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The development of depression in children and adolescents with ADHD

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CHAPTER 4

Anxiety and disruptive behaviour mediate pathways from Attention Deficit Hyperactivity Disorder to depression

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ABSTRACT

Objectives: 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 behaviour disorders; and 3) Mediation through anxiety is more prevalent in girls and mediation through disruptive behaviour disorders is more prevalent in boys.

Method: From October 2008 to September 2010, The Composite International Diagnostic Interview (CIDI) was used to assess ADHD, Major Depressive Episodes (MDE), anxiety disorders and disruptive behaviour disorders in 1584 participants from the TRacking Adolescents' Individual Lives Survey (TRAILS) cohort. Cox regression was used to model the effects of ADHD, anxiety and disruptive behaviours 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 behaviours mediated 32% of depression in ADHD. Pathways through anxiety and disruptive behaviour disorders were independent of gender. Disruptive behaviour disorder was a stronger mediator than anxiety for both genders (all $p < .01$).

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

Keywords: attention deficit hyperactivity disorder; anxiety; disruptive behaviour; depression; population-based sample

INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is a developmental disorder of childhood characterized by persistent symptoms of inattention, hyperactivity and impulsivity (American Psychiatric Association (APA), 2000). ADHD has been found to be associated with depression in epidemiological (Blackman, Ostrander, & Herman, 2005; Chronis-Tuscano et al., 2010; Jensen, Burke, & Garfinkel, 1988) and clinical studies (Butler, Arredondo, & McCloskey, 1995; Connor et al., 2003; Elia, Ambrosini, & Berrettini, 2008). However, not all studies found such an association (Bagwell, Molina, Kashdan, Pelham, & Hoza, 2006; Mannuzza, Klein, Bessler, Malloy, & LaPadula, 1998). 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 higher psychosocial impairment (Jensen, Shervette, Xenakis, & Richters, 1993; Waxmonsky, 2003). It is therefore important to identify children with ADHD who may be susceptible to depression, and subject them to preventive measures for depression. The first step towards achieving this goal is to refine our understanding of the pathway from ADHD to depression.

While ADHD has an early age of onset (Kessler et al., 2007; Spencer, Biederman, & Mick, 2007), depressive disorders show a peak incidence in adolescence and young adulthood (Oldehinkel, Wittchen, & Schuster, 1999). Thus, in most comorbid cases, onset of depression will follow onset of ADHD. Only a few studies however have focussed on the prospective association of ADHD and depression (Seymour et al., 2012). In addition, it is unknown whether subthreshold ADHD increases the risk of comorbid depression too. The purpose of our study was to address the likelihood of depression onset in both diagnosed and subthreshold cases of ADHD, and to examine two 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 behaviours arise often in ADHD and typically have their peak onset earlier than depression (Biederman, Newcorn, & Sprich, 1991; Bowen, Chavira, Bailey, Stein, & Stein, 2008; Harty, Miller, Newcorn, & Halperin, 2009; Manassis, Tannock,

Young, & Francis-John, 2007; March et al., 2000). Both disorders predispose an individual to develop depression (Silk, Davis, McMakin, Dahl, & Forbes, 2012; Zahn-Waxler, Shirtcliff, & Marceau, 2008). It could thus be argued that anxiety and disruptive behaviours 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 develop an anxiety disorder, boys, have a predisposition to develop disruptive behaviour problems (Oldehinkel, Verhulst, & Ormel, 2011). It is therefore possible that the pathway from ADHD to depression is mediated mostly through anxiety in girls, and through disruptive behaviour in boys.

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

METHODS

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 bi- or triennial measurements from age 11 to at least age 25 (de Winter et al., 2005; Huisman et al., 2008; Ormel et al., 2012).

Children were recruited from five municipalities in the north of The Netherlands, including both urban and rural areas. Primary school participation was a requisite for inclusion. Of the 2935 children who met these criteria, 2230 (76.0%) provided informed consent from both parent and child to participate in the study. Four assessment waves have been completed to date.

