The development of depression in children and adolescents with ADHD

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General Introduction

Overview

Attention Deficit/Hyperactivity Disorder (ADHD) is a major and a common childhood-onset mental health problem that is yet to be fully understood. One yet unresolved problem – amongst the plethora of questions that plague scientific enquiry into this elusive disorder – is the development of depression in many but not all affected individuals with ADHD. This thesis is aimed at clarifying some of the issues related to the development of depression in children and adolescents with ADHD. This chapter begins with a brief introduction into the origins of the term 'ADHD' and its definition. This is followed by a short discussion of one defining characteristic of ADHD: the development of multiple comorbidities. Next, the existing literature on depressive comorbidity in ADHD is presented and the context of the main scientific question of this thesis is introduced. Further, goals of this thesis are described and the respective chapters dealing with each of these are outlined.

Definition and evolution of the term ADHD

Attention Deficit/Hyperactivity Disorder or the more commonly used abbreviation, ADHD, is a mental health disorder that begins early in childhood. ADHD is often defined, as the name suggests, by the presence of hyperactive, impulsive and inattentive symptoms in multiple settings for at least six months, which are excessive in comparison to other children of the same age (American Psychiatric Association 2013). The earliest descriptions of ADHD have dated past back to the mid-eighteenth century. Back then, this disorder was poorly understood, and incorrectly classified as a 'moral defect' or a 'discipline problem'. Between the eighteenth century and the early twentieth century, not much progress was made in the understanding of ADHD. The first version of the DSM appeared in 1952, but did not recognize the disorder at all. It was only in the second version (DSM-II) in 1968 that ADHD was considered as a mental health disorder. The DSM-II labelled the disorder as 'hyperkinetic-impulse disorder' and did not include the inattention dimension. By 1980, a newer version of the DSM (DSM-III) arrived that included both the hyperactivity/impulsivity and the inattentive dimensions in its definition of ADHD.

Between the introduction of the DSM-III in 1980 and now, the conceptualisation of ADHD has undergone further changes. For example, while the DSM-III labelled the disorder as 'attention deficit' either with or without hyperactivity, the revised version in 1987 (DSM-III-R) did not subdivide the

disorder based on presence or absence of hyperactivity. Instead the DSM-III-R included hyperactivity as a core symptom. The next version, the DSM-IV, classified ADHD into three subtypes – hyperactive/impulsive, inattentive, and combined. The most recent changes were made in 2013, with the introduction of DSM-5, which changed one of the diagnostic criteria: a diagnosis of ADHD now requires symptoms to have arisen by the age of 12 instead of 7 years as in previous DSM versions.

More changes to the diagnostic criteria of ADHD may be expected in the future. One example would be that symptoms of sluggish cognitive tempo (SCT) may be included in the diagnostic criteria. SCT is a symptom complex characterised by day dreaming, drowsiness, sluggishness, and decreased activity (Fassbender, Krafft, & Schweitzer, 2015; Barkley 2014; Penny, Waschbusch, Klein, Corkum, & Eskes, 2009), and is present in many children with ADHD. It is correlated with inattentive symptoms and therefore often considered an integral symptom of ADHD (Carlson & Mann 2002; Garner, Marceaux, Mrug, Patterson, & Hodgens, 2010; McBurnett, Pfiffner, & Frick, 2001). Others point out that SCT also occurs in individuals without ADHD and may thus better be considered a separate disorder (Lee, Burns, Snell, & McBurnett, 2014; McBurnett et al., 2014; Wilcutt et al., 2014; Leopold, Bryan, Pennington, & Willcutt, 2015). Another criticism of the current diagnostic criteria concerns the emphasis the DSM puts on categorical definitions of ADHD and symptom score cut-offs to diagnose the disorder (Coghill & Sonuga-Barke, 2012), which ignores studies that have shown that symptoms of hyperactivity/impulsivity and inattention lie along a continuum and that the symptom severity of children with a diagnosis of ADHD ranges from moderate to severe levels (Lubke, Hudziak, Derks, van Bijsterveld, Boonsma, 2009; Polanczyk, 2014; Hudziak, Achenbach, Althoff & Pine, 2007; Kraemer, 2007). Future changes to the conceptualisation of ADHD may include replacing or complementing the categorical diagnoses with dimensional measures (Kraemer, 2007). These two examples of possible future changes in the DSM illustrate the heterogeneity of ADHD, which is one of the reasons that ADHD is difficult to define.

The changing definitions of ADHD complicate sampling for research, clinical decision making, diagnosis and initiation of therapy. Further, the conceptualisation of ADHD is complicated by the fact that individuals with ADHD may differ in characteristics such as presence or absence of SCT and symptom severity, and that several subgroups may exist in the ADHD population. Such considerations challenge not only clinical judgements but also research, as the changing standards have added to the heterogeneity in literature. Despite these concerns, it is well-established that ADHD is associated with significant distress and reductions in quality of life. It is also well-known that the symptoms of ADHD merely do not explain the full range of impairments that occur in affected individuals. Rather, impairments are unrelated, to a large extent, to the symptom severity or treatments received. Key among

the distress and impairments involved in ADHD is the emergence of comorbid mental health conditions over time (Pliszka, 1998; Pliszka, 2000).

Comorbid disorders

ADHD is diagnosed in 4-9% of children world-wide, of whom 30-50% have developed additional mental health problems by adolescence (Angold, Costello, & Erkanli, 1999; Biederman, Newcorn & Sprich, 1991). Amongst adults with ADHD, about 80% suffer from at least one comorbid condition, while about 50% have two or more comorbid disorders (McGough et al., 2005; Meinzer, Pettit, Viswesvaran, 2014). An individual with only ADHD, without comorbidity, is thus the exception rather than the norm (Jensen et al., 2011). Comorbidities lead to difficulties in assessing impairment levels, clinical judgements, and treatment decisions (MTA Cooperative Group, 1999; Pliszka, 2003), and inevitably increase problems in daily functioning (Biederman et al., 1991). Amongst all comorbid disorders, the occurrence of oppositional defiant disorder (ODD) and conduct disorder (CD) are the most common, affecting 30-50% and 25-35% of all children respectively (Angold et al., 1999; American Psychiatric Association, 2013; Jensen, Martin & Cantwell, 1997). Apart from ODD and CD, autism spectrum and learning disorders are also common, albeit both show a wide heterogeneity in rates across studies: between 20-70% of children with ADHD show symptoms of learning disorders, while 10-90% have symptoms of autism spectrum disorders (American Psychiatric Association, 2013; Jensen et al., 1997; Pliszka, 1998; Pliszka, 2000; Rommelse, Geurts, Franke, Buitelaar, & Hartman, 2011). Further, anxiety disorders are present in 25-30%, and mood disorders in 10-30% of children with ADHD (Angold et al., 1999; Biederman et al., 1991).

Comorbidity of ADHD and depression

To date, most studies have investigated the associations of ADHD with learning problems, ODD and CD. Fewer studies are present on the association of ADHD with anxiety and autism spectrum disorders. Of all ADHD comorbidities, the association with depression has been studied the least (Deault, 2010). Consequently, there is a lack of information on the mechanisms through which depression develops in individuals with ADHD (Steinberg & Drabick, 2015). The development of depression is associated with impaired social, emotional, cognitive and academic functioning of children with ADHD (Meinzer at al., 2014). Comorbid depression also leads to impairments in adulthood and to increased risks for substance misuse, social functioning problems, cognitive functioning difficulties, suicidal attempts, risky behaviour, and occupational difficulties (Bramham et al., 2012; Michielsen et al., 2013; Semeijn et al., 2015). In addition, the development of depression impairs the ability of affected individuals to perceive their symptoms and estimate their impairment levels (Bramham et al., 2012). This may negatively affect their

decision to seek professional help and also impair quality of life. Taken together, it is imperative that this comorbid condition be examined in-depth.

The lack of knowledge regarding the ADHD-depression association hampers timely and adequate intervention. Furthermore, treatment regimens for individuals with ADHD and comorbid depression are currently ill-established. The rule of thumb in these cases is to treat whichever of the two (ADHD or depression) is associated with higher severity (Daviss, 2008). This approach is often ineffective and requires changes to management protocols to adequately tackle the risks of deteriorating functioning associated with comorbid depression (Daviss, 2008). The optimum route to take involves preventing the development of depression in children and adolescents with ADHD. For this it is important to recognise or anticipate its occurrence in vulnerable groups. Identification of the correlates of comorbid depression in children and adolescents with ADHD is, however, an ongoing task.

Until recently, the association of ADHD with depression was considered an epiphenomenal co-occurrence, based on the idea that all psychiatric conditions are correlated and the occurrence of a single comorbidity can be predicted from the common co-occurrence of all other mental health problems (Angold et al., 1999). Recent research has shown that this view may not be true; individuals with ADHD are likely to show higher rates of depression than those without ADHD even after controlling for other comorbid conditions (Biederman et al., 2008; Meinzer et al., 2013).The co-occurrence of ADHD and depression may also be explained as an overlap in diagnostic criteria of the two disorders, such as concentration problems and sleep difficulties. This view too has been countered by studies that show associations between ADHD and depression after excluding overlapping symptoms (Biederman, Mick, & Faraone, 1998a; Biederman, Faraone, Mick, & Lelon, 1995; Milberger, Biederman, Faraone, Murphy, & Tsuang, 1995). In short, the relationship of ADHD with depression is not merely a spurious association, but a genuine comorbid association that has been established by several studies (Biederman et al., 1991; Meinzer et al., 2015; Meinzer et al., 2014).

Several explanations have been floated for the association of ADHD with depression. These include: (i) sharing of common vulnerabilities by ADHD and depression, leading to a simultaneous increase in risk for developing both disorders; (ii) increased risk for depression attributed by ADHD, and; (iii) existence of a separate disorder type. These three hypothesized rationales for the ADHD-depression association are further explained below.

First, previous studies indicate that ADHD and depression share common vulnerabilities that may lead to their co-development (Biederman et al., 1991).[1] For example, genetic factors such as the 5-HTTLPR, 40-basepair (bp) Variable Number Tandem Repeat (VNTR) of DAT1, and 48-bp VNTR of DAT1 may underlie both ADHD and depression by way of their effects on the serotonergic and dopaminergic pathways (Gatt, Burton, Williams, & Schofield, 2015; Meinzer et al., 2014). Variation in reward responsivity may be another common underlying factor for both ADHD and depression: depression is associated with blunting of responses to potentially rewarding stimuli (Forbes, 2009; Pizzagalli, Iosifescu, Hallett, Ratner, & Fava, 2008) and ADHD is associated with reduced neural activation during reward anticipation (Scheres, Milham, Knutson, & Castellanos, 2007; Stark et al., 2011). One study reported poor hedonic responsivity in both ADHD-inattentive subtype and depression (perhaps due to repeated social or academic failures) and suggested that it was a common factor, the development of which is associated with both ADHD and depression (Meinzer, Pettit, Leventhal, & Hill, 2012). These vulnerability factors explain only part of the ADHD-depression association though, and are based on a few studies. Moreover, the 'common vulnerability factor' explanation does not clarify why some individuals with such vulnerability factors escape development of one disorder, nor does it explain the absence of any (known) common vulnerabilities in many individuals with both ADHD and depression. Clearly, further research is needed to understand how common factors lead to the development of ADHD and depression, as well as to detect more such vulnerability factors. This, however, is not a topic of study for this thesis.[2]

Second, the co-occurrence of the two problems is attributed to an increased risk for depression induced by ADHD (Meinzer et al., 2014). The pathway from ADHD to depression is more plausible than the reverse pathway from depression to ADHD (Ostrander & Herman, 2006). However, information on the mediators involved in this pathway is currently limited (Deault, 2010; Meinzer, 2015; Seymour et al., 2012; Steinberg et al., 2015). One of the aims of this dissertation includes understanding some of the mediators involved in the pathway from ADHD to depression.

[1] While these common vulnerability factors are present early on, and some may even be present right since birth, the development of ADHD precedes the onset of depression, which is the age-norm for presentation of these disorders.

[2] To conduct this type of research, one would want to determine the genetic profile that explains both disorders. Such work needs to be done in very large samples, and cannot be done in the TRAILS sample on its own. It should be added that the success of such genetic work has been rather limited for psychiatric disorders so far. Moreover, the common environmental risk factors must be determined early on, prior to the development of ADHD, and be tracked continuously up to the development of depression in order to determine the relationships of such common factors to both disorders. This is not possible in TRAILS due to the age range of the sample studied, which was recruited only after the development of ADHD.

Third, some researchers have proposed that ADHD with depression constitutes a separate and new disorder type (Meinzer et al., 2014). To define a new disorder, this hypothesised disorder must have no semblance to another existing disorder type. In case of ADHD-depression, aetiology, correlates, and consequences of the combined condition must be uniquely identifiable as compared to ADHD alone or depression alone. Current guidelines on the identification and definition of a new disorder type, distinct from existing disorders, require to determine its validity as a uniquely identifiable phenomenon (Milich et al., 2001; Widiger & Clark, 2000). Criteria for determining the validity of a hypothesized new disorder were first established by Emil Kraepelin (Widiger et al., 2000) and later modified by Cantwell and Baker (1988), and Feighner et al. (1972). According to these criteria, a six-step procedure should be followed to establish validity of a disorder, including: (i) a description of features of the disorder; (ii) a clinical description of the disorder using physical and neurological features; (iii) laboratory studies; (iv) family psychopathology and family interaction studies; (v) follow-up and characterization studies, and (vi) treatment outcome studies. It is generally agreed that more of these approaches indicate unique featurs, the stronger is the evidence to support a disorder classification (Milich et al., 2001; Widiger et al., 2000). Based on the above-mentioned criteria, there is a scarcity of useful information to determine whether ADHD-depression constitutes a separate disorder. A few cluster analytic studies found no evidence for a subgroup with combined ADHD and depressive symptomatology, showing that it may be difficult to delineate the combined condition from ADHD alone (Nigg, Goldsmith, & Sachek, 2004; Pauli-Pott, Dalir, Mingebach, Roller, & Becker, 2014; Wilens et al., 2002). Of note is that studies do show an aggregation of ADHD and depressive symptoms in affected families. That is, unaffected parents and siblings of children with ADHD are more likely to be depressed than families of children without ADHD (Bhatia, Nigam, Bohra, & Malik, 1991; Grigoroiu-Serbanescu, et al., 1991; Mick, Biederman, Santangelo, & Wypij, 2003). Although such a familial aggregation may suggest the presence of a separate disorder type, it is insufficient evidence by itself (Feighner et al., 1972). A second aim of this thesis is to further explore the validity of the ADHD-depression disorder, with a particular focus on the first of the above-mentioned criteria: characterization of individuals affected with the both ADHD and depression to see whether this combination could qualify as a separate disorder. Evidence for classification of ADHD-depression as a separate disorder would be delivered if it could be shown that individuals affected with the combined condition show unique qualitative characteristics that differ from cases of ADHD without depression and depression without ADHD, which are not merely their sum of the characteristics seen in the two component disorders (Rutter, 1978).

Summarizing, knowledge of the ADHD-depression relationship is still lacking in many respects, and at least two major issues remain to be tackled. First, it is still unclear whether co-occurring ADHD

and depression constitutes a separate disorder type. Second, the mechanisms through which depression may develop in individuals with ADHD are not clear. In particular, mediators and moderators of the pathways from ADHD to depression are to be further determined.

