symptoms in young adulthood.

Given the stratified sampling procedure used at T3 (i.e., all participants with a history of Axis I psychiatric disorder by T2 and a random sample with no history of psychiatric disorder were invited to participate in the T3 evaluation), weights reflecting the probability of selection for the T3 follow-up were used in analyses. Cox proportional hazards models including the weighting variable were run in Mplus, Version 6.1.[47] Collinearity diagnostics were run for multivariate models. All tolerance values exceeded 0.33 and no variance inflation exceeded 3.01. These values fall well within recommended ranges.[48] Thus, no multicollinearity was evident. Missing data on T1 predictor variables was minimal: One participant had missing data on T1 Academic Impairment and three participants had missing data on the T1 Stress variable. Missing T1 data was modeled using maximum likelihood estimation.

Results

Cross-Sectional Associations at T1

T1 lifetime prevalence rates of psychiatric disorders by T1 ADHD status are reported in Table 1. The rates of externalizing disorders were lower and the rate of MDD was higher than the rates reported in some epidemiologi-cal studies of adolescents,[49,50] but similar to others.[51] Of the 40 (2.7%) participants with a positive history of ADHD, 10 (25%) reported taking medication to treat ADHD. The mean onset age of ADHD was 5.25 years (SD=1.43 years). Three (7.5%) of the 40 participants with lifetime ADHD met current diagnostic criteria for ADHD at T1.

In contrast to our expectations, the association between lifetime ADHD and lifetime MDD at T1 was not statistically significant (OR = 1.07; 95 CI 0.49, 2.36). Consistent with past research, participants with a positive history of ADHD were significantly more likely to have a positive history of SUD, CD, and ODD, as compared to those with no history of ADHD.

Risk of MDD Onset

Of the 1222 participants with no T1 history of MDD, the numbers and unweighted percentages of participants who developed new onset psychiatric disorders after the T1 assessment were as follows: MDD (n=309, 25.29%), SUD (n=244, 19.97%), ANX (n=106, 8.67%), CD (n=12, 0.98%), and ODD (n=12, 0.98%). Age of new onset ODD ranged from 14.75 years to 17.66 years (mean age=16.33 years, SD=11.66 months). There were no new onsets of ADHD after T1.

As hypothesized, T1 lifetime ADHD significantly predicted later MDD onset (Table 2, model 1). The un-weighted rate of MDD onset after T1 was 43.75% among participants with a positive history of ADHD (n = 32) and 24.78% among participants with no history of ADHD (n = 1190). Median time to MDD onset was 52.01 months among participants with a history of ADHD and 58.79 months among those with no history of ADHD. All other T1 risk factors (gender, ANX, SUD, coping, loneliness, stress, and family and friend support) significantly predicted MDD onset in univariate models, with the exceptions of ODD, CD, and academic impairment (ps > .05).

As shown in Table 2, ADHD remained a significant predictor of MDD onset after gender and T1 psychiatric disorders were entered as predictors (model 2), after loneliness, coping skills, life stress and social and academic impairment were added as predictors (model 3), and after new onset psychiatric disorders were added as predictors (model 4). The inclusion of all covariates led to a 2.41% reduction in the HR for MDD. Several other variables remained significant predictors in the final model, including gender, T1 ANX, and T1 coping skills. The HR for gender (0.51) indicates men, as compared to women, were at lower risk for MDD onset. New onset of ODD, ANX, and SUD also were significant predictors of MDD onset in the final model.

In ancillary analyses, we examined whether the predictive effect of T1 ADHD on MDD onset remained significant after controlling for ADHD symptoms in early adulthood as measured by the CAARS. Data for this analysis were available for 478 participants, 16 (3.35%) of whom met criteria for T1 ADHD. ADHD symptom scores at T4 were significantly associated with T1 ADHD, $t(476) = 2.83$, $p < .01$, and with MDD onset between T1-T4, $t(476) = 6.36$, $p < .001$. A Cox proportional hazards model including all predictors in model 4 of Table 2 indicated that the presence of T1 ADHD predicted MDD onset in this subsample at a nonsignificant trend level, HR=1.89, 95 CI =.95– 3.78, $p = .07$. When T4 ADHD symptom score was added as a predictor, the HR for T1 ADHD decreased by 41.75%, HR=1.52, 95 CI =.076–3.07, $p > .20$, suggesting that a sizeable portion of the association between T1 ADHD and MDD onset in this subsample was accounted for by continued ADHD symptoms in adulthood.

