Anxiety and Disruptive Behavior Mediate Pathways From Attention-Deficit/Hyperactivity Disorder to Depression

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ABSTRACT

Objective: The progression to depression in children with attention-deficit/hyperactivity disorder (ADHD) is not clearly understood. To clarify this relationship, we tested the following hypotheses in a population-based study: (1) children with ADHD have a higher risk of developing depression than children without ADHD; (2) the pathway from ADHD to depression is mediated (partly) through anxiety and disruptive behavior disorders; and (3) mediation through anxiety is more prevalent in girls, and mediation through disruptive behavior disorders is more prevalent in boys.

Method: From October 2008 to September 2010, the Composite International Diagnostic Interview was used to assess ADHD, major depressive episodes, anxiety disorders, and disruptive behavior disorders in 1,584 participants from the TRacking Adolescents' Individual Lives Survey (TRAILS) cohort. Cox regression was used to model the effects of ADHD, anxiety, and disruptive behaviors on depression. Risk of and pathways to depression were studied in both children with ADHD and children with subthreshold ADHD.

Results: Comorbid depression was present in 36% of children with a diagnosis of ADHD, 24% of children with subthreshold ADHD, and 14% of children with no ADHD. Anxiety and disruptive behaviors mediated 32% of depression in ADHD. Pathways through anxiety and disruptive behavior disorders were independent of gender. Disruptive behavior disorder was a stronger mediator than anxiety for both genders (all $P < .01$).

Conclusions: These findings may help forewarn of impending depression and therefore allow opportunities for interventions when comorbid anxiety and/or disruptive behavior disorders are present in a child with ADHD.

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Attention-deficit/hyperactivity disorder (ADHD) is a developmental disorder of childhood characterized by persistent symptoms of inattention, hyperactivity, and impulsivity.[1] ADHD has been found to be associated with depression in epidemiologic[2–4] and clinical studies.[5–7] However, not all studies found such an association.[8,9] This discrepancy warrants a search for more evidence supporting or refuting the possibility of an increased risk of depression in ADHD.

Comorbid depression in ADHD is associated with an increased severity and duration of ADHD and greater psychosocial impairment.[10,11] It is therefore important to identify children with ADHD who may be susceptible to depression and then implement preventive measures. The first step toward achieving this goal is to refine our understanding of the pathway from ADHD to depression.

While ADHD has an early age at onset,[12,13] depressive disorders show a peak incidence in adolescence and young adulthood.[14] Thus, in most comorbid cases, onset of depression will follow onset of ADHD. Only a few studies, however, have focused on the prospective association of ADHD and depression.[15] In addition, it is unknown whether subthreshold ADHD also increases the risk of comorbid depression. The purpose of our study was to address the likelihood of depression onset in both diagnosed and subthreshold cases of ADHD and to examine 2 possible pathways leading to such an onset.

ADHD may influence development of depression directly, but the association may also develop through intermediate psychiatric problems that are highly associated with both ADHD and depression. Anxiety and disruptive behaviors arise often in ADHD and typically have their peak onset earlier than depression.[16–20] Both types of disorders predispose an individual to develop depression.[21,22] It could thus be argued that anxiety and disruptive behaviors are likely mediators of the pathway from ADHD to depression.

Pathways from ADHD to depression may differ in boys and girls. While girls tend to be more vulnerable to developing an anxiety disorder, boys have a predisposition to develop disruptive behavior problems.[23] It is therefore possible that the pathway from ADHD to depression is mediated mostly through anxiety in girls and through disruptive behavior in boys.

The aim of this study was to improve our understanding of the relationship between ADHD and depression and the pathways involved. In the long run, this knowledge may help in developing prevention protocols. Using a large population cohort of adolescents with lifetime diagnostic data collected at a mean age of 19 years, we tested the following hypotheses: (1) children with ADHD have an increased risk of developing depression, (2) the pathway to depression is (partly) mediated by anxiety or disruptive behavior disorders, and (3) mediation through anxiety is more prevalent in girls, and mediation through disruptive behavior disorders is more prevalent in boys.