Goals of this thesis

This thesis aims at: a) characterising adolescents with ADHD and comorbid depression, and; b) identifying mediators of the pathways from ADHD to depression. To achieve these goals, I conducted a number of studies, which are described in the following chapters of this thesis. First, I assessed and compared the cognitive functioning of adolescents with ADHD and comorbid depression to that of adolescents with only ADHD, only depression and neither ADHD nor depression (chapter 2). Second, I compared the family functioning characteristics of adolescents with ADHD and depression to that of adolescents with either disorder alone or no disorders (chapter 3). Third, the role of comorbid ODD/CD and anxiety disorders as mediators of the ADHD-depression pathway was explored (chapter 4). Fourth, I studied the effects of peer functioning difficulties on the risk for depression (chapter 5). Fifth, the pathways from ADHD through peer difficulties to depression were examined in-depth in a narrative review (chapter 6). This thesis ends with a summary of the evidence gathered from all above-mentioned studies, followed by a discussion that puts these results in context of information from existing research findings, deliberates on the translation of these research findings to practical use, and suggests avenues for future investigations (chapter 7). Results from this research will assist in the early identification of individuals at risk for comorbid depression, clarify processes leading to comorbid depression, and add to our understanding as to whether or not ADHD plus depression constitutes a separate disorder, and thereby improve understanding of the ADHD-depression association.

Framework of studies

Studies included in this thesis were carried out using data from the TRacking Adolescents' Individual Lives (TRAILS) cohort. The TRAILS cohort is a notable and well-characterised sample of adolescents, who have been followed-up repeatedly, for a period of over twelve years now (Oldehinkel et al., 2015). This cohort provides a sound framework to reach the goals outlined previously. Thus far, studies on the associations of ADHD and depression have utilised cross-sectional samples. The longitudinal nature of the TRAILS cohort stands to provide additional information on the ADHD-depression relationship, especially on the pathways that lead from one disorder to the other.

TRAILS included participants from the general population (population cohort) as well as clinically referred subjects (clinical cohort; referral only in part for ADHD). Most studies described in

this thesis used data from the general population sample of TRAILS, with the exception of chapter 5 that included participants from both the population and clinical cohort. Much of the ADHD literature is based on information from referred samples, and little is known of this disorder in the general population (Daviss, 2008; Meinzer et al., 2013). Clinically referred participants, who tend to have high symptom severity, multiple comorbidities and functional impairments, are the norm in ADHD-related research. Thus, use of the TRAILS population cohort will provide new and more balanced information on ADHD and its characteristics in the general population.

Diagnoses of ADHD and depression in the TRAILS participants were made using criteria of the DSM-IV (American Psychiatric Association, 1994; Kessler et al., 2004; Wittchen, Robins, Semler, & Cottler, 1993). For ADHD, the criteria required presence of hyperactivity/impulsivity symptoms and/or inattentive symptoms by the age of 7 years. For assessments of depression, lifetime diagnoses of depressive disorders were used (please see table A for the complete DSM checklist of symptoms). As all participants were 19 years at the time of the last assessment, the development of comorbid depression up to only this time-point was assessed. Although it is certainly possible that comorbid depression developed (and will develop) later in these participants with age, the likelihood of such an occurrence is probably much less than in (late) adolescence. A recent study showed that the development of depression in individuals with ADHD reaches peak levels at 18 years of age, and that the risks thereafter reduce dramatically (Meinzer et al., 2015). Hence, the studies in this thesis give a fairly inclusive picture of individuals with ADHD and comorbid depression.

Table A DSM checklist of symptoms for ADHD and depression

DSM symptom checklist
ADHD
I] Inattention (six of the following nine symptoms must have been present in at least two settings for a minimum of six months for a diagnosis of ADHD-inattentive subtype)
Often does not give close attention to details or makes careless mistakes in schoolwork, work or other activities
Often has trouble keeping attention on tasks or play activities
Often does not seem to listen when spoken to directly
Often does not follow through on instructions and fails to finish schoolwork, chores or duties in the work place (loses focus, gets sidetracked)
Often has trouble organizing activities
Often avoids, dislikes, or doesn't want to do things that require sustained metal effort
Often loses things necessary for tasks or activities
Is often easily distracted
Is often forgetful in daily activities
II] Hyperactivity (six of the following nine symptoms must have been present in at least two settings for a minimum of six months for a diagnosis of ADHD-hyperactive impulsive subtype)
Often fidgets with hands or feet or squirms in seat when sitting still is expected
Often gets up from seat when remaining in seat is expected
Often excessively runs about or climbs when and where it is not appropriate
Often has trouble playing or doing leisure activities quietly
Is often "on the go" or often acts as if "driven by a motor"
Often talks excessively
Often blurts out answers before questions have been finished
Often has trouble waiting one's turn
Often interrupts or intrudes on others
Additional criteria for ADHD diagnosis: - Age of onset at or before 7 years - Presence of at least 6 inattentive and six hyperactive symptoms for a diagnosis of ADHD-combined subtype - Clear evidence of clinically significant impairment in social, academic, or occupational functioning - Determining that the symptoms are not better accounted for by another mental health disorder
Major depressive disorder
Depressed mood or a loss of interest or pleasure in daily activities for at least two weeks
Presence of at least 5 out of the following nine specific symptoms[3]: - Depressed mood or irritable most of the day - Decreased interest or pleasure in most activities, most of the day, each day - Significant weight change (5%) or change in appetite - Insomnia or hypersomnia - Change in activity levels such as psychomotor agitation or retardation - Fatigue or loss of energy - Guilt/worthlessness

[3] For minor depression must have at least two but not five of the nine symptoms listed

- Diminished ability to think or concentrate, increased indecisiveness - Suicidal thoughts
Additional criteria: - Mood represents a change from person's baseline - Symptoms cause significant impairment in functioning - Screening for conditions that may mimic or co-exist with major depressive disorder (substance abuse, medical illnesses, mania, hypomania, bipolar disorder, schizophrenia, schizoaffective disorder, bereavement)
Dysthymic disorder
Depressed mood most of the day, for more days than not, for at least two years
Presence of two or more of the following symptoms: - Poor appetite or overeating - Insomnia or hypersomnia - Low energy or fatigue - Low self-esteem - Poor concentration or difficulty in decision-making - Feeling of hopelessness
Symptoms cause significant impairment in functioning

CHAPTER 2

Cognitive functioning in adolescents with self-reported ADHD and depression: results from a population-based study

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Based on:

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ABSTRACT

This study aims to assess cognitive functioning differences among adolescents with retrospectively self-reported: ADHD and an onset of depression, only ADHD, only depression, and neither ADHD nor depression. Data from the Tracking Adolescents' Individual Lives Survey (TRAILS) cohort was used in this study. Neuropsychological functioning was assessed in 1549 adolescents, at baseline and follow-up (mean ages 11 and 19 years). The Composite International Diagnostic Interview was used to classify adolescents into four groups: ADHD with onset of depression, only ADHD, only depression, and neither ADHD nor depression. Linear mixed effects models were used to analyse group differences in cognitive functioning at baseline and follow-up, and the change in cognitive functioning between these two time-points. Results showed a significant main effect of group on response time variability at baseline, working memory maintenance at follow up, and change in response time variability scores between baseline and follow-up. As compared to the healthy and depressed-only groups, adolescents with only ADHD showed longer response time variability at baseline and, which declined between baseline and follow-up. Adolescents with ADHD plus depression showed higher reaction time for working memory maintenance than the depressed only and healthy groups at follow-up. In conclusion, adolescents with self-reported ADHD show poorer cognitive functioning than healthy adolescents and those with only depression. Amongst adolescents with ADHD, specific cognitive domains show poor functioning depending on the presence or absence of comorbid depression. While adolescents with only ADHD have lower reaction time variability, those with comorbid depression have poorer working memory maintenance.

Keywords: ADHD; depression; cognition; adolescents

INTRODUCTION

Attention Deficit Hyperactivity Disorder or ADHD is a neurodevelopmental disorder of childhood that often persists into adolescence and adulthood (American Psychiatric Association, 2013). Apart from symptoms of hyperactivity, impulsivity and inattentiveness, affected individuals show a wide range of cognitive functioning deficits, such as problems in planning, working memory, inhibition and attention (Cortese et al., 2015; Sebastian et al., 2014; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Cognitive dysfunction in ADHD is heterogeneous; not only are cognitive deficits absent in many cases of ADHD, affected cognitive domains also vary widely across individuals with ADHD (Martel, Roberts, Gremillion, von Eye, & Nigg, 2011). There is, thus, poor consensus regarding the specific cognitive profile associated with ADHD (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005; Sergeant, Geurts, & Oosterlaan, 2002; Sergeant, Geurts, Huijbregts, Scheres, & Oosterlaan, 2003; Sjowall, Roth, Lindqvist, & Thorell, 2013; Sonuga-Barke, 2003). A suspected source of this variability may be the high comorbidity of ADHD with other psychiatric disorders (Pauli-Pott, Dalir, Mingebach, Roller, & Becker, 2014). Comorbidities may increase the severity of existing cognitive deficits in children and adolescents with ADHD (Crawford, Kaplan, & Dewey, 2006). In addition, comorbid disorders may modify the cognitive functioning profile associated with ADHD. Although not much is known yet about the deficits associated with ADHD in combination with specific comorbid disorders, it is likely that cognitive profiles differ for each of these conditions (Larochette, Harrison, Rosenblum, & Bowie, 2011; Pauli-Pott et al., 2014; Vloet, Konrad, Herpertz-Dahlmann, Polier, & Gunther, 2010; Willcutt et al., 2001). In this study we will focus on the cognitive functioning and development of depression in adolescents with and without ADHD.

Depression develops in 30 to 70% of individuals with ADHD (Chronis-Tuscano et al., 2010; Fergusson, Boden, & Horwood, 2010; Jensen, Shervette, Xenakis, & Richters, 1993; Meinzer, Pettit, & Viswesvaran, 2014) Results from these studies show that both boys and girls with ADHD, across a wide age range from 4 to 18 years, are likely to develop depression. Comorbid depression leads to further impairments in prognosis and quality of life (Angold, Costello, & Erkanli, 1999; Bagwell, Molina, Pelham, & Hoza, 2001; Biederman et al., 1993; Blackman, Ostrander, & Herman, 2005; Coleman, 2008). A knowledge of the cognitive profile associated with ADHD and comorbid depression may assist in understanding the ADHD-

depression relationship better. Not many studies though, exist on the cognitive functioning of individuals with ADHD and depression. A recent meta-analysis indicated that depression is weakly to moderately associated with deficits in various cognitive domains (Snyder, 2013), several of which are also common to ADHD (Nigg, 2005).

The combined condition of ADHD and depression may give rise to a unique cognitive profile that is distinguishable from that of either disorder alone (either ADHD or depression) in the following manners. First, as found in previous studies, comorbidities may increase the severity of cognitive deficits (Crawford et al., 2006). Therefore, individuals with ADHD plus depression may have a worse cognitive functioning than those with either ADHD or depression. Second, cognitive deficits may be a vulnerability factor, facilitating the onset of depression (Austin, Mitchell, & Goodwin, 2001). Thus, in adolescents with ADHD too, cognitive dysfunction may precede an onset of depression. Prospective studies on long-term outcomes of cognitive (dys)function in ADHD are limited and consequently this idea has not been explored yet. Third, cognitive maturation is often delayed amongst individuals with ADHD (Rajendran et al., 2013; Shaw et al., 2006; Shaw et al., 2007). A development of depression during this period may further interfere with the process of cognitive maturation and thereby differentiate cases of ADHD plus depression from cases with either ADHD or depression.

This study aims to understand if ADHD with an onset of depression is associated with a unique cognitive profile. In a large population-based sample with retrospective self-reports of ADHD and depression, we assess cognitive functioning differences at two time-points among adolescents with ADHD plus depression, only ADHD, and controls with or without depression. Further, we also assess group differences in the change in cognitive functioning between the two-time points.

METHODS

Cohort

The data were collected as part of the TRacking Adolescents' Individual Lives Survey (TRAILS), an ongoing Dutch prospective cohort study on psychosocial development and mental health of adolescents. TRAILS involves bi- or triennial measurements from ages 11 onwards and consists of two separate cohorts: one population-based and another clinic-based. (de Winter et

al., 2005; Huisman et al., 2008; Oldehinkel et al., 2015; Ormel et al., 2012). This study is based on data from the TRAILS population cohort.

Children were recruited from five municipalities in the north of The Netherlands, including both urban and rural areas. Primary school participation was 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. The present study utilises data from the first and fourth wave. The first wave (T1) ran from March 2001 to July 2002, the fourth (T4) from October 2008 to September 2010 (T4). Mean age at T1 was 11.1 years (SD = 0.56), and 50.8% were girls. 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. (For an overview of the mean age and gender distributions of participants please see appendix 1). To ensure all onsets of depression were between T1 and T4, we excluded participants who developed a depression prior to T1 (n = 35). This gave a final sample size of 1549 adolescents. T1 is referred to as baseline and T4 as follow-up in following sections of the paper.

The Amsterdam Neuropsychological Tasks, used in this study to assess cognitive function, was also part of two previous TRAILS publications on depressive problems in adolescents (but not specific to ADHD) (Nederhof, Ormel, & Oldehinkel, 2014; Oldehinkel, Hartman, Van Oort, & Nederhof, 2015). These studies used different ANT parameters than here focusing on either attention style (Nederhof et al., 2014) or emotion recognition (Oldehinkel et al., 2015) in relation to depressive symptoms (rather than disorder). Further, data from the TRAILS cohort has been used in two studies to study mediators (other than cognitive function) of the ADHD-depression association (Roy, Hartman, Veenstra, & Oldehinkel, 2015; Roy, Oldehinkel, Verhulst, Ormel, & Hartman, 2014). Thus, the content of the current manuscript does not overlap with these previous publications.

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

Cognitive functions were assessed at baseline and follow-up using the Amsterdam Neuropsychological Tasks program (ANT) (please see appendix 2 for further details). The ANT has proven to be a sensitive and valid tool in assessing cognitive functions (de Sonneville, Geeraets, & Woestenburg, 1993), especially for population and clinic based samples of attention-deficit/hyperactivity disorder (Hanisch, Konrad, Günther, & Herpertz-Dahlmann, 2004; Slaats-Willemse, Swaab-Barneveld, De Sonneville, Van Der Meulen, & Buitelaar, 2003). Previously, studies have used the ANT to assess sustained attention, processing speed (Huijbregts et al., 2002), focused attention, working memory, cognitive flexibility (Lazeron, de Sonneville, Scheltens, Polman, & Barkhof, 2006) and response inhibition (Groot, de Sonneville, Stins, & Boomsma, 2004). A detailed description of the ANT is available in previous studies (Nederhof, Ormel, & Oldehinkel, 2014; van Deurzen et al., 2012). In short, the ANT is a computer-aided test to assess cognitive capacities, with high sensitivity and validity. We used five subtasks from the ANT: (a) Baseline Speed task, (b) Pattern Recognition task, (c) Sustained Attention - dots task, (d) Memory Search - letters task, and (e) Shifting Attentional Set - visual task. All children were tested individually by trained undergraduate psychology students. Use of prescribed medications (if any) was not withheld prior to the assessments. Verbal instructions, emphasizing both speed and accuracy of performance, and practice trials preceded each task. Six output measures were calculated from the above tasks: processing speed (from Baseline Speed), focussed attention (from Pattern Recognition), response time variability (from Sustained Attention Dots), working memory maintenance (from Memory Search - letters), response inhibition (from Shifting Attentional Set – visual), and cognitive flexibility (from Shifting Attentional Set – visual). For all output measures, except response time variability, mean Reaction Time (RT) in milliseconds was defined as the outcome parameter (for response time variability, within-subject variability in RT of the sustained attention – dots task was defined as the outcome). Only RTs to correct trials were used in the analyses. The Baseline Speed task required responses from both the dominant and the non-dominant hand. The outcome parameter for this task was defined as mean RT of responses from both hands. For all outcomes, RTs with an absolute z-score greater than or equal to 4 were defined as missing (Stevens, 2009). Correlations between the measures were generally weak (mean r = 0.24, range = .07-.55), suggesting limited overlap.