Discussion

Adolescents from a non-referred, school-based sample were tracked prospectively into young adulthood to investigate the impact of ADHD on risk of MDD onset. As hypothesized, a positive history of ADHD by mid-adolescence was associated with significantly elevated risk of later MDD onset, even after controlling for other comorbid psychiatric disorders, poor coping skills, social and academic impairment, and gender. These findings are consistent with the majority of prior studies conducted on referred samples from independent research groups.[8,12,18–20] To our knowledge, this is the first empirical demonstration of a prospective relation between ADHD and MDD in a non-referred sample. Confirmation in non-referred samples verifies that the elevated risk of MDD among youth with ADHD is not due to biases associated with referred samples.

Consistent with Biederman et al.,[6] support was not obtained for a demoralization model. Therefore, although adolescents with ADHD experience impairment in school, academic, and social settings, ADHD remained a significant predictor of subsequent MDD after controlling for such impairment. Similarly, the association between ADHD and MDD onset remained significant after controlling for the presence of other psychiatric disorders by mid-adolescence or new onset disorders at later assessment waves. One prior report concluded that ADHD may be associated with MDD via its co-occurrence with anxiety disorders.[24] The present findings are inconsistent with that view, as controlling for anxiety disorders had

minimal impact on the association between ADHD and MDD. Rather, preliminary evidence from a subsample of the present study's participants suggests that continued ADHD symptoms into young adulthood may account for a substantial portion of the association between ADHD and MDD onset. The persistence of ADHD symptoms represents a promising avenue for future research on the mechanisms linking ADHD and MDD into adulthood. Additionally, recent findings from cross-sectional studies suggest poor emotion regulation and reward responsivity may mediate the relationship between ADHD and depressive symptoms.[22,23] Future work is encouraged to examine these mediators using prospective designs.

Also consistent with past research, gender, history of anxiety disorder, and coping skills were significant T1 predictors of subsequent MDD onset. A large literature has demonstrated a higher risk of MDD among adolescent and young adult women, as compared to men,[52,53] and among individuals with anxiety disorders.[54,55] In addition, the new onsets of anxiety, ODD, and substance use disorder after T1 also significantly and robustly predicted MDD onset. These findings indicate that the emergence of clinical levels of anxiety and externalizing problems after mid-adolescence increased the risk of MDD through early adulthood.[56–59] Onset of anxiety and substance use disorders in adolescence have been well established as risk factors for MDD.[54,60] Adolescent onset ODD is also common,[61] and the present findings indicated that it was associated with an increased risk of MDD.

Several limitations should be noted stemming from the original focus of the study being MDD rather than ADHD. The number of participants with ADHD in the sample was small (n=40 at T1), and we were unable to examine the associations between ADHD subtypes and MDD onset. The low number of participants receiving ADHD medication prevented an examination of pharmacotherapy as a moderator of the association between ADHD and MDD onset. Only 7.5% of participants with a history of ADHD met current diagnostic criteria at T1 which may be partially due to the absence of parent and teacher reports of ADHD,[62,63] with the exception of a subset of participants for whom parent report data were available at T1. Finally, it should be noted that the majority of participants who developed MDD did not have a history of ADHD. This highlights the importance of other etiological paths to MDD.

The present study also has several important strengths, including the use of a large, school-based sample and the prospective tracking of adolescents through a later developmental period than has been examined in past studies of ADHD-MDD comorbidity, as well as assessment of ADHD symptoms in early adulthood in a subset of the sample.

Consistent with previous findings in referred samples, a positive history of ADHD by mid-adolescence significantly increased risk of MDD onset in this school-based sample. As such, individuals with positive histories of ADHD should be routinely screened for MDD, at least through early adulthood. Adolescents with ADHD represent good candidates for depression prevention programs.[64,65] The median time to MDD onset in this study was four years among adolescents with ADHD, indicating that half of those who developed MDD experienced an onset by approximately age 20. This suggests that late adolescence may be an important developmental period in which to implement depression prevention programs for ADHD youth. If persisting ADHD symptoms account for the elevated risk of MDD, as our preliminary findings in a subsample suggest, then future research is encouraged to examine whether maintenance treatment for ADHD into early adulthood may decrease risk of MDD. In support of the potential protective effect of ADHD treatment, two longitudinal studies have observed that youth receiving stimulant pharmacotherapy for ADHD had subsequently lower rates of mood disorders compared to untreated ADHD youth.[66,67] Given