Clinical Points

- Development of anxiety or disruptive behaviors in children with attention-deficit/hyperactivity disorder forewarns depression.
- Interventions aimed at reducing anxiety and disruptive behavior may prevent depressive outcomes.

METHOD

Cohort

The data were collected as part of the TRacking Adolescents' Individual Lives Survey (TRAILS), a Dutch prospective cohort study focusing on psychosocial development and mental health of adolescents from the general population. TRAILS involves biennial or triennial measurements from 11 to at least 25 years of age.[24–26]

Children were recruited from 5 municipalities in the north of The Netherlands, including both urban and rural areas. Primary school participation was a requisite for inclusion. Of the 2,935 children who met these criteria, 2,230 (76.0%) provided informed consent from both parent and child to participate in the study. Four assessment waves have been completed to date. Figure 1 presents a flowchart of participants included at each wave. The first wave (T1) was from March 2001 to July 2002, and the fourth wave (T4) was from October 2008 to September 2010 (T4). The mean age at T1 was 11.1 years (SD = 0.56), and 50.8% of the participants were girls. The response rate at T4 was 83.4% (N = 1,881, mean age = 19.1 years [SD = 0.60], 52.3% girls), of whom 84.2% (N = 1,584) completed the diagnostic interview described below. The study was approved by the Dutch Central Committee on Research Involving Human Subjects. Participants were treated in accordance with the Declaration of Helsinki, and all measurements were carried out with their adequate understanding and written consent.

Measures

During the fourth assessment wave, psychiatric disorders were assessed by means of the World Health Organization Composite International Diagnostic Interview (CIDI), version 3.0. The CIDI is a structured diagnostic interview that yields lifetime and current diagnoses according to the definitions and criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision. The CIDI has been used in a large number of surveys worldwide and been shown to have good concordance with clinical diagnoses.[27–29] In addition to the occurrence of psychiatric disorders, the CIDI yields the age at onset and age at last occurrence of the disorders. The CIDI was administered in the TRAILS sample by well-trained lay interviewers. Training was provided by 2 official CIDI trainers. An intensive 1-week training period was followed by practice interviews, which continued until satisfactory levels were achieved. During the data collection, regular interview meetings and evaluations of audio-recorded interviews were carried out to maintain high levels of trainee performance.

The CIDI has good reliability and validity for most diagnoses, including anxiety and depression.[30] Reliability of the CIDI regarding disruptive behaviors and ADHD has not yet been tested in adults. We nevertheless decided to use the CIDI because it is, to the best of our knowledge, the only lay interview for the assessment of ADHD and disruptive behavior disorders in adult samples available to date. In addition, validity of the CIDI data was supported by prospective parent reports and self-reports as assessed with the Child Behavior Checklist,[31] Youth Self Report,[32] and Adult Self Report[33] from the first wave onward (details available upon request).

The ADHD section of the CIDI was administered if at least 1 of the following 2 stem questions was endorsed: (1) a history of concentration problems (such as quickly losing interest in work and games, inability to concentrate on and finish work, not listening to other people when spoken to) prior to 7 years of age that lasted a minimum of 6 months and seemed excessive compared to peers and (2) a history of hyperactivity-impulsivity (such as fidgeting, restlessness, and impatience) present before 7 years of age that lasted a minimum of 6 months. ADHD was categorized into 3 groups: no ADHD (ie, a negative score on both stem questions), subthreshold ADHD (endorsement of at least 1 of the 2 stem questions but no diagnosis), and a clinical diagnosis of ADHD. Depression was operationalized as major depressive episode (MDE), either with or without (hypo)manic symptoms. Anxiety disorder was defined as a diagnosis of separation anxiety disorder, simple phobia, social phobia, specific phobia, panic disorder, agoraphobia, or generalized anxiety disorder. Disruptive behavior disorder was defined as a diagnosis of oppositional defiant disorder or conduct disorder. Lifetime diagnoses of the abovementioned disorders were used. "Age at onset" refers to the age at which these disorders emerged for the first time. If adolescents had multiple anxiety or disruptive behavior disorders, we used the age at the earliest onset.