Psychiatric disorders were assessed at follow-up 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 (DSM-IV). The CIDI has been used in a large number of surveys worldwide, and 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 has good reliability and validity for most diagnoses (Wittchen, 1994). In this study, information on CIDI diagnoses of ADHD and depression were used. The ADHD screening questions were operationalised as: (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/or (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. A positive response to either of these two questions was followed up by a full DSM-IV based assessment of ADHD. This includes the presence of the requisite number of ADHD symptoms as defined in DSM-IV, an onset before the age of 7, and the presence of functioning impairments. Depression was operationalized as a lifetime diagnosis of Major Depressive Episode (with or without (hypo)manic symptoms), Dysthymia, or Minor Depressive Disorder. Validity of the CIDI data was supported by prospective parent-, self-, and teacher-reports as assessed with the Child Behaviour Checklist (CBCL), Youth Self Report (YSR), Adult Self Report (ASR), and Teacher's Checklist of Pathology (TCP) from the first wave onwards (appendix 3, Tables III-IV) (Achenbach, 1991a; Achenbach, 1991b). The TCP, developed by the TRAILS team (de Winter et al., 2005), is based on items from the Teacher's Report Form (Achenbach & Rescorla, 2001). As several participants in the TRAILS cohort were from the same class, the TCP was developed to ease the filling up of questionnaires by teachers. Teacher-reported ADHD scores in this study combined the attention and hyperactivity/impulsivity problem items of the TCP (corresponding to the CBCL-YSR attention problems scales).

Information on medication use between baseline and follow-up was collected using parent and self-report questionnaires. Use of anti-depressants included imipramine,

clomipramine, amitriptyline, nortriptyline, fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, escitalopram, moclobemide, venlafaxine; while medications for ADHD involved methylphenidate, atomoxetine, and dexamphetamine.

Analyses

Based on lifetime CIDI diagnoses at follow-up, participants were categorized into four groups: (1) ADHD with an onset of depression (Group A + D), (2) only ADHD (Group A), (3) only an onset of depression (Group D), and (4) comparison: neither ADHD nor an onset of depression (Group C). Mean self-reported ADHD and depressive symptom scores (assessed using the YSR at T1, T2, T3 and the ASR at T4) at the four assessment waves were plotted to visualise the approximate time-point of divergence in symptom scores amongst the four groups.

Linear mixed effects models were used to analyse differences in cognitive functioning among these groups at baseline and follow-up as well as change in cognitive functioning between baseline and follow-up (slope). We adjusted for the effects of age at baseline, gender, and medication use in the analyses by including these variables as covariates. The (co)variance matrix was set to unstructured (i.e. freely estimated) for all analyses. For the cognitive outcome measures that showed group differences, we additionally plotted the standardized RTs per group at baseline and follow-up and estimated the effect sizes of comparisons with group C using Cohen's d.

A sensitivity analysis was conducted as a second step to determine if (lack of) differences in cognitive functioning among groups were due to the presence of psychiatric disorders other than ADHD or depression in the comparison group. For this, a new comparison group (Group H: healthy) was formed by excluding participants with CIDI diagnoses of other psychiatric disorders from group C, and the above-described linear mixed effects analyses were re-run to test cognitive functioning differences among groups A + D, A, D and H. Age at baseline, gender and medications were included as covariates.

A second sensitivity analysis was additionally performed to explore the validity of the CIDI diagnoses. Data on parent-reported ADHD as assessed by the Diagnostic Interview Schedule for Children (DISC) were available for the parallel TRAILS Clinical (high-risk) Cohort at baseline. A comparison of the DISC with the CIDI outcomes showed that almost 80% of

children with an ADHD diagnosis at baseline according to the DISC did not have a CIDI diagnosis of ADHD in adulthood (note that both interviews required an onset of ADHD before age 7). Conversely, 80% of those who had a CIDI diagnosis of ADHD also had a DISC diagnosis of ADHD in childhood. These results suggest the presence of relatively few false positives in our current sample (with the use of CIDI), yet many false negatives. To assess the possibility of false negative ADHD diagnoses using the CIDI, we reformed the comparison group by excluding participants with a high baseline CBCL or TCP ADHD symptom score (i.e., scores higher than 1.5 SD in the total sample).

Analyses were performed using SPSS v. 22.0.0 (IBM Corp., Armonk, NY) and graphs were plotted using MATLAB 2012b (The MathWorks, Inc. Natick, MA). All tests were two-tailed and a $p \leq 0.05$ was considered statistically significant. For the post-hoc pairwise tests, results were adjusted using the Benjamini-Hochberg False Discovery Rate (FDR) (Benjamini & Hochberg, 1995) and the threshold for statistical significance was set at $p \leq 0.05$.

RESULTS

Of the 1549 adolescents in our study, and based on the CIDI, 3.6% received a diagnosis of ADHD (n = 56), and 19.6% a diagnosis of depression (n = 303). Amongst those with ADHD, 37.5% developed depression between baseline and follow-up (n = 21). These numbers are consistent with estimates of lifetime mental health problems obtained in late adolescence (Merikangas et al., 2010). Of the total sample, 37.5% of adolescents with ADHD and 5.6% of adolescents with depression received medication at some point between the four assessment waves. Participants with and without medications did not differ in their cognitive functioning scores at baseline or follow-up (for further details please see appendix 3 [Tables I-II]).

Parent- (CBCL) and teacher- (TCP) reports, available at baseline, were used to estimate the number of adolescents in the A+D and A groups with ADHD scores >1.5 SD. Parent-reports showed > 1.5 SD scores in 5 participants from group A + D (n = 21) and 12 participants from group A (n = 35). Using teacher-reports, these numbers were 5 in group A + D and 7 in group A. Scores greater than 1.5 SD on either parent or teacher reports were found among 10 participants from group A + D and 13 participants from group A. Mean parent-reported ADHD symptom scores in group A + D and A were 0.87 (SD = 0.58) and 1.01 (SD = 0.45), respectively. Mean

teacher-reported ADHD symptom scores were 1.41 (SD = 1.20) and 1.16 (SD = 1.18) for groups A + D and A, respectively.

Figure 2.1 presents mean self-reported ADHD and depressive symptom scores assessed (using the YSR and ASR) at each time point for the four groups. At T1, group A + D had higher self-reported ADHD symptoms than group C (d = 0.53, p = .019), while group A had higher ADHD symptoms than groups D (d = 0.67, p < .001) and C (d = 0.88, p < .001). ADHD symptom scores at T4 of group A + D was higher than groups A (d = 0.66, p = 0.004), D (d = 1.41, p < .001) and C (d = 2.05, p < .001), and of group A was higher than groups D (d = 0.66, p < .001) and C (d = 1.24, p < .001). Depressive symptoms at T1 were higher amongst groups A + D (d = 0.53, p = .023), A (d = 0.48, p = .002) and D (d = 0.43, p < .001) than group C. At T4, mean depressive scores were high for group A + D as compared to group A (d = 0.98, p < .001), group D (d = 0.64, p < .001) and group C (d = 1.73, p < .001). For group D at T4, depressive symptoms were higher than group A (d = 0.35, p = .010) and group C (d = 1.01, p < .001).

Table 2.1 presents mean age at onsets of ADHD and depression, and mean RTs for cognitive outcome measures in the five groups A + D, A, D, C, and H. Pearson's correlations revealed statistically significant relationships between RTs at baseline and follow-up for all cognitive outcome measures (processing speed: r = 0.44; focussed attention: r = 0.37; response time variability: r = 0.50; working memory maintenance: r = 0.46; inhibition: r = 0.34; cognitive flexibility: r = 0.34; all p < .001). For further details on the association between baseline and follow-up cognitive functions in the TRAILS sample, please see (Boelema et al., 2013).

Linear mixed model analyses with sex, age, and ADHD and depression medication use as covariates revealed significant group differences in response time variability at baseline ($F_{(3,1517)}$ = 3.92, η^2 = 0.004, p = .008), working memory maintenance at follow up ($F_{(3,1515)}$ = 2.56, η^2 = 0.004, p = .05), and change in response time variability scores between baseline and follow-up ($F_{(3,1515)}$ = 3.35, η^2 = 0.005, p = .01). Baseline response time variability RT was higher in group A than group C (p = .001). Working memory maintenance RT at follow-up was higher in group A + D than group C (p = .007). Between baseline and follow-up, the slope of change in response time variability RT for group A was significantly more negative (p = .002) than that of group C. The covariates-corrected effect sizes for these three differences were d = 0.44, d = 0.60, and d = -0.47, respectively. Finally, results of post-hoc pairwise comparisons are presented in table 2.2.

Figure 2.2 presents RTs of the four groups for response time variability and working memory maintenance functions at the two time-points. Linear mixed model analyses on these RT scores (without including covariates) yielded similar group differences in response time variability at baseline ($F_{(3,1521)}$ = 4.23, η^2 = 0.003, p = .005), working memory maintenance at follow up ($F_{(3,1521)}$ = 2.56, η^2 = 0.002, p = .05), and change in response time variability scores between baseline and follow-up ($F_{(3,1516)}$ = 3.36, η^2 = 0.004, p = .01) and likewise indicated a higher baseline response time variability RT in group A than group C (p = .001); higher working memory maintenance RT at follow-up in group A + D than group C (p = .007); and a more negative slope of change in response time variability RT for group A relative to group C (p = .002). The effect sizes for these three differences were d = 0.52, d = 0.60, and d = -0.55, respectively.

For the first sensitivity analysis, participants from group C with psychiatric diagnoses (other than ADHD or depression) were excluded (separation anxiety: n = 19; agoraphobia: n = 6; conduct disorder: n = 71; generalised anxiety disorder: n = 22; oppositional defiant disorder: n = 65; panic disorder: n = 13; separation anxiety disorder: n = 25; social phobia: n = 110; specific phobia: n = 110, total n = 323) to form a new group of 888 adolescents (group H; healthy). Linear mixed effects analyses revealed group differences in baseline response time variability ($F_{(3,1207)}$ = 4.64, η^2 = 0.007, p = .003), change in response time variability between baseline and follow-up ($F_{(3,1200)}$ = 3.99, η^2 = 0.005, p = .008), and follow-up working memory maintenance ($F_{(3,1198)}$ = 2.76, η^2 = 0.005, p = .041). Results of group and posthoc pairwise comparisons for response time variability and working memory maintenance were comparable to results from the main analysis. In addition, group differences in baseline processing speed ($F_{(3,1201)}$ = 2.90, η^2 = 0.006, p = .03) were found. None of the group differences in processing speed remained significant after applying FDR corrections.

For the second sensitivity analysis, 158 participants with a CBCL or TCP ADHD score with SD > 1.5 were excluded from the comparison group to form a new comparison group of 1391 adolescents. Linear mixed effects analyses revealed group differences in baseline response time variability ($F_{(3, 1373)}$ = 7.05, η^2 = 0.007, p < .001), follow-up working memory maintenance ($F_{(3, 1358)}$ = 3.62, η^2 = 0.005, p = .013) and change in response time variability between baseline and follow-up ($F_{(3, 1369)}$ = 5.42, η^2 = 0.006, p = .001). Results of group and posthoc pairwise

comparisons for response time variability and working memory maintenance were comparable to the results from the main analysis. Additionally, group differences in baseline processing speed ($F_{(3, 1353)} = 3.13$, $\eta^2 = 0.006$, $p = .025$) were found. Post hoc pairwise comparisons showed that group A was significantly slower (FDR corrected) than group C (mean difference = 12.78, SE = 4.63, p = .006).

DISCUSSION

This study was aimed at assessing if ADHD with an onset of depression is associated with a unique cognitive functioning profile in adolescents with retrospectively self-reported ADHD and depression. Results show that cognitive functioning in adolescents with ADHD plus depression and only ADHD differed from the control groups either with or without depression. In particular, working memory maintenance of adolescents with ADHD plus depression at mean age 19 years was poor as compared to healthy adolescents and adolescents with only depression. Furthermore, the group of adolescents with only ADHD performed worse in response time variability at mean age 11 than the depressed and comparison groups. Our results also suggest that response time variability function improved between early adolescence and young adulthood in adolescents with only ADHD. We found no evidence, however, for cognitive functioning differences between adolescents with ADHD who did and did not develop depression.

The presence of comorbidities in individuals with ADHD is believed to increase the severity of cognitive deficits (Crawford et al., 2006). Consequently, we suspected that adolescents with ADHD and comorbid depression may have a poorer cognitive functioning than adolescents with only ADHD. We found no differences specifically between these two groups on our measures. Further, based on previous research, we suspected that an onset of depression in adolescents with ADHD may be preceded by impaired cognitive functioning (Austin, Mitchell, & Goodwin, 2001). Our results did not support this either; adolescents with ADHD who developed depression did not differ from healthy comparisons at the baseline assessments. We also suspected that the development of depression would interfere with the process of cognitive maturation in adolescents with ADHD. Results show that adolescents with only ADHD showed an improvement in their cognitive (response time variability) functioning between ages of 11 and 19 years. Adolescents with ADHD who developed additional depression, did not show any cognitive improvements.

Adolescents with ADHD plus an onset of depression showed poorer working memory maintenance than comparison adolescents at a mean age of 19 years. The presence of memory maintenance difficulties at late adolescence in our sample may be related to the development of comorbid depression in adolescents with ADHD. Based on self-reported symptoms, we found that these adolescents showed increasing depressive symptoms for at least 6 years between the second and fourth assessment waves. ADHD symptom scores, on the other hand, did not change much for this comorbid group. It is possible that the upcoming depression and not ADHD played a role in the poor working memory maintenance performance at late adolescence. However, adolescents with only depression had a similarly increasing depressive symptom profile but did not show poor cognitive functioning in any domain (possible reasons for which we discuss later). It can be speculated that the development of depression may have increased the cognitive burden associated with ADHD and led to working memory maintenance difficulties. Alternately, poor cognitive functioning may have led to the development of depression in adolescents with ADHD.

Working memory maintenance, at age 11, of adolescents with ADHD and either with or without depression was comparable to that of the comparison group. Previous studies though, show impaired working memory in children with ADHD at an early age. Three related reasons as to why we did not find any group differences in working memory maintenance at age 11 in this study are worth mentioning. First, previous studies have been mostly based on recall tasks, which unlike recognition based tasks, such as the memory search task of the ANT, are more likely to show differences between children with and without ADHD early on (Rapport, Chung, Shore, Denney, & Issacs, 2000). Second, working memory maintenance assessed by visual array tasks, as in the ANT, is the 'amount of information held in working memory at any given point' (Rapport, Orban, Kofler, & Friedman, 2013; Shipstead, Redick, Hicks, & Engle, 2012). This component of working memory has been shown to be only minimally affected in children with ADHD (Raiker, Rapport, Kofler, & Sarver, 2012). In contrast, the central executive components of working memory, as assessed by complex span tasks, differ from working memory maintenance by being involved in the active processing of information held internally and are not related to the storage or maintenance of information. The central executive components of working memory are more often impaired than working memory maintenance in children with ADHD (Kasper, Alderson, & Hudec, 2012; Rapport et al., 2013; Shipstead et al., 2012). Third, it

is possible that the memory search task of the ANT measures short-term memory (Cowan, 2008), which is likewise less impaired in children with ADHD (Dovis, van der Oord, Huizenga, Wiers, & Prins, 2015).

Adolescents with only ADHD showed poorer response time variability than comparison adolescents. Response time variability performance, however, improved with time in the group with only ADHD. For this group, self-reported ADHD symptoms also showed a decrease between early and late adolescence. It is likely that a decline in ADHD symptom severity was related to the improving response time variability performance.

Amongst adolescents with ADHD, results showed that the response time variability domain was affected at early adolescence while working memory maintenance was affected at young adulthood. The maturation of various cognitive domains occurs at different ages (Anderson, 2002; Anderson, Anderson, Northam, Jacobs, & Catroppa, 2001; Boelema et al., 2013; Huizinga, Dolan, van der Molen, & Maurits, 2006; Luna & Sweeney, 2004), which may explain why response time variability was affected first followed by working memory maintenance later and not the other way around. The maturation of working memory peaks late in adolescence (Boelema et al., 2013; Huizinga et al., 2006; Luna & Sweeney, 2004) and response time variability may therefore be affected prior to working memory maintenance.