that history of an anxiety disorder and new onset of an anxiety disorder also were significant predictors of MDD, future research should investigate the moderating effects of anxiety on the prospective relationship between ADHD and MDD, or the possibility that successful treatment of comorbid anxiety may decrease the risk subsequent MDD. ADHD and anxiety comorbidity is common in younger children.[68] Children who display this pattern of comorbidity may represent an important subgroup to target at younger age periods in the prevention of later MDD.

In summary, the association between ADHD and risk for depression has now been demonstrated in a non-referred sample. No evidence was found to support that demoralization or shared comorbidity drives the association between ADHD and MDD. These findings suggest a more direct association between ADHD and subsequent onset of depression. Future research is encouraged to examine that possibility, to explore the impact of ADHD treatments on mood outcomes, and to design depression prevention programs for adolescents and young adults with a history of ADHD.

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Table 1

Prevalence of lifetime psychiatric disorders by ADHD Status at T1

	No T1ADHD *n* (%)	**T1 ADHD *n* (%)**	**Total *n* (%)**
MDD	277(18.88%)	8(20.00%)	285 (18.91%)
ANX	118(8.04%)	6(15.00%)	124 (8.23%)
CD	33(2.25%)	7(17.50%)*	40 (2.65%)
ODD	18(1.23%)	7(17.50%)*	25 (1.66%)
SUD	117(7.98%)	7(17.50%)*	124 (8.23%)

Note: Total N = 1507. N for No T1 ADHD = 1467, n for T1 ADHD = 40. ADHD = Attention Deficit/Hyperactivity Disorder; MDD = Major Depressive Disorder; ANX = Anxiety Disorder; CD = Conduct Disorder; ODD = Oppositional Defiant Disorder; SUD = Substance Use Disorder.

*significant difference at $p < .05$.

Table 2

Multivariate prospective relationships between ADHD and MDD

	Model 1 HR (95 CI)	Model 2 HR (95 CI)	Model 3 HR (95 CI)	Model 4 HR (95 CI)
T1 ADHD	1.83 * (1.03, 3.25)	1.99 * (1.12, 3.55)	1.89 * (1.07, 3.34)	1.81 * (1.04, 3.06)
Male Gender		0.48 ** (0.38, 0.62)	0.45 ** (0.35, 0.59)	0.42 ** (0.32, 0.55)
T1 ANX		2.44 ** (1.76, 3.39)	2.29 ** (1.62, 3.24)	1.97 ** (1.35, 2.89)
T1 CD		0.99 (0.39, 2.50)	0.92 (0.36, 2.36)	0.90 (0.37, 2.19)
T1 ODD		1.00 (0.52, 1.92)	0.86 (0.44, 1.66)	0.76 (0.41, 1.40)
T1 SUD		1.64 * (1.11, 2.42)	1.32 (0.86, 2.04)	1.45 (0.91, 2.32)
T1 Fam Support			1.01 (0.99, 1.03)	1.00 (0.99, 1.02)
T1 Fri Support			1.01 (0.95, 1.06)	0.98 (0.93, 1.04)
T1 Loneliness			1.02 (0.97, 1.07)	1.03 (0.98, 1.08)
T1Academic			1.01 (0.96, 1.04)	1.00 (0.96, 1.04)
T1 Coping			0.97 ** (0.95, 0.99)	0.97 * (0.95, 0.99)
T1 Stress			1.11 (0.98, 1.22)	1.12 (0.99, 1.25)
New ANX				1.90 ** (1.40, 2.59)
New CD				2.22 (0.73, 6.78)
New ODD				3.39 ** (1.89, 6.09)
New SUD				1.89 ** (1.42, 2.51)

Note: N = 1222.

** $p < .01$;

* $p < .05$.

ADHD = Attention Deficit/Hyperactivity Disorder; ANX = Anxiety Disorder; CD = Conduct Disorder; ODD = Oppositional Defiant Disorder; SUD = Substance Use Disorder; New = new onset after T1 assessment. FAM= Family; FRI= Friend.