Imputation of missing data was not done, as the study sample was representative of the original cohort. Extensive recruitment efforts were made at the first wave, which reduced nonresponse bias and laid the basis for a high generalizability until the last wave.[34] In addition, participants with and without completed CIDI interviews were found to have comparable gender distributions, internalizing problems, externalizing problems, and attention problems.

Statistical Analysis

For each ADHD group, the probability of depression onset was calculated using Kaplan-Meier survival curves. Between-group differences in probability of depression were tested using a log-rank test. Cox proportional hazards regression models were used to estimate differences in the probability to develop an MDE, referred to as hazard ratios, both with and without adjusting for anxiety and disruptive behavior disorders. Anxiety and disruptive behavior disorders were

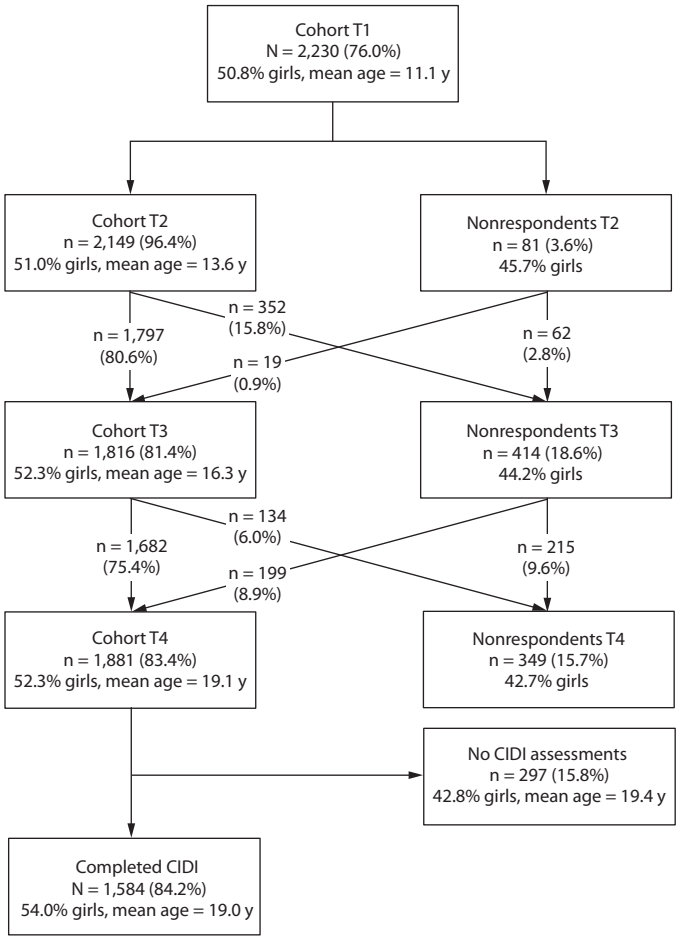
included as time-dependent variables in these models. Gender differences in the association between ADHD and MDE were tested by means of an interaction term, and additional gender-stratified analyses were performed in order to corroborate possible differences in mediational pathways.

In addition to the overall measures of disruptive behavior and anxiety disorders, the analyses were also performed for conduct disorder, oppositional defiant disorder, and the commonest anxiety disorders (social phobia, specific phobia, generalized anxiety disorder, and separation anxiety disorder) individually. All statistical analyses were performed using the SPSS v. 20.0 (IBM Corp; Armonk, New York). Statistical tests were 2-tailed, and a P value < .01 was considered statistically significant.