Previous studies have reported cognitive flexibility, focused attention, and response inhibition impairments in individuals with ADHD (Nigg, 2005). We did not find deficits in these three cognitive domains amongst adolescents with ADHD. One explanation for this could relate to the age of assessments in our sample (van Lieshout, Luman, Buitelaar, Rommelse, & Oosterlaan, 2013). The vast majority of research on ADHD-related cognitive deficits involves younger children, while we included adolescent participants. Further, core cognitive deficits proposed to be etiologically related to ADHD are less evidently present in adolescence (despite the presence of ADHD), suggesting that some children have sufficient cognitive maturation and do not show deficits (Thissen et al., 2014). Moreover, various cognitive domains mature at different ages (Anderson, 2002; Anderson et al., 2001; Boelema et al., 2013; Luna & Sweeney, 2004). It is thus, possible that several cognitive functions had matured sufficiently in our sample by the first assessment time point and therefore did not show group differences.

Some studies have suggested that only response inhibition deficits persist in the longer term while other cognitive domains mature sufficiently irrespective of remission from ADHD (Lei et al., 2015; McAuley, Crosbie, Charach, & Schachar, 2014). In this respect, our results may be remarkable in showing a lack of response inhibition deficits at young adulthood. However, these studies were based on patient populations of ADHD with severe problems and often multiple comorbidities. Our research findings are based on ADHD cases selected from the general population, who may not show severe cognitive functioning problems. Another alternative explanation comes from recent studies suggesting that ADHD-related cognitive deficits may be seen only for domains of working memory and sustained attention (Rapport et al., 2013), but not response inhibition (Alderson, Rapport, & Kofler, 2007; Lijffijt, Kenemans, Verbaten, & van Engeland, 2005). A final explanation for not finding response inhibition deficits, as in many previous studies that reported no deficits, may be related to the task differences among studies. Withholding a response on some trials (such as in the Stop task and Go/NoGo task) and withholding a compatible and automatic response on all trials (as in the ANT) may tap into different cognitive processes (Rommelse et al., 2007). Overall, the association of response inhibition deficits with ADHD is widely debated and further research may be needed to fully understand the heterogeneity in current literature.

A recent review of the literature has revealed that several domains of cognitive functioning including flexibility, attention, speed, and inhibition are affected in individuals with depression (Snyder, 2013). Our results did not show impaired functioning in any domain for adolescents with only depression. The majority of studies on cognitive dysfunction in depressed individuals are limited to adulthood or even late-adulthood (Han et al., 2012). Cognitive dysfunction in adolescents with depression may not necessarily be similar to that in adults. It is also likely that depression-related cognitive deficits are not present pre-morbidly or shortly after onset, but develop only gradually if the depression persists or re-occurs over time. In this case, these deficits may not have fully emerged in our sample of young adults with relatively recently developed depressive problems.

An important limitation of our study concerns the use of the CIDI to establish diagnoses of ADHD. Based on parent and teacher reports available at baseline, it was found that ADHD symptom scores were low in the CIDI diagnosed ADHD groups: less than half the participants in

the two ADHD groups scored greater than 1.5 standard deviations on either the parent or teacher ratings. The CIDI is a well-validated interview (Wittchen, 1994), but the ADHD section is of a relatively recent date, and has therefore been used in only a limited number of studies so far (de Graaf et al., 2008; Kessler et al., 2006; Kessler et al., 2010; Lara et al., 2009). The CIDI assesses the presence of self-reported symptoms during a structured interview which are used to construct lifetime as well as current diagnoses according to the DSM-IV. The CIDI- based ADHD diagnosis includes the presence of functioning impairments. Given the age of the sample at the time of the diagnostic interview (about 19 years) and the availability of fully standardized diagnostic interviews at this age, we used the best possible interview to determine the presence or absence of ADHD. Furthermore, the prevalence rates derived from the CIDI are comparable to that obtained from other population-based studies in adulthood (Merikangas et al., 2010). Although previous studies have used information form the respondent to establish ADHD diagnoses in adulthood (de Graaf et al., 2008; Kessler et al., 2006; Lara et al., 2009), in childhood this practice is uncommon. The use of the respondent-only assessments as opposed to multiple-informant based assessments, may underestimate the actual prevalence of ADHD or misdiagnose individuals as having ADHD (Sibley et al., 2012), and this likely also holds for adults (Privitera, Agnello, Walters & Bender 2015). Young adults, like children and adolescents, may not have a full appreciation of their symptoms or impairments and in our sample we may have found additional individuals with a diagnosis of ADHD had we also conducted a parent-interview. Currently, those individuals with (possible) parent but not self-recognized ADHD are part of the no problem group and this misclassification may have led to finding less outspoken cognitive differences between the groups. However, additional post-hoc analyses indicated that removing participants with a high parent/teacher ADHD score at baseline and without a CIDI ADHD diagnosis yielded highly similar findings. One exception was that children with ADHD only were slower on baseline speed at age 11. We conclude that current findings pertain to participants diagnosed with ADHD who themselves recognize their childhood onset ADHD symptoms and impairments. We have nonetheless no reason to doubt the validity of these findings since removal of possible false negatives (i.e. cases we would have identified through a parent interview) did not alter the conclusions of our study.

Other limitations to the manuscript include the following: first, the number of adolescents with ADHD only and ADHD combined with depression was low in our sample. Because of this,

some group differences may not have reached statistical significance. Conversely, some group differences may have reached significance at smaller effect sizes. Second, as the incidence of depression remains high after 19 years of age, a part of the group with only ADHD (as well as part of the control group) may still develop depression later on. This may have led to an incorrect grouping of adolescents, and possible under-estimation of effects. Third, we did not withdraw participants from stimulant medication prior to cognitive testing although this did not seem to influence our findings.

Thus far, it has been difficult to pinpoint the exact cognitive profile associated with ADHD with affected cognitive domains varying widely across studies. Cognitive function is assumed to change throughout development in patients with ADHD and to generally improve with time (Coghill, Hayward, Rhodes, Grimmer, & Matthews, 2014; Halperin & Schulz, 2006; Rajendran et al., 2013). These age-dependent changes may explain some of the discrepancies found in studies. Apart from age-related cognitive deficits, the presence of comorbidities may also explain the heterogeneity of cognitive profiles associated with ADHD. Previously, studies have shown that comorbid anxiety and oppositional defiant disorder can markedly change the cognitive profiles of children and adolescents with ADHD (Rhodes, Park, Seth, & Coghill, 2012; Vance, Ferrin, Winther, & Gomez, 2013). Our results also show cognitive differences amongst adolescents with and without comorbid depression, and further reveal that these profiles vary with age. Future studies may benefit from including assessments of comorbidities and age-dependent changes to better capture the nature of cognitive functioning associated with ADHD.

Table 2.1 Summary of group characteristics, including age at onset of ADHD and depression, and reaction time for cognitive measures at baseline and follow-up

	Groups*				
	A + D N = 21, 52% girls (mean ± SD)	**A** N = 35, 37% girls (mean ± SD)	**D** N = 282, 73% girls (mean ± SD)	**C** N = 1211, 50% girls (mean ± SD)	**H** N = 888, 49% girls (mean ± SD)
Age at onset of ADHD**	6 ± 2	5 ± 2	--	--	--
Age at onset of depression**	14 ± 2.4	--	15 ± 2.2	--	--
Processing speed#					
Baseline	328 ± 38	345 ± 42	329 ± 38	327 ± 39	325 ± 37
Follow-up	243 ± 24	256 ± 25	252 ± 23	250 ± 25	250 ± 24
Focused attention#					
Baseline	1467 ± 604	1533 ± 356	1462 ± 469	1420 ± 443	1404 ± 442
Follow-up	795 ± 301	787 ± 238	810 ± 259	808 ± 258	799 ± 252
Response time variability#					
Baseline	1898 ± 956	2095 ± 762	1688 ± 828	1652 ± 810	1617 ± 806
Follow-up	974 ± 391	916 ± 365	862 ± 366	858 ± 366	849 ± 367
Working memory maintenance#					
Baseline	621 ± 331	576 ± 244	499 ± 267	517 ± 265	517 ± 267
Follow-up	347 ± 173	276 ± 174	257 ± 149	255 ± 146	252 ± 145
Cognitive flexibility#					
Baseline	637 ± 241	645 ± 210	644 ± 250	622 ± 236	621 ± 236
Follow-up	374 ± 143	356 ± 126	377 ± 161	348 ± 146	341 ± 133
Response inhibition#					
Baseline	214 ± 173	235 ± 190	251 ± 191	248 ± 183	245 ± 185
Follow-up	245 ± 207	179 ± 189	210 ± 171	201 ± 164	202 ± 163

*A+D=ADHD with onset of depression, A= only ADHD, D=only depression, C=comparison; neither ADHD nor depression, H=healthy; no psychiatric diagnoses

**in years; #Reaction time in milliseconds

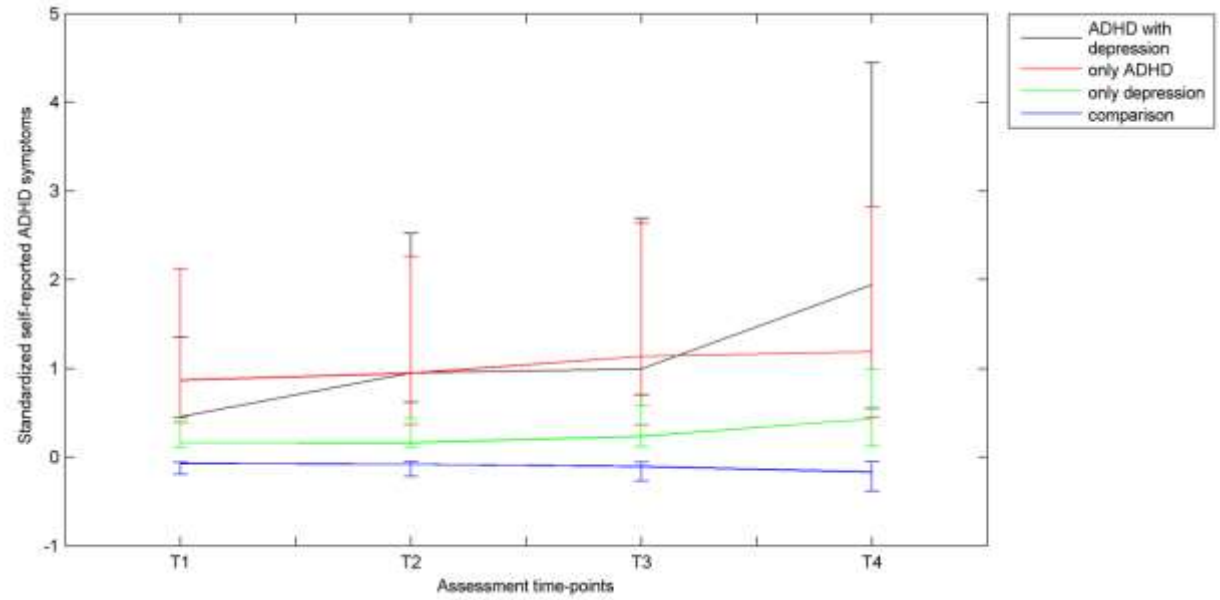
Table 2.2 Posthoc pairwise comparisons of groups for differences in reactions times for response time variability and working memory maintenance

Groups compared*	Response time variability-baseline			Working memory maintenance-follow-up		
	Mean Difference	SE	p#	Mean Difference	SE	p#
A+D v/s A	-123.74	147.66	0.40	64.38	50.19	0.20
A+D v/s D	134.99	121.22	0.26	97.79	41.28	0.01
A+D v/s C	151.50	117.95	0.19	95.97	40.16	0.01
A v/s D	258.74	96.71	0.008	33.40	32.94	0.31
A v/s C	275.25	92.45	0.003	31.59	31.47	0.31
D v/s C	16.51	35.78	0.64	-1.81	12.22	0.88

* Groups: A+D = ADHD with depression, A = only ADHD, D = only depression, C = comparison

p values adjusted for multiple testing using the Benjamini-Hochberg False Discovery Rate

Figure 2.1 Mean ADHD and depressive symptom scores (assessed using Youth Self Reports at T1, T2, T3 and Adult Self Reports at T4) between ages 11 and 19 years for all four groups



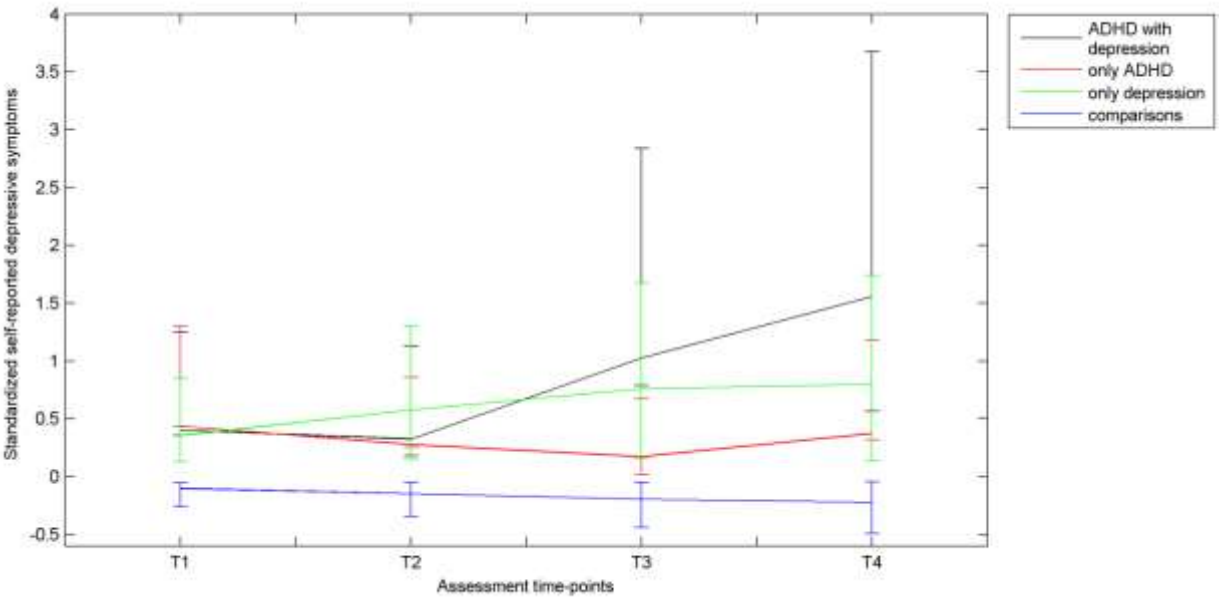
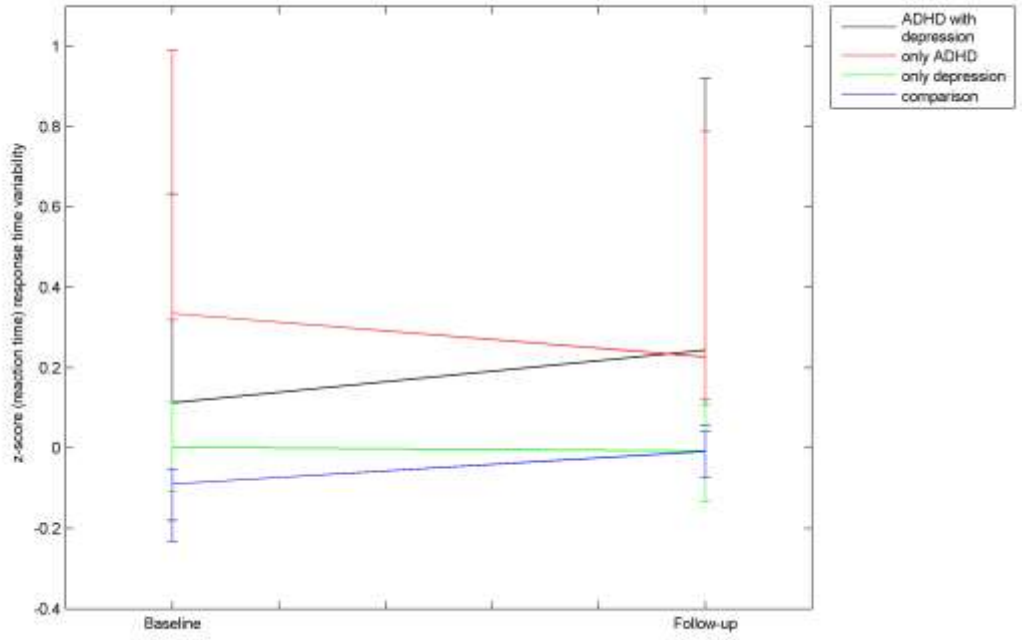
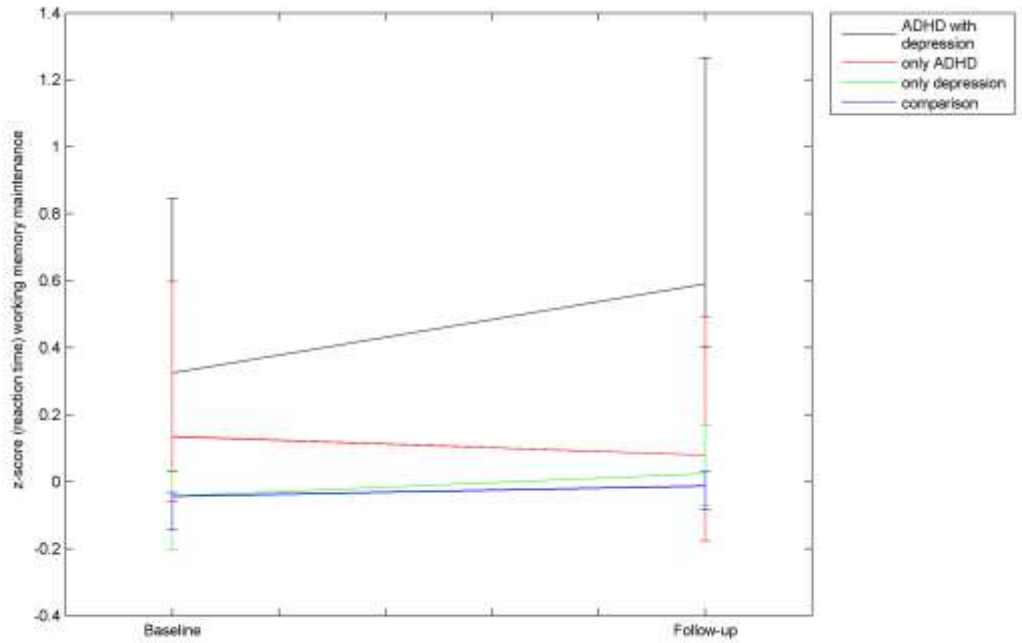