Figure 4.1 presents a flowchart of participants included at each wave. The first wave (T1) ran from March 2001 to July 2002, the fourth (T4) from October 2008 to September 2010 (T4). The mean age at T1 was 11.1 years ($SD = 0.56$), and 50.8% were girls. The response rate at T4 was 83.4% ($N = 1881$, mean age 19.1, $SD = 0.60$, 52.3% girls), of whom 84.2% ($N = 1584$) completed the below described diagnostic interview. The study was approved by the Dutch Central Committee on Research Involving Human Subjects (CCMO). 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 which yields lifetime and current diagnoses according to the definitions and criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). The CIDI has been used in a large number of surveys worldwide, and been shown to have good concordance with clinical diagnoses (Haro et al., 2006; Kessler et al., 2004; Kessler et al., 2009). In addition to the occurrence of psychiatric disorders, the CIDI yields their age at onset and age at last occurrence. The CIDI was administered in the TRAILS sample by well-trained lay interviewers. Training was provided by two official CIDI trainers. An intensive one-week training was followed by practice interviews which continued till 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 (Wittchen, 1994). Reliability of the CIDI regarding disruptive behaviours and ADHD has not yet been tested in adults. We nevertheless decided to use the CIDI since it is, to the best of our knowledge, the only lay interview for the assessment of ADHD and disruptive behaviour disorders in adult samples available to date. In addition, validity of the CIDI data was supported by prospective parent and self-reports as assessed with the Child Behaviour Checklist (CBCL) (Achenbach, 1991a), Youth Self Report (YSR) (Achenbach, 1991b), and Adult Self Report (ASR) (Achenbach & Rescorla, 2001) from the first wave onwards (details available upon request).

The ADHD section of the CIDI was administered if at least one of the following two 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 the age of seven that lasted a minimum of six months and seemed excessive compared to peers, and (2) a history of hyperactivity-impulsivity (such as fidgeting, restlessness and impatience) present before the age of seven that lasted a minimum of six months. ADHD was categorized into three groups: no ADHD (i.e., a negative score on both stem questions), subthreshold ADHD (endorsement of at least one of the two stem questions but no diagnosis), and a clinical diagnosis of ADHD. Depression was operationalized as Major Depressive Episode, 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 behaviour disorder was defined as a diagnosis of Oppositional Defiant Disorder or Conduct Disorder. Lifetime diagnoses of the above-mentioned disorders were used. Age of onset refers to the age these disorders emerged for the first time. If adolescents had multiple anxiety or disruptive behaviour disorders, we used the age of 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 non response bias and laid the basis for a high generalizability, up until the last wave (Nederhof et al., 2012). In addition, participants with and without completed CIDI interviews were found to have comparable gender distributions, internalising problems, externalising 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 (HR), both with and without adjusting for anxiety and disruptive behaviour disorders. Anxiety and disruptive behaviour 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 behaviour and anxiety disorders, the analyses were also performed for, respectively, conduct disorder and 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, NY). Statistical tests were two-tailed and a p-value < .01 was considered statistically significant.

RESULTS

Table 4.1 shows the distribution of variables used in this study in each of the three 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 behaviour disorders: $\chi^2 = 83.2$, $p < .01$; depression: $\chi^2 = 32.4$, $p < .01$). Posthoc 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 behaviour disorders. Comorbid depression was present in 24% of children with subthreshold ADHD and 36% of children with a diagnosis of ADHD.

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 behaviour 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 behaviour were also concurrent. In adolescents with ADHD and anxiety, symptoms of anxiety were present at the time of onset of depression, and in only one adolescent with ADHD and disruptive behaviour disorder had the disruptive behaviours remitted prior to onset of depression.

Figure 4.2 presents Kaplan-Meier curves reflecting the fraction of adolescents developing a major depressive episode across adolescence for each of the three ADHD groups. Consistent with the above mentioned χ^2 - test, log-rank tests revealed statistically significant ($\chi^2 = 36.1$, $p < .01$) differences among the three curves. Both Table 4.1 and Figure 4.2 show that the risk of

depression of the group with subthreshold ADHD was about half the risk of those with a diagnosis of 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 behaviour are presented in Table 4.2. In the unadjusted model, a unit increase in ADHD (i.e., 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 behaviours 22% of the effect of ADHD on depression. When included simultaneously in the model, anxiety and disruptive behaviours mediated 32% of the depression in ADHD, exemplifying that their effects were largely non-overlapping.

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 behaviour mediated 24% of the effect in boys and 21% in girls (details available upon request).

Post hoc analyses at the level of specific disorders revealed that mediation of the effect of ADHD on depression was roughly similar for conduct and oppositional defiant disorder, as well as for the individual anxiety disorders (details available upon request).