RESULTS

Table 1 shows the distribution of variables used in this study in each of the 3 ADHD groups. Chi-square analyses indicated significant differences among the groups for all variables (gender: $\chi^2 = 18.4$, $P < .01$; anxiety: $\chi^2 = 28.9$, $P < .01$; disruptive behavior disorders: $\chi^2 = 83.2$, $P < .01$; depression: $\chi^2 = 32.4$, $P < .01$). Post hoc pairwise tests revealed significant differences between no ADHD and subthreshold ADHD and between no ADHD and diagnosis of ADHD for all variables. Differences between subthreshold ADHD and diagnosis of ADHD were significant only for anxiety and disruptive behavior disorders. Comorbid depression was present in 24% of children with subthreshold ADHD and 36% of children with a diagnosis of ADHD.

Figure 1. Flowchart of Participants at Each Wave of the TRacking Adolescents' Individual Lives Survey (TRAILS)



Abbreviation: CIDI = Composite International Diagnostic Interview.

For all adolescents in our sample, the onset of ADHD preceded the onset of depression. In all adolescents with ADHD, onsets of anxiety and disruptive behavior disorders preceded onset of depression. For all adolescents with comorbid ADHD and depression, ADHD symptoms were still present at the time of depression onset. Hence, both disorders were present concurrently. Comorbidities of ADHD with anxiety and of ADHD with disruptive behavior were also concurrent. In adolescents with ADHD and anxiety, symptoms of anxiety were present at the time of onset of depression, and in only 1 adolescent with ADHD and disruptive behavior disorder had the disruptive behaviors remitted prior to onset of depression.

Figure 2 presents Kaplan-Meier curves reflecting the fraction of adolescents developing an MDE across adolescence for each of the 3 ADHD groups. Consistent with the abovementioned χ^2 test, log-rank tests revealed statistically significant ($\chi^2 = 36.1$, $P < .01$) differences among the 3 curves. Both Table 1 and Figure 2 show a trend of increasing risk for depression from groups of no ADHD to a diagnosis of ADHD. Figure 2 also shows that the risk for depression in subthreshold ADHD was approximately half of that in diagnosed ADHD. Therefore, we decided not to use dummy variables, but to include ADHD as an ordinal variable (with possible values 0, 1, and 2) in further analyses.

The estimated effects of ADHD on major depression onset before and after adjusting for anxiety and disruptive behavior are presented in Table 2. In the unadjusted model, a unit increase in ADHD (ie, from no ADHD to subthreshold or from subthreshold to diagnosis) was associated with an 89% increased risk of developing depression. Anxiety mediated 14% and disruptive behaviors mediated 22% of the effect of ADHD on depression. When included simultaneously in the model, anxiety and disruptive behaviors mediated 32% of the depression in ADHD, exemplifying that their effects were largely nonoverlapping.

None of the pathways from ADHD to depression showed significant gender differences ($P > .12$ for all interactions), suggesting that the amount of mediation was approximately similar for boys and girls. Gender-stratified analyses confirmed this supposition: anxiety mediated 17% of the effect of ADHD in boys and 15% in girls; disruptive behavior mediated 24% of the effect in boys and 21% in girls (all $P < .01$) (details available from the corresponding author on request).

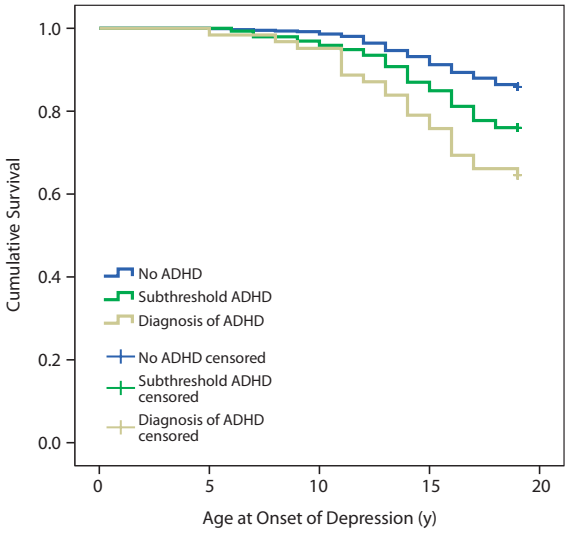
Post hoc analyses at the level of specific disorders revealed that mediation of the effect of ADHD on depression was