Figure 2.2 Reaction times for working memory maintenance and response time variability at baseline and follow-up





CHAPTER 3

Trajectories of family functioning in adolescents with ADHD and depression

Roy, A., Hartman, C.A.H., Kretschmer, T., Oldehinkel, A.J.

Based on:

Roy, A., Hartman, C.A.H., Kretschmer, T., Oldehinkel, A.J. (*under review*). Trajectories of family functioning in adolescents with ADHD and depression.

ABSTRACT

Objective: To assess whether family functioning trajectories differ amongst adolescents with no Attention Deficit Hyperactivity Disorder (ADHD) and no depression, only ADHD, only depression, and ADHD plus an onset of depression.

Methods: Using DSM-IV diagnostic criteria, 1875 adolescents were classified into four groups: comparison (with neither ADHD nor depression), only ADHD, only an onset of depression, and ADHD plus an onset of depression. Family functioning was assessed at four time-points (mean ages 11, 13, 16 and 19 years) using the McMaster Family Assessment Device (FAD). Mean-centred FAD scores were used to calculate family functioning trajectories (mean, linear trend, quadratic trend) for each participant. Multinomial logistic regressions were used to assess whether family functioning trajectories were associated with membership in any of the four groups.

Results: Adolescents with an onset of depression, either with or without ADHD, showed on average poorer family functioning than the comparison healthy adolescents. Adolescents with ADHD plus depression did not differ in their family functioning from adolescents with only ADHD or only depression. Adolescents with only ADHD showed an improving trend of family functioning.

Conclusion: These results suggest that adolescents with an onset of depression show poorer family functioning than those without depression, irrespective of a diagnosis of ADHD. If adolescents with ADHD do not develop a depression, their family functioning tends to improve over time.

Keywords: ADHD; Depression; Family functioning; Prospective study; Adolescents

INTRODUCTION

Attention Deficit/Hyperactivity Disorder (ADHD) is a common childhood-onset psychiatric problem that often continues into adolescence (American Psychiatric Association, 2013). Symptoms of ADHD include hyperactivity, impulsivity and inattention. Affected individuals face difficulties in daily functioning and problems in maintaining social relationships (Danckaerts et al., 2010; Wehmeier, Schacht, & Barkley, 2010). In particular, difficult family relationships and poor family functioning has been reported in children and adolescents with ADHD (Johnston & Mash, 2001).

Family functioning may be defined as the ability of a family to support the social, psychological, and biological development of its members (Epstein & Keitner, 2005). According to the McMaster Model of Family Functioning, six characteristics of the family are important for a healthy mental and physical functioning: problem solving, communication, roles (how the family shares responsibility), affective responsiveness, affective involvement, and behaviour control (Epstein, Bishop, & Levin, 1978). Numerous studies have shown that difficulties in these functioning domains are associated with psychiatric problems (Staccini, Tomba, Grandi, & Keitner, 2014).

Specific to ADHD, studies on family functioning have mostly focussed on children (Deault, 2010; Johnston & Mash, 2001), and shown that relationships among family members are often strained and conflicting. Parents are likely to be assertive and less warm in their interactions with their children (Gerdes et al., 2007). Additionally, poor parenting practices, parental criticism, and impaired marital relationships are common features in the families of children with ADHD (Deault, 2010; Johnston & Mash, 2001; Ostrander & Herman, 2006; Theule, Wiener, Tannock, & Jenkins, 2013). While studies on the families of adolescents with ADHD are few, evidence suggests that several domains of functioning may be affected in them as well (Deault, 2010; Johnston & Mash, 2001). The developmental changes in family functioning that may happen during adolescence are less well documented (Johnston & Mash, 2001). Family functioning may worsen over time due to stress accumulation or may improve due to an adaptation or reduction in ADHD symptoms. How these trajectories may be further influenced by the development of a comorbid disorder during adolescence is also not yet understood.

When studying family functioning during adolescence, the development of depression is highly relevant and must be considered. Comorbid depression is a common occurrence in

adolescents with ADHD (Biederman, Mick, & Faraone, 1998; Biederman, Ball, Monuteaux, Mick, Spencer, McCreary, Cote, & Faraone, 2008), and is further known to impair prognosis (Blackman, Ostrander, & Herman, 2005; Brunsvold, Oepen, Federman, & Akins, 2008). Depression by itself is known to be associated with an impaired family functioning (Davies & Windle, 1997; Lucia & Breslau, 2006; Martin, Rotaries, Pearce, & Allison, 1995; Heru & Ryan, 2004). In adolescents with ADHD, an additional development of depression may change the existing patterns of family functioning.

This study was set up to better understand trajectories of family functioning associated with diagnoses of ADHD and depression, separately and as comorbid disorders. To achieve this, we compared longitudinal family functioning characteristics of adolescents with no ADHD and no depression, only ADHD, only an onset of depression, and ADHD plus an onset of depression.

METHODS

Cohort

The data were collected as part of the TRacking Adolescents' Individual Lives Survey (TRAILS), an ongoing Dutch prospective cohort study on psychosocial development and mental health of adolescents. A detailed description of the TRAILS cohort is available in previous reports (de Winter et al., 2005; Huisman et al., 2008; Oldehinkel et al., 2014; Ormel et al., 2012). In brief, TRAILS involves bi- or triennial measurements from ages 11 onwards, and consists of two separate cohorts: one population-based and another clinic-based. In both cohorts largely the same data were collected at the same ages. The general aims of TRAILS are to assess the development of mental health throughout adolescence; identify determinants and mechanisms of normal and abnormal mental health development; evaluate existing therapeutic interventions; to develop newer strategies to optimize mental health care for adolescents and young adults; and describe the impact of mental health problems on academic, professional, and social functioning.

For the population cohort of TRAILS, children and adolescents were recruited from five municipalities in the north of The Netherlands, including both urban and rural areas. Primary school participation was requisite for inclusion. Exclusion criteria were incapability to participate due to intellectual disability or a serious physical illness or handicap, and lack of available Dutch-speaking parent or parent surrogate. Of the 2935 children who were eligible

for inclusion, 2230 (76.0%) provided informed consent from both parent and child to participate in the study. Comparisons between the response and non-response groups showed no significant differences regarding gender, parental education, proportion of single-parent families, teacher-rated problem behaviour, and school absence. The present study used data from the first four assessment waves, which ran from March 2001 to July 2002 (T1), September 2003 to December 2004 (T2), September 2005 to August 2007 (T3), and October 2008 to September 2010 (T4). The mean age at T1 was 11.1 years (SD = 0.56), and 50.8% were girls. Of the 2230 participants at T1, 96.4% participated at T2 (N = 2149, mean age 13.6, SD = 0.53, 51.0% girls). The response rates at T3 and T4 were, respectively, 81.4% (N = 1816, mean age 16.3, SD = 0.73, 52.3% girls) and 83.4% (N = 1881, mean age 19.1, SD = 0.60, 52.3% girls). Of the 1881 participants at T4, 1584 (84.2%) completed the below-described diagnostic interview.

The clinical cohort of TRAILS consists of children and adolescents who contacted one of two child psychiatric outpatient clinics in the Northern Netherlands before the age of 10 years. Exclusion criteria were unknown address, and incapability to participate due to intellectual disability. In total, 1264 children met these criteria, of whom 543 (42.9%) provided informed consent from both parent and child to participate in the study. The clinical cohort of TRAILS is representative for the population of children referred to child psychiatric outpatient clinics in the northern Netherlands. Four assessment waves have been completed to date, between September 2004 and December 2005 (T1; N = 543, mean age = 10.6 years, SD = 0.56, 34% girls), September 2006 and November 2007 (T2; N = 462, mean age = 12.9, SD = 0.62, 33.8% girls), September 2009 and February 2011 (T3; N = 419, mean age = 15.9, SD = 0.66, 33.9% girls), and September 2012 to February 2014 (T4; N = 392, mean age = 19.1, SD = 0.71, 37.2% girls).

In total, data from 1933 participants were available; 81.9% from the population and 18.1% from the clinical cohort. In order to study the association between family functioning trajectories and an onset of depression during adolescence, we excluded participants who developed depression prior to T1 (n=58). This resulted in a final sample size of 1875 adolescents. 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

Psychiatric disorders were assessed at T4 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 (DSM-IV). The CIDI has been used in a large number of surveys worldwide, and shown to have good concordance with clinical diagnoses. In addition to the occurrence of psychiatric disorders, the CIDI yields their age at onset and age at last occurrence. The CIDI has good reliability and validity for most diagnoses (Kessler et al., 2009; Wittchen, 1994). In this study, information on CIDI diagnoses of ADHD and depression were used. Criteria for a diagnosis of ADHD were: (1) a history of concentration problems prior to the age of seven that lasted a minimum of six months and seemed excessive compared to peers, and/or (2) a history of hyperactivity-impulsivity present before the age of seven that lasted a minimum of six months. Depression was operationalized as a lifetime diagnosis of Major Depressive Episode (with or without (hypo)manic symptoms), Dysthymia, or Minor Depressive Disorder. In addition to the CIDI, prospective parent, teacher and self-reports (as assessed by the Child Behaviour Checklist, Teacher's Checklist of Pathology, Youth Self Report, and Adult Self Report respectively) of ADHD and depressive symptoms were available from the first wave onwards. The validity of the CIDI diagnoses for ADHD and depression was supported by these reports (please see appendix 4).

Family functioning was assessed using the McMaster Family Assessment Device (FAD) (Epstein, Baldwin, & Bishop, 1983; Mansfield, Keitner, & Dealy, 2014) at all four waves (from T1 to T4). The version used is a 12-item General Functioning scale, which is a short version of the original 60-item FAD, and assesses emotional relationships and functioning within the family. Parents have to report their agreement with statements about their families on a 4-point scale ranging from 1 = strongly disagree to 4 = strongly agree. Family dysfunction as measured with this scale reflects avoiding discussing concerns or fears, having bad feelings within the family, not being able to turn to each other for support or to confide in each other, not being able to talk about sadness or express feelings to each other, difficulty in making decisions, not accepting family members as they are, and difficulty planning family activities. A low score on the scale indicates a healthy family climate; a high score a dysfunctional family climate. The general functioning scale scores represent the average of the 12-item scores. The general functioning scale has been shown to be a valid and

reliable (Cronbach's $\alpha = 0.85$) measure of family functioning in surveys (Byles, Byrne, Boyle, & Offord, 1988) with adequate test-retest reliability (Miller, Epstein, Bishop, & Keitner, 1985).

Analysis

Based on lifetime CIDI diagnoses at T4, participants were categorized into four groups: (1) comparison: no ADHD and no depression (Group C), (2) only ADHD (Group A), (3) only an onset of depression (Group D), and (4) ADHD with an onset of depression (Group A + D). Self-reported ADHD and depressive symptom scores (as assessed using the Youth Self Reports at T1, T2, T3 and the Adult Self Reports at T4) were plotted for each group at the four time-points to visualise mean symptom severity in each group.

At all four assessment waves, data on family functioning was missing in some individuals (missing FAD_{T1} : 4.9%, FAD_{T2} : 7.6%, FAD_{T3} : 16.4%, FAD_{T4} : 9.4%). A fully conditional specification method of multiple imputations was used to impute missing data (10 iterations; linear regression model). The results across 20 imputed data sets were averaged. Using mean-centred FAD scores, family functioning trajectories were calculated (Kleinbaum, Kupper, & Muller, 1988) for each participant as follows:

Mean family functioning = $(FAD_{T1} + FAD_{T2} + FAD_{T3} + FAD_{T4})/4$

Linear trend family functioning = $(-3 \times FAD_{T1}) + (-1 \times FAD_{T2}) + (1 \times FAD_{T3}) + (3 \times$ FAD $T_4)$

$= 3(FAD_{T4} - FAD_{T1}) + (FAD_{T3} – FAD_{T2})$

Quadratic trend family functioning = $(FAD_{T2} + FAD_{T3}) – (FAD_{T1} + FAD_{T4})$

$= FAD_{T2} + FAD_{T3} – FAD_{T1} – FAD_{T4}$

Multinomial logistic regressions were used to determine associations between family functioning trajectories (mean, linear trend, and quadratic trend) and the four groups, after adjusting for age at the first assessment wave. Multinomial logistic regressions predict the odds of membership in a particular group relative to a comparison group as a function of the independent variables. First, the associations between family functioning and the four groups were tested using group C (comparison group) as the reference category. Next, to assess if FAD trajectories differed among groups A + D, A and D, additional multinomial regressions

were conducted using groups A and D as reference categories. Results are presented as odd ratios (ORs) and their 95% confidence intervals (CIs).

Analyses were performed using SPSS v. 22.0 (IBM Corp., Armonk, NY) and plots were made with MATLAB (2011b, The MathWorks, Inc.). All tests were two-tailed, and a p-value $\leq .05$ was considered statistically significant.

RESULTS

Of the 1875 adolescents in our study, 5.4% received a diagnosis of ADHD (n=102), and 19.8% a diagnosis of depression (n=371). Amongst those with ADHD, 35.3% developed depression between the first and the fourth assessment waves (n=36). Table 3.1 presents mean ages at onsets of ADHD and depression, and mean FAD scores at all four assessment waves for the four groups.