The ratio of ODD to CD 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 the risk for future depression. Further, we found that the pathway from ADHD to depression was partially mediated by anxiety and disruptive behaviour disorders, the latter being the strongest path. In contrast to our hypothesis, mediating pathways through anxiety and disruptive behaviour disorders were comparable in boys and girls.

Previous studies have estimated prevalence rates of depression in ADHD to range between 12% and 50% (Angold, Costello, & Erkanli, 1999; Daviss, 2008; Pliszka, 1998). The estimate from our study falls within this range and suggests that one in every three children with

ADHD eventually develops depression. This is a substantial proportion, which warrants attention to recognise and prevent or treat depressive 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 behaviour 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 (Young, 2008). Thus 'pure' ADHD without development of any other comorbid illness may only be rarely seen in practice (Angold et al., 1999). 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 behaviours increased the risk of depression. Anxiety and disruptive behaviour 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 (Derefinko et al., 2008; Semrud-Clikeman, 2010; Thorell & Rydell, 2008). Further on, the path to depression may be attributed to the social and peer relationship problems that arise commonly in anxiety and disruptive behaviour disorders. Anxiety as well as disruptive behaviour disorder lead to rejection and social isolation (Rubin, Coplan, & Bowker, 2009), which are highly depressogenic experiences (Brendgen et al., 2009; McLeod, Weisz, & Wood, 2007; Rockhill, Vander, Stoep, McCauley, & Katon, 2009).

We combined conduct disorder and oppositional defiant disorder into the single category of disruptive behaviour disorders. Evidence on overlap of conduct disorder and oppositional defiant disorder is mixed, with some studies suggesting that the two disorders are distinct (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Rowe, Costello, Angold, Copeland, & Maughan, 2010), while others report significant overlap (Maughan, Rowe, Messer, Goodman, & Meltzer, 2004). In our study the paths to depression through conduct and oppositional defiant disorder appeared approximately alike, and combining the two into the overarching term of 'disruptive behaviour disorders' seems justified. The same is true for the category of combined anxiety disorders.

Consistent with literature, girls had more often an anxiety disorder (Brendgen et al., 2009; Rockhill et al., 2009) and boys a disruptive behaviour disorder (Ingram, Miranda, & Segal, 1998). Contrary to our hypothesis, however, we did not find any gender differences in the pathways to depression: mediating pathways through anxiety and disruptive behaviour disorders were comparable for boys and girls. In other words, ADHD did not confer an additional risk for anxiety in girls and disruptive behaviour disorders in boys, over and above the existing gender difference. Instead, we found that disruptive behaviour 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, even though TRAILS is a longitudinal study, we analysed 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 in our sample of 18 to 20 years can be considered as optimal, in light of adequately remembering onset and occurrence of symptoms of ADHD, while at the same time having experienced the majority of first onsets of depression (Wittchen, 2012). Secondly, 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 (Gurkan et al., 2010). Conversely, however, use of stimulant medications have also been reported to give rise to depression, and may cause side effects such as loss of appetite and insomnia which mimic depressive symptoms (Daviss, 2008). 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. Thirdly, the reliability of CIDI in diagnosing ADHD has not yet been established. However, the CIDI has been used previously to assess ADHD in adults (De Ridder, Bruffearts, Danckaerts, Bonnewyn, & Demyttenaere, 2008; Tuithof, ten Have, van den Brink, Vollebergh, & de Graaf, 2012). In addition, young adults may not be the best reporters of their behavioural problems and ADHD status. To address this potential limitation we performed additional analyses which show 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 which, in contrast to clinical samples, does not represent 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 presence of even mild ADHD symptoms of ADHD 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 over-representation of cases with comorbidity (Angold et al., 1999). 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 (Gaub & Carlson, 1997).

Due to limited power we could not carry out analyses on differences in mediator pathways between ADHD subtypes. Future research may benefit from focussing on this aspect. The divergence in progressing from ADHD to either anxiety or disruptive behaviours may be related to the presence of different symptoms of ADHD. Children with the inattentive type ADHD have been reported to have a higher predisposition to develop an anxiety disorder, and children with the combined or hyperactive/impulsive type to develop disruptive behaviour disorders (Eiraldi, Power, & Nezu, 1997; Lahey, Schaughency, Hynd, Carlson, & Nieves, 1987; Murphy, Barkley, & Bush, 2002).