Table 1. Summary Statistics of Variables Used in the Study[a]

Variable	No ADHD[b] (n = 1,230)	Subthreshold ADHD (n = 292)	Diagnosis of ADHD[c] (n = 62)
Male	530 (43)	162 (55)	36 (58)
Anxiety disorder[b]	290 (24)	99 (34)	32 (48)
Disruptive behavior disorder[b]	121 (10)	62 (21)	28 (45)
Depression[b]	174 (14)	70 (24)	22 (36)

[a]Values expressed as n (%).
[b]Measurement of lifetime prevalence at a mean age of 19 years.
[c]Ongoing at the time of assessment.
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

Figure 2. Kaplan-Meier Curves for Age at Onset of Depression Across Categories of Attention-Deficit/Hyperactivity Disorder (ADHD)



roughly similar for conduct and oppositional defiant disorder, as well as for the individual anxiety disorders (details available upon request).

The ratio of oppositional defiant disorder to conduct disorder diagnoses in adolescents without ADHD was 0.92. For adolescents with subthreshold ADHD and diagnosis of ADHD, these ratios were 1.11 and 1.40, respectively.

DISCUSSION

In our study, both subthreshold ADHD and ADHD diagnosis increased risk for future depression. Further, we found that the pathway from ADHD to depression was partially mediated by anxiety and disruptive behavior disorders, the latter being the stronger path. In contrast to our hypothesis, mediating pathways through anxiety and disruptive behavior disorders were comparable in boys and girls.

Previous studies have estimated prevalence rates of depression in ADHD to range between 12% and 50%.[35–37] The estimate from our study falls within this range and suggests that 1 in 3 children with ADHD eventually develops depression. This is a substantial proportion, which warrants attention to recognize and prevent or treat depressive

Table 2. Cox Regression Estimates of the Effect of ADHD on Depression Onset Before and After Adjusting for Anxiety and Disruptive Behaviors

Covariate	*B*	SE	Wald χ^2	*P*	Hazard Ratio	95% CI
Model 1						
ADHD	0.63	0.10	44.84	<.01	1.89	1.57–2.27
Gender	0.91	0.14	43.96	<.01	2.48	1.89–3.24
Model 2						
ADHD	0.54	0.10	30.68	<.01	1.71	1.41–2.06
Gender	0.77	0.14	30.95	<.01	2.16	1.65–2.84
Anxiety disorder	0.97	0.13	58.50	<.01	2.63	2.05–3.37
Model 3						
ADHD	0.49	0.10	24.59	<.01	1.63	1.35–1.98
Gender	0.97	0.14	49.30	<.01	2.63	2.01–3.44
DBD	0.84	0.16	26.79	<.01	2.32	1.68–3.18

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, DBD = disruptive behavior disorder.

symptoms in children with ADHD. In addition, the increased depression risk in children with subthreshold ADHD suggests that the risk of depression associated with ADHD lies along a continuum. ADHD also often co-occurred with anxiety and disruptive behavior disorders, showing that comorbidity in ADHD is quite common. Previous studies support that children with ADHD are likely to develop many other psychiatric problems, not limited to depression, during the course of the illness.[38] Thus, "pure" ADHD without development of any other comorbid illness may be seen only rarely in practice.[35] Finally, ADHD comorbid with other disorders may be representing distinct patterns of illnesses, and these distinct clinical entities may require different approaches for their management.

Both anxiety and disruptive behaviors increased the risk of depression. Anxiety and disruptive behavior problems are said to arise in ADHD due to problems in interacting with peers, harsh parenting, and negative reactions from parents, teachers, and peers in response to their symptoms.[39–41] Further on, the path to depression may be attributed to the social and peer relationship problems that arise commonly in anxiety and disruptive behavior disorders. Anxiety as well as disruptive behavior disorder lead to rejection and social isolation,[42] which are highly depressogenic experiences.[43–45]

We combined conduct disorder and oppositional defiant disorder into the single category of disruptive behavior disorders. Evidence on overlap of conduct disorder and oppositional defiant disorder is mixed; some studies suggest that the 2 disorders are distinct,[46,47] while others report significant overlap.[48] In our study, the paths to depression through conduct and oppositional defiant disorder appeared approximately alike, and combining the 2 into the overarching term of *disruptive behavior disorders* seems justified. The same is true for the category of combined anxiety disorders.