Figure 3.1 illustrates mean self-reported ADHD and depressive symptoms for each group from T1 to T4. In accordance with the CIDI diagnoses, the groups A + D (ADHD with depression) and A (only ADHD) showed higher mean ADHD symptoms than groups D (only depression) and C (comparison). Mean depressive symptom scores increased between T1 and T4 for the CIDI diagnosed depressed groups (A + D and D). For groups A and C, depressive scores remained more or less stable between T1 and T4.

Figure 3.2 presents the mean-centered FAD scores and their SEs across the four assessment waves for all participant groups. A low FAD score indicates healthy family functioning while a high score indicates poor family functioning. Figure 2 illustrates that groups A + D, A, and D have higher FAD scores at T1 than group C. Between T1 and T4, groups A + D and D showed an increase in their FAD scores, while the scores of group A declined during that time-period. Overall, group A + D had the highest FAD scores throughout all assessment time-points.

Table 3.2 presents results from the multinomial logistic regression analyses on the associations between FAD scores and group membership. Compared to the comparison group C, mean FAD was significantly higher in groups A + D and D. Further, the linear trend of group A was (marginally) significantly more negative than that of groups C and D, indicating that family functioning in the group with only ADHD improved more than in the other two groups. Although figure 3.2 and the effect sizes of the associations indicated a substantially higher mean (estimated) FAD in group A+D than in groups A and D, these differences were

not statistically significant. There were no associations between group membership and quadratic trends in FAD scores.

DISCUSSION

This study assessed whether family functioning trajectories differed among adolescents with no ADHD and no depression, only ADHD, only an onset of depression, and ADHD plus an onset of depression. Results indicated that families of depressed adolescents, either with or without ADHD, functioned on average worse than families of non-depressed adolescents. Thus, whether ADHD was associated with poor family functioning over time depended on the emergence of comorbid depression. Family functioning of adolescents with ADHD but no depression showed an improving trend over time.

The intrusive and disruptive behaviours shown by adolescents with ADHD evoke negative reactions from family members and have been associated with poor family functioning. These family functioning characteristics are not stable (Johnston & Mash, 2001) and, as our findings suggest, may actually improve over time. An onset of depression seems to moderate this positive prospect, probably because family characteristics and depression are also interlinked. Although the differences between adolescents with ADHD with and without depression did not reach statistical significance, the effect sizes of these differences were large, and this lack of statistical significance can be attributed to the small group sizes. We therefore postulate that ADHD with an adolescent onset of depression is associated with a unique family functioning trajectory, worse than that of ADHD or depression alone and without the improvement over time seen in adolescents with only ADHD. Considering the relative weakness of the evidence provided by this study, however, this postulation needs confirmation in future studies.

As mentioned before, an onset of depression was associated with poor family functioning irrespective of a diagnosis of ADHD. It is possible that poor family functioning partly underlies the development of depression in adolescents. Conversely, a development of depression may lead to deterioration in family functioning. In either of these scenarios, family functioning appears to be independently associated with depression, not solely in the presence of ADHD.

Thus far, most studies have associated family functioning with ADHD symptom severity or comorbid disruptive disorders. We found only three studies on the association

between family functioning and depression in those with ADHD. First, Harris, Boots, Talbot, and Vance (2006) in a cross-sectional study compared 6-10 year olds with ADHD and comorbid dysthymia to those with only ADHD, and found all children, irrespective of comorbid dysthymia, to show poor family functioning. We did not find evidence for poor family functioning in all adolescents with ADHD, and this may have been related to the age range of our sample. Family functioning improved between age 11 and 19 in adolescents with only ADHD, and it is possible that this group differed from comparisons at preadolescence. Second, Biederman et al. (2008) found that poor family functioning did not predict comorbid depression in 6-18 year-old girls with ADHD. Third, and in contrast to Biederman et al. (2008), Drabick, Gadow, and Sprafkin (2006) reported that poor family functioning did predict depressive outcomes in boys with ADHD aged 6 to 10 years. These contrasting findings hint at gender differences in the associations between family functioning and depressive outcomes, but our study lacked the statistical power to investigate that.

Limitations of this study must be taken into account while interpreting its results. First, and most importantly, it is recommended that the Family Assessment Device be administered to all members in a family in order to accurately assess functioning (Sawyer, Sarris, Baghurst, Cross, & Kalucy, 1988). Especially adolescents are known to rate family functioning more poorly than their parents (Sawyer et al., 1988). In our study, this questionnaire was administered to one parent (usually the mothers) and adolescents' perception of family functioning was not included. This may have led to an underestimation of family dysfunction. Second, family characteristics are influenced by other members in the family. Considering that psychopathology in family members of individuals with ADHD is high (Deault, 2010; Larsson et al., 2013; Ma, Roberts, Winefield, & Furber, 2014), disrupted family functioning may have been exacerbated due to affected siblings or parents. Clearly, in such cases, family functioning characteristics may not be attributable to the course of ADHD of one family member alone. Third, as explained above, effects of family functioning characteristics on depressive outcomes may differ between boys and girls with ADHD. Due to a lack of sufficient power, possible gender-based differences could not be assessed.

It is well understood that family plays an important role in the development of children and adolescents. As explained by Johnston and Mash (2001), most studies have studied the concurrent associations of family functioning with ADHD and further prospective studies are needed to address the developmental changes that may occur in family characteristics. Our study took these developmental issues into account and assessed family

functioning at multiple time points, linking it to changes in psychopathology over the course of adolescence.

This study reveals functioning differences among families of adolescents with neither ADHD nor depression, only ADHD, only an onset of depression, and ADHD plus an onset of depression. In short, the development of depression in adolescence is associated with worsening family functions. In adolescents with ADHD, the development of depression hampers an age-dependent improvement in family functioning. It cannot be said with certainty whether depression drives the worsening family functioning or vice versa. Future studies may focus on understanding this aspect and incorporate an assessment of the possible gender differences in these associations.

Table 3.1 Means and standard deviations of ages at onset and recency of ADHD and depression, and FAD* scores at four assessment time-points for all groups

	C N = 1438 (mean, SD)	**A** N = 66 (mean, SD)	**D** N = 335 (mean, SD)	**A + D** N = 36 (mean, SD)
Age at onset of ADHD (in years)	-	5.33, 1.75	-	5.47, 2.05
Age at onset of depression (in years)	-	-	15.04, 2.23	13.89, 2.34
ADHD recency (in years)	-	16.86, 3.20	-	18.22, 1.76
Depression recency (in years)			17.53, 1.82	17.82, 1.71
FAD_{T1}	1.80, 0.38	1.85, 0.33	1.82, 0.37	1.88, 0.42
FAD_{T2}	1.64, 0.38	1.72, 0.41	1.69, 0.37	1.82, 0.42
FAD_{T3}	1.64, 0.38	1.64, 0.41	1.73, 0.37	1.83, 0.42
FAD_{T4}	1.69, 0.38	1.69, 0.41	1.74, 0.37	1.84, 0.48

C = comparison; A = only ADHD; D = only depression; A + D = ADHD with an onset of depression
**Family assessment device: measures family functioning on a scale of 1-4. Raw mean scores of the groups are presented here. Lower scores represent better functioning*

Table 3.2 Multinomial regression analyses of FAD scores (mean, linear slope and quadratic slope) as predictors of CIDI diagnosed groups (only ADHD, only depression, ADHD with depression) at the fourth assessment wave

Adjusted[4] odd ratio of membership in groups[5] A, D or A + D relative to group C						
Predictor	A v/s C		D v/s C		A + D v/s C	
	OR (CI)	p	OR (CI)	p	OR (CI)	p
Mean FAD	1.73 (0.77 – 3.90)	0.18	1.81 (1.22 – 2.68)	.003	4.67 (1.56 – 14.01)	.006
Linear slope FAD	0.84 (0.70 -1.01)	.056	1.02 (0.93 – 1.12)	.72	1.04 (0.79 – 1.37)	.77
Quadratic slope FAD	0.91 (0.56 – 1.49)	.71	1.09 (0.86 – 1.39)	.47	1.29 (0.67 – 2.49)	.44
Adjusted[1] odds ratios contrasting groups A, D, and A + D						
Predictor	A v/s D		A + D v/s A		A + D v/s D	
	OR (CI)	p	OR (CI)	p	OR (CI)	p
Mean FAD	0.96 (0.40 – 2.28)	.91	2.70 (0.71 – 10.33)	.14	2.58 (0.83 – 8.04)	.10
Linear slope FAD	0.82 (0.68 – 1.00)	.053	1.24 (0.91 – 1.71)	.17	1.02 (0.77 – 1.36)	.87
Quadratic slope FAD	0.84 (0.50 – 1.39)	.49	1.42 (0.64 – 3.13)	.38	1.19 (0.60 – 2.35)	.62

[4] Adjusted for age at the first assessment wave

[5] A + D: ADHD with an onset of depression; A: only ADHD; D: only an onset of depression; C: comparison

Figure 3.1 Mean self-reported ADHD and depressive symptom scores of groups at all four assessment waves

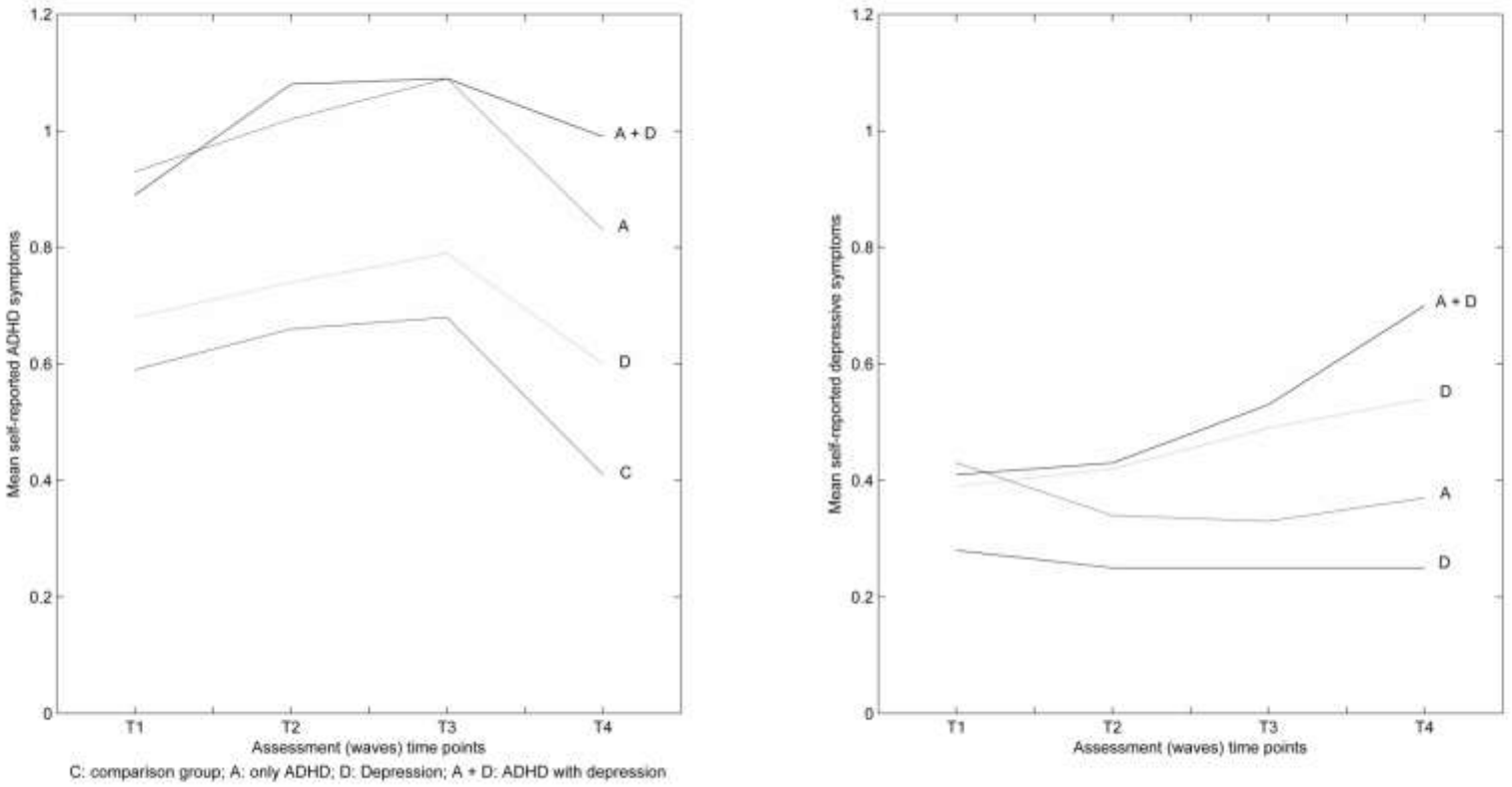
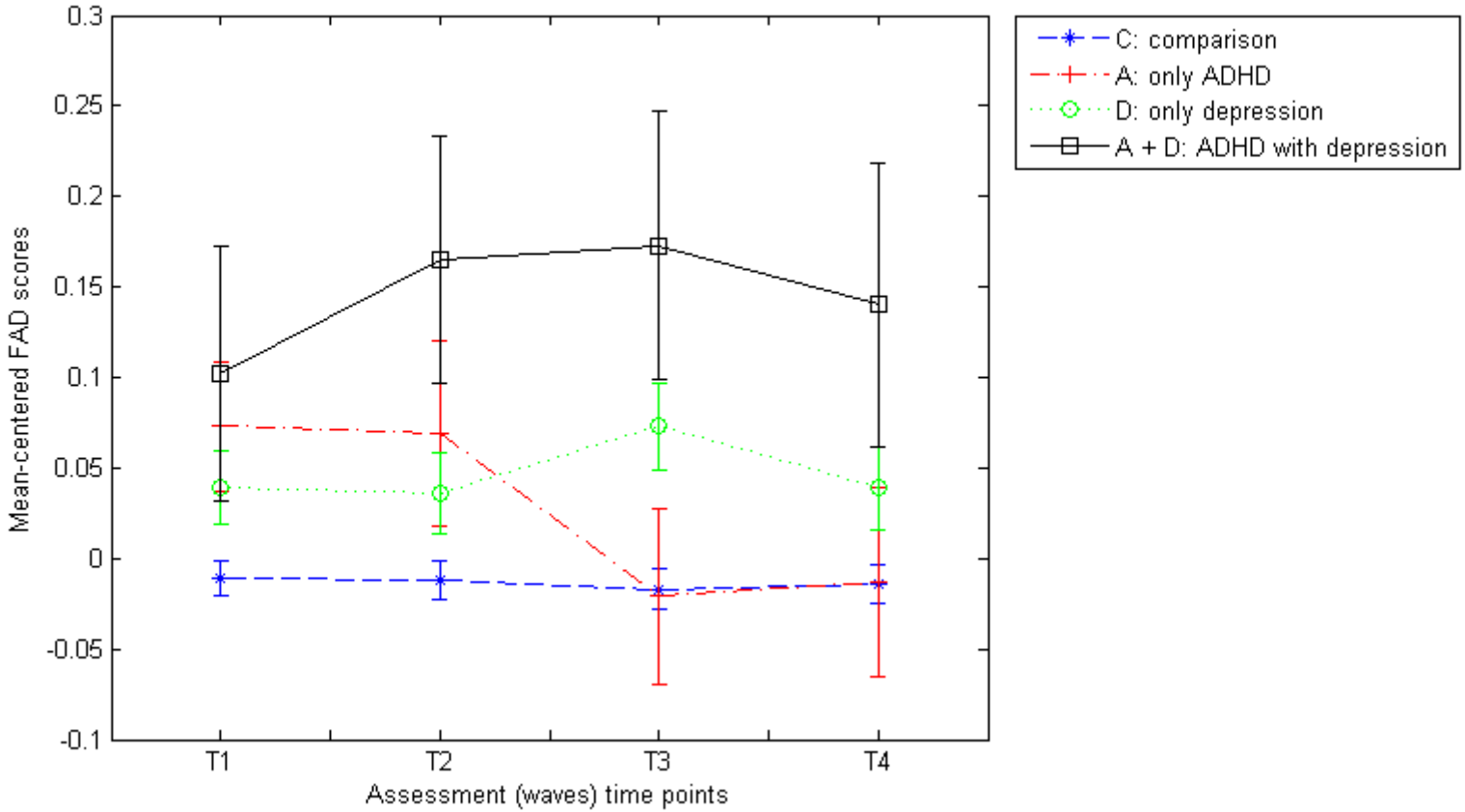


Figure 3.2 Family functioning (mean-centred scores from the Family Assessment Device) of groups at all four assessment waves



CHAPTER 4

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

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Based on:

Roy, A., Oldehinkel, A. J., Verhulst, F. C., Ormel, J., & Hartman, C. A. (2014). Anxiety and disruptive behavior mediate pathways from attention-deficit/hyperactivity disorder to depression. *The Journal of clinical psychiatry*, *75*(2), 1-478.