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

Table 4.1 Summary statistics of variables used in the study

	No ADHD ^{ab} n = 1230	Subthreshold ADHD n = 292	Diagnosis of ADHD n = 62
Males	530 (43%)	162 (55%)	36 (58%)
Anxiety disorder	290 (24%)	99 (34%)	32 (48%)
Disruptive behaviour disorder	121 (10%)	62 (21%)	28 (45%)
Depression	174 (14%)	70 (24%)	22 (36%)

^a Measurement of lifetime prevalences at mean age 19 years

^b Attention Deficit Hyperactivity Disorder (ongoing at the time of assessment)

Covariate	B	SE	Wald χ^2	<i>P</i>	Hazard Ratio	95% CI
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Table 4.2 Cox regression estimates of the effect of ADHD^a on depression onset before and after adjusting for anxiety and disruptive behaviours

Model 1						
ADHD	.63	.10	44.84	<.01	1.89	1.57 to 2.27
Gender	.91	.14	43.96	<.01	2.48	1.89 to 3.24
Model 2						
ADHD	.54	.10	30.68	<.01	1.71	1.41 to 2.06
Gender	.77	.14	30.95	<.01	2.16	1.65 to 2.84
Anxiety disorder	.97	.13	58.50	<.01	2.63	2.05 to 3.37
Model 3						
ADHD	.49	.10	24.59	<.01	1.63	1.35 to 1.98
Gender	.97	.14	49.30	<.01	2.63	2.01 to 3.44
DBD ^b	.84	.16	26.79.	<.01	2.32	1.68 to 3.18

^a Attention Deficit Hyperactivity Disorder
^b Disruptive Behaviour Disorder

Figure 4.1 Flowchart of participants at each wave with mean ages (in years)

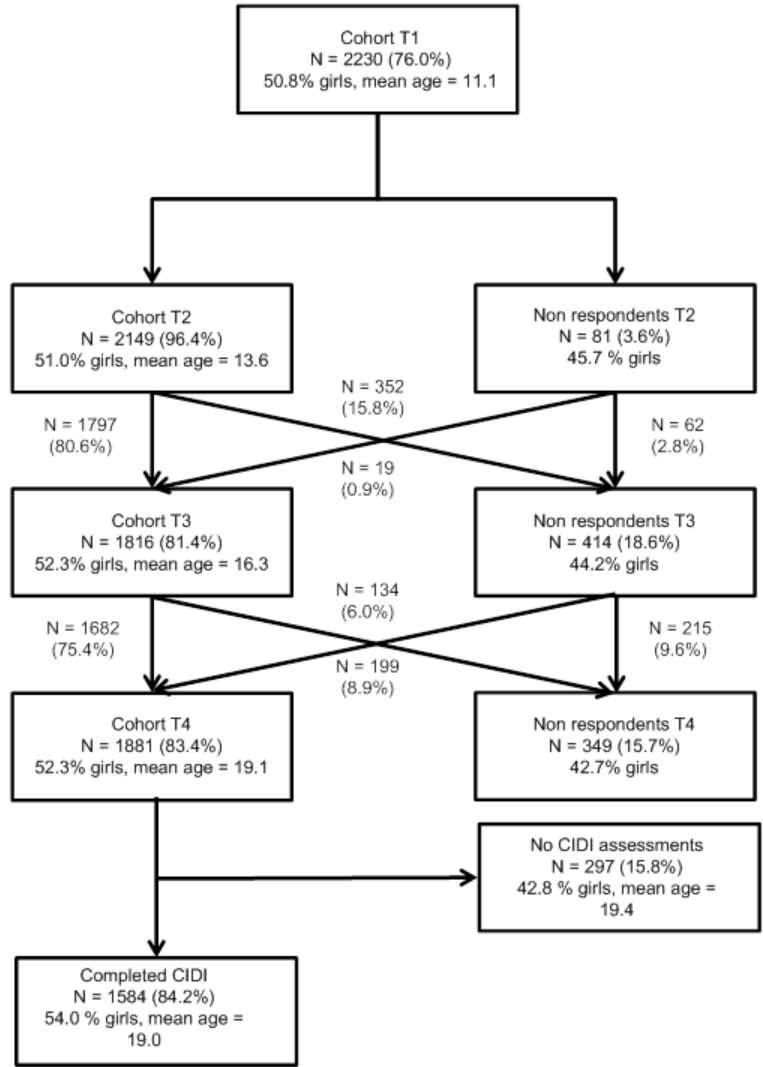


Figure 4.2 Kaplan-Meier curves for age of onset of depression across categories of attention deficit hyperactivity disorder (ADHD)