Consistent with literature, girls more often had an anxiety disorder,[44,45] and boys more often had a disruptive behavior disorder.[49] Contrary to our hypothesis, however, we found no gender differences in the pathways to depression:

mediating pathways through anxiety and disruptive behavior disorders were comparable for boys and girls. In other words, ADHD did not confer an additional risk for anxiety in girls and disruptive behavior disorders in boys over and above the existing gender difference. Instead, we found that disruptive behavior disorder was a stronger mediator than anxiety in both genders.

Although this study provides further evidence for the association of ADHD and depression, results should be interpreted bearing in mind its limitations. First, although TRAILS is a longitudinal study, we analyzed data that relied on retrospective recollection, which may have given rise to recall bias. In an ideal study, we would have interviewed participants repeatedly. Nonetheless, given a single interview, the age range of 18 to 20 years in our sample can be considered as optimal, with regard to studying a sample that adequately remembers onset and occurrence of symptoms of ADHD while at the same time having experienced the majority of first onsets of depression.[50] Second, treatment status of participants and success of such treatment were not known. Treatment for ADHD may reduce the likelihood of developing depression by terminating the antecedent cause, that is, ADHD itself. Furthermore, stimulant medications used in the treatment of ADHD have been shown to reduce symptoms of depression in ADHD.[51] Conversely, however, use of stimulant medications has also been reported to give rise to depression and may cause side effects such as loss of appetite and insomnia that mimic depressive symptoms.[36] Treatment can thus alter the occurrence of depression in ADHD in both directions and may yield a false-negative or false-positive diagnosis of comorbid depression. Third, the reliability of the CIDI in diagnosing ADHD has not yet been established. However, the CIDI has been used previously to assess ADHD in adults.[52,53] In addition, young adults may not be the best reporters of their behavioral problems and ADHD status. To address this potential limitation, we performed additional analyses, which showed that in our sample the CIDI diagnoses at age 19 converged with prospective parent reports.

The strengths of our study include the large sample size and use of a population cohort that, in contrast to clinical samples, represents not only the most challenging cases of ADHD but also individuals with less complex and less severe symptoms. This additionally allowed us to study subthreshold ADHD and show that the presence of even mild ADHD symptoms is sufficient to enhance the risk for depression. Moreover, referred children in clinical cohorts are known to have higher rates of comorbid disorders, causing an overrepresentation of cases with comorbidity.[35] Finally, a population cohort has the advantage of a balanced representation of genders in the sample in contrast to a clinical cohort with higher numbers of referred boys.[54]

Due to limited power, we could not carry out analyses of differences in mediator pathways between ADHD subtypes. Future research may benefit from focusing on this aspect. The divergence in progressing from ADHD to either anxiety or disruptive behaviors may be related to the presence of different symptoms of ADHD. Children with the inattentive type of ADHD have been reported to have a higher predisposition to develop an anxiety disorder, and children with the combined or hyperactive/impulsive type have been reported to develop disruptive behavior disorders.[55–57]

This study showed that the association between ADHD and depression runs partly through anxiety and disruptive behavior disorders. This finding brings us a step closer to understanding the pathway from ADHD to depression and consequently the mechanisms of association of these 2 disorders. Clinicians can be alert to the possibility of subsequent depression in children with ADHD, especially when comorbid anxiety or disruptive behavior disorders are present, and can take necessary steps early on for monitoring and prevention.

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Additional information: The TRAILS database can be accessed through submitting a publication proposal (contact address: trails@umcg.nl). TRAILS has no copyright on the data.

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