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**Error! Bookmark not defined.**	290 (24%)	99 (34%)	32 (48%)
Disruptive behaviour disorder**Error! Bookmark not defined.**	121 (10%)	62 (21%)	28 (45%)
Depression**Error! Bookmark not defined.**	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	*P*	Hazard Ratio	95% CI

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)

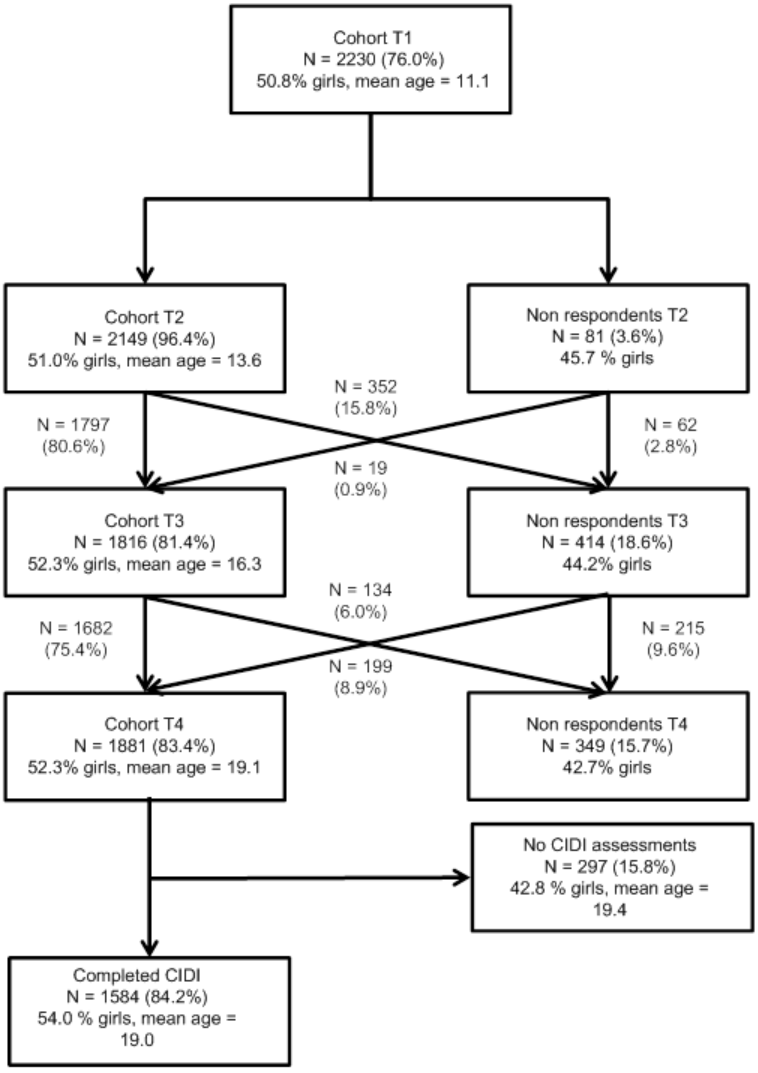
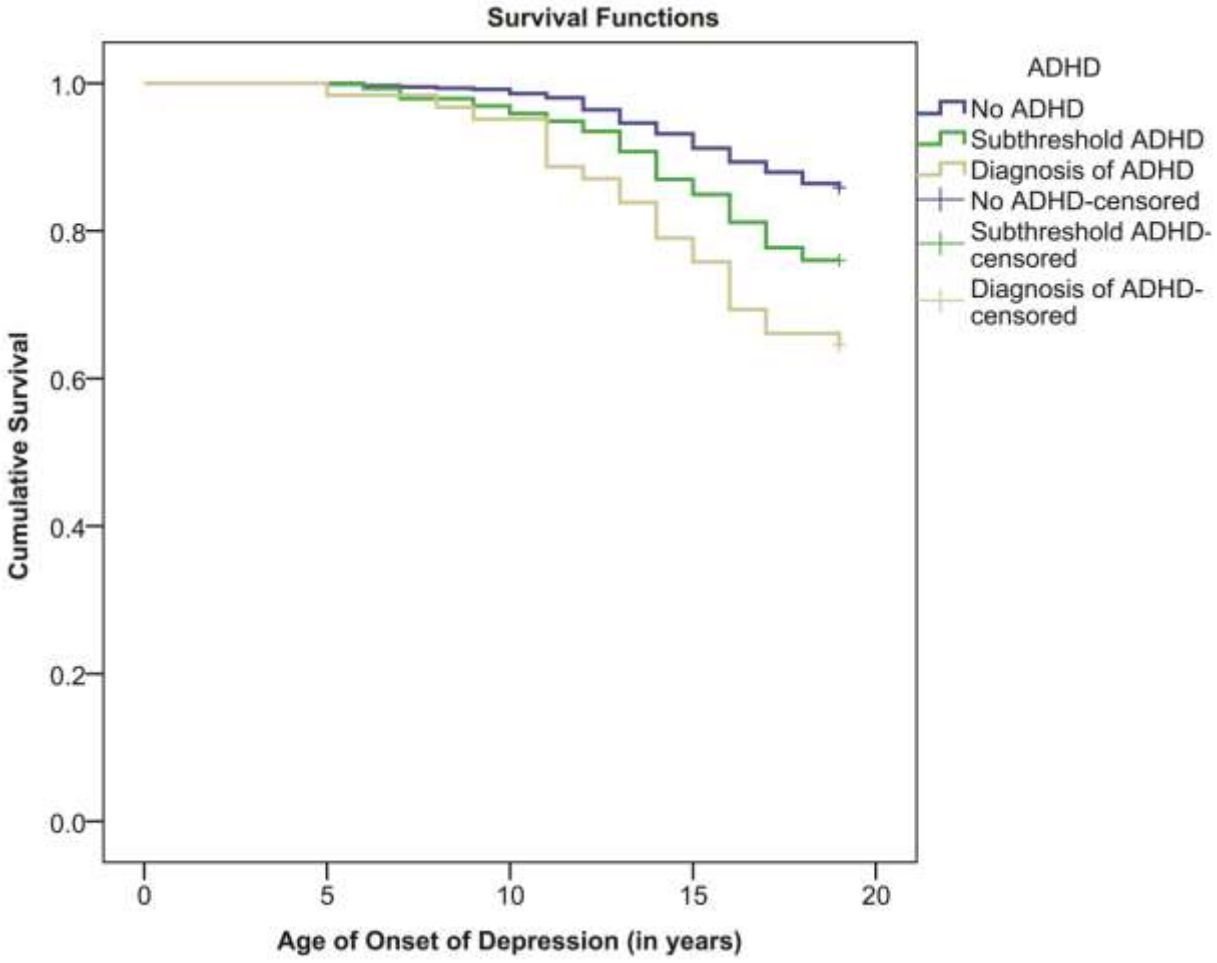


Figure 4.2 Kaplan-Meier curves for age of onset of depression across categories of attention deficit hyperactivity disorder (ADHD)


Survival Functions
ADHD
No ADHD
Subthreshold ADHD
Diagnosis of ADHD
No ADHD-censored
Subthreshold ADHD-censored
Diagnosis of ADHD-censored
Cumulative Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
20
Age of Onset of Depression (in years)

CHAPTER 5

Peer dislike and victimisation in pathways from ADHD symptoms to depression

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Based on:

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ABSTRACT

Background: The following hypotheses were tested in a longitudinal, population-based study: 1) ADHD symptoms are associated with peer dislike and victimisation; 2) Peer dislike and victimisation increase the risk for subsequent depression; and 3) The effect of ADHD symptoms on depression is partly mediated through peer dislike and victimisation. Gender differences in mediating pathways through peer dislike and victimisation to depression were additionally explored.

Method: The Child Behaviour Checklist (CBCL), Youth Self Report (YSR) and Teacher's Checklist of Pathology (TCP) assessed ADHD symptoms in 728 adolescents. Peer nominations were used to assess peer dislike and victimisation. The Composite International Diagnostic Interview (CIDI) was used to assess depression. Effects of peer dislike, victimisation, and ADHD symptoms on depression were modelled using Cox regression.

Results: ADHD symptoms were associated with peer dislike (rs=.17, p<.001) and victimisation (rs=.11, p=.001). Dislike, victimisation, and ADHD symptoms increased risk for depression. Risk for depression associated with victimisation and ADHD symptoms reduced with time. Dislike and victimisation mediated 7% of the effect of ADHD symptoms on depression. Pathways through dislike and victimisation were present in girls but not in boys.

Conclusion: Peer dislike and victimisation explain, to a limited extent, the prospective association between ADHD and depression, particularly in girls.

Keywords: Attention Deficit Hyperactivity Disorder; Depression; Peer Dislike; Victimisation; Prospective Study

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD), a common neurodevelopmental disorder (American Psychiatric Association, 2013), is often comorbid with depression (Connor et al., 2003). Depression not only leads to morbidity by itself, but when associated with ADHD also increases the severity and duration of ADHD and worsens prognosis (Jensen, Shervette, Xenakis, & Richters, 1993). Consequently, it is of importance to prevent the development of depression in ADHD. A better understanding of the comorbid association of ADHD and depression is required as a first step in order to develop preventive measures and interventions. Since ADHD manifests at an early age (Kessler et al., 2007), while depressive disorders typically have an onset in adolescence and young adulthood (Oldehinkel, Wittchen, & Schuster, 1999), it could be said that the onset of depression generally follows the onset of ADHD. Depression may arise in ADHD either directly or through the development of other, intermediate problems. Being disliked and being a victim of bullying by peers may be two such intermediate problems.

Adolescents with ADHD have problems in regulating their behaviours, and exhibiting behaviours deemed aberrant by peers could lead to being disliked (Diamantopoulou, Henricsson, & Rydell, 2005). Impairments in the development of age-appropriate social skills in ADHD can further compound the peer dislike (Murray-Close et al., 2010). Being disliked may in turn spiral into further difficulties in forming and maintaining relationships with peers (Oldehinkel, Rosmalen, Veenstra, Dijkstra, & Ormel, 2007). The resulting social disconnection can increase feelings of stress, anxiety, and loneliness, setting the stage for development of depression (Lansford et al., 2007; Oldehinkel et al., 2007).

Due to difficulties in controlling behaviours, adolescents with ADHD often respond aggressively to bullying, making them not only easy but also attractive victims for bullies (Perry, Kusel, & Perry, 1988). Victimisation involves infliction of purposeful hurtful actions by bullies, which ostracize and demoralize the victims (Olweus, 1994). Being victimised may intensify the spiral of isolation and rejection (Dake, Price, & Telljohann, 2003; Rigby & Slee, 1997), providing an increased risk for depression.

The above-mentioned influences of dislike and victimisation on the risk for future depression may act differently in adolescent boys and girls with ADHD. Boys with ADHD face greater social impairment at school (de Boo & Prins, 2007), which in turn may make them more likely to be disliked or victimised. Girls, meanwhile, tend to be more sensitive to peers' opinions,

and thus may be affected more by peer dislike and victimisation (Bakker, Ormel, Verhulst, & Oldehinkel, 2010; Oldehinkel et al., 2007; Oldehinkel, Verhulst, & Ormel, 2011). The net outcome of these contrasting predispositions might lead to a roughly similar influence of dislike and victimisation on pathways to depression in the two genders. On the other hand, the higher likelihood of social impairment in boys and the greater sensitivity to peer problems in girls might as well produce unexpected differences in these pathways between boys and girls.

Existing studies on the influences of peer problems in the ADHD-depression relationship have shown mixed results. In a short-term prospective study, Mikami and Hinshaw (2003) found peer nominated rejection measures to be associated with depressed-anxious behaviour in girls diagnosed with ADHD (Mikami & Hinshaw, 2003). Humphreys et al. (2013) in a population-based cohort of individuals followed-up from birth to 20 years of age, found that teacher- and, self-reported peer rejection and popularity mediated the pathways from ADHD symptoms to depressive symptoms (Humphreys et al., 2013). In another retrospective study, Humphrey, Storch, and Geffken (2007), found a correlation between victimisation and depression in children diagnosed with ADHD (Humphrey, Storch, & Geffken, 2007). Finally, Mrug et al. (2012) found no evidence to suggest that peer rejection specifically predicted depression in boys and girls diagnosed with ADHD (Mrug et al., 2012).

Previously, we demonstrated that not only a full diagnosis of ADHD, but subthreshold ADHD too increased the risk for depression (Roy, Oldehinkel, Verhulst, Ormel, & Hartman, 2014). Relatively mild symptoms of ADHD in adolescents may therefore be sufficient to increase the risk for being disliked by peers or being victimised, which in turn could increase the risk for depression. The present study was set up to better understand pathways from ADHD symptoms to depression through peer dislike and victimisation. Using a prospective general population sample of adolescents, we tested the hypotheses that: 1) ADHD symptoms are associated with peer dislike and victimisation; 2) Peer dislike and victimisation increase the risk for subsequent depression; and 3) The effect of ADHD symptoms on depression is partly mediated through peer dislike and victimisation. In addition, we explored gender differences in mediating pathways through peer dislike and victimisation to depression.

METHODS

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). The methodology has been described in detail elsewhere (Ormel et al., 2012) and is summarized briefly below. 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.

Cohort

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.

The present study used data from the second (T2) and fourth wave (T4) which ran from September 2003 to December 2004 (T2), and October 2008 to September 2010 (T4) respectively. The response rate at T2 was 96.4% (N=2149, mean age 13.6, SD=0.53, 51.0% girls) of whom 47% (N= 1007) completed the peer assessments. 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. Adolescents without peer nomination data at T2 (N=827) were excluded. Adolescents who had developed depression before T2 (N=29) were also excluded, to allow only participants who either did not develop depression, or developed depression between T2 and T4. These led to a total of 728 participants (54% girls) being included in this study. Figure 5.1 presents a flowchart of participants included at each wave. 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

ADHD symptoms were measured using the Child Behaviour Checklist (CBCL) filled out by parents, the Youth Self Report (YSR) filled out by the children, and the Teacher's Checklist of Psychopathology (TCP) filled out by teachers in the second measurement wave (T2) (Achenbach, 1991b; Achenbach, 1991c). The CBCL and YSR are internationally validated questionnaires for child emotional and behavioural problems at ages 4-18 (Achenbach, Dumenci, & Rescorla, 2003). We used the attention problem scale, which consists of ten items in the CBCL (M = .32, SD = .30) and nine items in the YSR (M = .55, SD = .33). The TCP was developed by the TRAILS team and is a shorter version of the Teacher's Report Form (TRF) (Achenbach, 1991c). The TCP requires a shorter time than the TRF to be completed and therefore is easier to use in classrooms with many pupils. It contains nine descriptions of behaviours with response options for these behaviours ranging from 1 = 'not applicable' to 5 = 'very clearly applicable'. Information from teacher-reported attention and hyperactivity/impulsivity problems (corresponding to the CBCL-YSR attention problems scales) were used in this study (M = -.001, SD = .91). Multi-informant scores have been reported to give better estimates for ADHD than single-informant scores (Loeber, Green, Lahey, & Stouthamer-Loeber, 1989; Tripp, Schaughency, & Clarke, 2006). We used mean ADHD symptom scores, calculated from standardized parent, adolescent and teacher ratings (M = .005, SD = .14).

Information on peer dislike and victimisation was obtained through peer nominations at the second measurement wave (T2) (Kupersmidt & Coie, 1990). Peer nominations were collected in classes with at least 3 TRAILS participants. This led to the inclusion of 3798 adolescents (54.1% girls) from 150 classes in 34 schools, of whom 1078 were TRAILS participants (Dijkstra, Cillessen, Lindenberg, & Veenstra, 2010). Participants received a list of all classmates and were asked to indicate, among other things, whom in their classroom they disliked and who they bullied. The number of nominations participants could make ranged from none to all classmates. All participants completed the peer nominations independently. Variables used in this study reflect the percentage of classmates nominating the TRAILS participants as being disliked (M = 11, SD = 0.13) and victimised (M = 2, SD = 0.05). Percentage nominations were used to offset differences in the number of participants per classroom.

During the fourth assessment wave, psychiatric disorders were assessed by means of the World Health Organization Composite International Diagnostic Interview (CIDI), version 3.0

(N=1584). 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 (Kessler et al., 2004), and has shown to have a good concordance with clinical diagnoses (Haro et al., 2006; Kessler et al., 2009). In addition to the occurrence of psychiatric disorders, the CIDI yields their age of onset. In the present study data on Major Depressive Episode (MDE) was used and depression was operationalized as MDE, either with or without (hypo)manic symptoms. Age of onset refers to the age depression emerged for the first time.

Participants with and without completed CIDI interviews differed significantly in terms of dislike ($t = 2.8$, $p = .005$), victimisation ($t = 3.2$, $p = .002$) and ADHD symptom ($t = 4.1$, $p < .001$) scores at T2. ADHD symptoms scores differed significantly between (excluded) participants with an MDE prior to T2 ($N = 29$, $M = .63$, $SD = 1.2$) and included participants ($N = 728$, $M = -.02$, $SD = 1.0$) ($t = -3.5$, $p = .001$). The two groups had comparable dislike ($t = -1.6$, $= .11$) and victimisation ($t = .40$, $p = .69$) scores.

Statistical analysis

Spearman rank correlations were used to estimate associations between ADHD symptoms, and peer dislike and victimisation. ADHD symptom, peer dislike and victimisation variables were non-normally distributed for which Spearman correlations are better suited. Cox proportional hazards regression was used to estimate the effects of peer dislike and victimisation on the probability to develop an MDE. Next, the effect of ADHD symptoms on the probability to develop an MDE was examined by means of Cox regression both with and without adjusting for dislike and victimisation. The percentage change (reduction) in the hazard ratio (HR) before and after adjusting for dislike and victimisation was computed to assess mediation by these two variables. Lastly, Cox regression models estimating mediation through dislike and victimisation were stratified by gender to explore gender differences.

Continuous variables (i.e., ADHD symptoms, peer dislike, victimisation) were standardised to mean 0 and SD 1 before analysis to ease interpretation of the regression coefficients. The proportional hazards assumption was tested using Schoenfield residuals. For significant residuals, time-dependent variables were additionally included in the regression

models. Time-dependant variables were computed by multiplying the continuous variables with survival-time. Survival-time was the number of years between assessment of peer data (T2) and onset of depression. Peer dislike and victimisation were included both separately and simultaneously in the above described regression models to assess their individual and combined effects. Except for the gender-stratified analysis, all models were adjusted for gender. Analyses were performed using SPSS v. 20.0 (IBM Corp., Armonk, NY). All tests were two-tailed and a p-value of<.05 was considered statistically significant.

RESULTS

In the sample, 12% (n = 90) of the adolescents eventually developed a depressive episode between T2 and T4, of whom 76% (n = 68) were girls. While 66% (n = 483) of the adolescents received one or more nominations for being disliked, only 21% (n = 149) received at least one nomination for being victimised. Nominations (at least one) for both peer dislike and victimisation were received by 18% (n = 130) of the adolescents.

Spearman's rho revealed weak but statistically significant relationships between ADHD symptoms and peer dislike (rs = .17, p < .001), and between ADHD symptoms and victimisation (rs = .11, p = .001).

Table 5.1 presents the effects of peer dislike and victimisation on major depression onset. With each unit rise in the standardized peer dislike score, the risk for depression increased by 1.4 times. Victimisation but not peer dislike was found to have a time-varying effect (Schoenfield residual = -0.25; p = .018), and a time-dependent victimisation variable was additionally included in the model. The initial (i.e. at T2) effect of victimisation was stronger, that is, a 1.6 times increased depression risk per unit change in standardized victimisation score which gradually decreased over time and disappeared after about 2 years. When included simultaneously, the effects of dislike and victimisation were roughly similar to their effects on including them separately in the model, suggesting that the effects were non-overlapping.

Table 5.2 presents the effect of ADHD symptoms on major depression onset before and after adjusting for a low peer status and victimisation. ADHD symptoms violated the proportional hazards assumption (Schoenfield residual = -0.30; p = .005), and an additional time-dependent ADHD symptom variable was included in the model. Peer dislike mediated 4%,

while victimisation mediated 3% of the effect of ADHD symptoms on depression. When included simultaneously, the peer variables explained 7% of the effect of ADHD symptoms on depression.

The time-varying effect of ADHD symptoms on the risk for depression, before and after adjusting for dislike and victimisation, is illustrated in Table 5.3. While ADHD symptoms were strongly associated with an increased risk for depression at T2, the estimated risk declined over time and after 6 years, no excess risk remained.

In order to explore gender differences in pathways from ADHD symptoms to depression, gender stratified analyses were carried out. Table 5.4 presents results of these exploratory analyses. In boys, peer dislike and victimisation did not mediate the effect of ADHD symptoms on depression. For girls, peer dislike mediated 7% and victimisation mediated 3% of the effect of ADHD symptoms on depression. Please note that the estimated effect of victimisation on depression in girls was not significant when adjusted for ADHD symptoms.

In a previous study, we showed that disruptive behaviours and anxiety problems mediated the pathways from ADHD to depression (Roy et al., 2014). We carried out post-hoc analyses to assess if effects of peer dislike and victimization on depression were confounded by disruptive behaviours and anxiety problems. Inclusion of these additional covariates in the models did not change the essence of the results (please see supplementary material), suggesting that effects of peer dislike and victimization on depression are largely independent of disruptive behaviour and anxiety problems.

DISCUSSION

Through this study, we aimed to further our understanding of the paths to depression in adolescents with symptoms of ADHD. We found that ADHD symptoms were associated with peer dislike and victimisation. Peer dislike, victimisation, and symptoms of ADHD were associated with an increased risk for depressive outcomes. Peer problems of dislike and victimisation mediated to a limited extent the paths to depression. Lastly, exploratory gender analyses showed mediation through peer dislike and victimisation only in girls and not in boys with ADHD symptoms.

Studies on clinical samples have shown a high risk for dislike and victimisation in children with ADHD as compared to other classmates (Humphrey et al., 2007; Murray-Close et al., 2010). We found ADHD symptoms to be only weakly associated with dislike and victimisation. These weak associations could be related to the use of a population sample and a continuous measure of ADHD in our study. Moreover, some peers may admire the disruptive and aggressive behaviours of adolescents with ADHD (Glass, Flory, & Hankin, 2012; Sandstrom & Coie, 1999), and peer support from a few classmates can protect against dislike and victimisation (Sainio, Veenstra, Huitsing, & Salmivalli, 2011). Consequently, not all adolescents with ADHD symptoms may be susceptible to face dislike or victimisation, explaining the weak associations of ADHD with these problems.

In accordance with previous literature, we found that peer dislike, victimisation, and ADHD symptoms independently increase the risk for depression (Angold, Costello, & Erkanli, 1999; Bukowski, Laursen, & Hoza, 2010; Kaltiala-Heino, Rimpela, Marttunen, Rimpela, & Rantanen, 1999; Rajendran, O'Neill, & Halperin, 2013). In this study, we found that pathways from ADHD symptoms to depression were mediated by peer dislike and victimisation, but to only a limited extent. The limited mediation may be attributable to positive illusory bias (Hoza, Pelham, Milich, Pillow, & McBride, 1993). Adolescents with ADHD tend to make inaccurate and overtly positive evaluations of their social skills and classroom peer status (Hoza, Murray-Close, Arnold, Hinshaw, & Hechtman, 2010), which, even though erroneous, may protect against negative outcomes such as depression. Alternatively, the use of a population sample and a continuous measure for ADHD symptoms may have contributed to the lack of substantial mediating effects. It is also possible that peer relationship difficulties indeed play a little role in the development of depression in ADHD, and other factors such as comorbid psychiatric illnesses, poor parental relationships, and traumatic life events mediate these paths to a greater extent (Daviss, Diler, & Birmaher, 2009).

The strength of the association between ADHD symptoms and depression decreased during the course of adolescence. In part, this decrease may be due to transitory state effects at the time ADHD symptoms were assessed. Yet another part may be explained by the fact that adolescents who are most vulnerable to the depressogenic effects of ADHD symptoms are likely to develop a depression first, thereby gradually leaving a more and more resilient group

(Hillegers et al., 2004; Surtees & Wainwright, 1999). The reduced risk for depression could also be related to changes in peer perceptions of problem behaviours with age such that, from childhood to adolescence, the symptoms of ADHD become more and more acceptable to peers (Moffitt, 1993; Sandstrom & Coie, 1999). Reduction in social impact of ADHD symptoms with age may consequently reduce the risk for depression.

Exploratory analyses of gender differences showed that dislike and victimisation mediated the paths to depression in girls but not in boys. This finding could be explained on the basis of girls' higher sensitivity to peer opinions (Bakker et al., 2010). In addition, symptoms and behaviours of ADHD in girls are considered gender inappropriate and are less well tolerated by peers than in boys (de Boo & Prins, 2007). This may give rise to more negative appraisals by peers and in turn increase risk for depressive outcomes in girls. Alternatively, the lack of mediation in boys could be related to a lack of power. Since our gender-stratified analyses were conducted in a relatively small sample of boys, our findings have to be corroborated by future research.

The main limitation of our study was that we did not follow up on the peer relationships of the participants. Thus, we could not assess how ADHD symptoms might have affected peer relationships over a period of time, and if this contributed to changes in depressive outcomes. It was also not known whether participants utilised any interventions for their ADHD symptoms. Interventions may lead to cessation of ADHD symptoms, reducing the risk of developing depression. Furthermore, stimulant medications used in the treatment of ADHD may reduce symptoms of depression in ADHD (Gurkan et al., 2010). Treatment can thus alter the occurrence of depression in ADHD and lack of this information may bias interpretations.

The strengths of our study include the use of multi informant ratings for assessment of ADHD, and peer nominations for assessment of peer relationships. We also used a longitudinal, population-based sample, which allowed us to follow up the effects of ADHD on depression in time. Population based samples also have the benefit of providing more accurate estimates of prevalences (Goodman et al., 1997), and a balanced representation of genders compared to clinical and referred samples (Gaub & Carlson, 1997). Lastly, in light of findings suggesting that dimensional approaches depict ADHD more accurately than categorical ones (Hyman, 2010; Levy, Hay, McStephen, Wood, & Waldman, 1997), our study, which used ADHD symptom

scores, may provide a better picture of this mental health problem than studies based on diagnoses.

Peer problems not only prove to be a possible hindrance to development of adolescents with ADHD but also, as we found in our study, increase the risk for depression. Therefore, interventions aimed at improving peer relationships in ADHD may be of importance. However, such interventions have failed in many instances to modify or improve peer problems (McQuade & Hoza, 2008; Nijmeijer et al., 2008). In addition, negative perceptions of peers and teachers may make it difficult for adolescents with ADHD to interact and form friendships (Atkinson, Robinson, & Shute, 1997; Chi & Hinshaw, 2002; Martin, Pescosolido, Olafsdottir, & McLeod, 2007). This points to the need for developing newer modalities of interventions, which focus on development of a sensitive environment in schools and in the community, responsive to the symptoms of ADHD. Peer problems in ADHD are resistant to change, such that adolescents who cease to show symptoms of ADHD may yet continue to face peer problems (Bagwell, Molina, Pelham, & Hoza, 2001). Thus, it is difficult for adolescents to ease into social situations and establish a normal life even with effective treatment and control of ADHD symptoms. In short, interventions aimed at making school and community environments more conducive for adolescents with ADHD may have a better effect in the long term than attempts at 'integrating' these adolescents into non-favourable and incompatible environments. A recent study aimed at increasing peers' social inclusion of children with ADHD has shown promising results in this direction (Mikami et al., 2013).

To conclude, this study elaborates the role of problems in peer relationships as partial mediators of the pathways from ADHD to depression. Though these may not be at work singly and may be complicated by presence of other factors, they provide an insight into the underlying mechanisms leading to depression. Knowledge of the possible precursors to depression in ADHD could help in the development of effective interventions, prevention of depression, and an improvement in the quality of life.

Table 5.1 Cox regression estimates of the effect of peer dislike and victimisation on depression onset controlling for gender

Covariate	**B (SE)**	***p***	**Wald χ^2**	**Hazard Ratio**	**95% CI**
Model 1					
Peer dislike	0.32 (0.09)	0.001	12.10	1.37	1.14 to 1.64
Model 2					
Victimisation	0.47 (0.17)	0.005	7.79	1.60	1.15 to 2.22
Victimisation*time	-0.21 (0.10)	0.033	4.56	0.82	0.68 to 0.98
Model 3					
Peer dislike	0.35 (0.10)	0.001	11.56	1.41	1.16 to 1.73
Victimisation	0.30 (0.19)	0.112	2.53	1.35	0.93 to 1.96
Victimisation*time	-0.22 (0.10)	0.029	4.76	0.80	0.66 to 0.98

Table 5.2 Cox regression estimates of the effect of ADHD symptoms on depression onset before and after adjusting for peer dislike and victimisation and controlling for gender

Covariate	**B (SE)**	***p***	**Wald χ^2**	**Hazard Ratio**	**95% CI**
Model 1					
ADHD	0.77 (0.18)	<0.001	18.05	2.16	1.52 to 3.09
ADHD*time	-0.15 (0.06)	0.021	5.36	0.86	0.76 to 0.98
Model 2					
ADHD	0.72 (0.18)	<0.001	16.08	2.06	1.45 to 2.93
ADHD*time	-0.14 (0.06)	0.024	5.11	0.87	0.77 to 0.98
Peer dislike	0.29 (0.10)	0.003	9.01	1.33	1.10 to 1.60
Model 3					
ADHD	0.74 (0.18)	<0.001	16.01	2.09	1.46 to 2.99
ADHD*time	-0.13 (0.06)	0.042	4.15	0.88	0.77 to 1.00
Victimisation	0.39 (0.18)	0.026	4.96	1.48	1.05 to 2.09
Victimisation*time	-0.20 (0.10)	0.047	3.96	0.82	0.68 to 1.00
Model 4					
ADHD	0.69 (0.18)	<0.001	14.71	1.99	1.40 to 2.85
ADHD*time	-0.13 (0.06)	0.047	3.94	0.88	0.78 to 1.00
Peer dislike	0.33 (0.11)	0.002	9.61	1.38	1.13 to 1.70
Victimisation	0.25 (0.20)	0.200	1.64	1.28	0.88 to 1.88
Victimisation*time	-0.21 (0.10)	0.041	4.19	0.81	0.66 to 0.99

Table 5.3 Time varying effects of ADHD symptoms on the risk for depression with and without controlling for dislike and victimisation

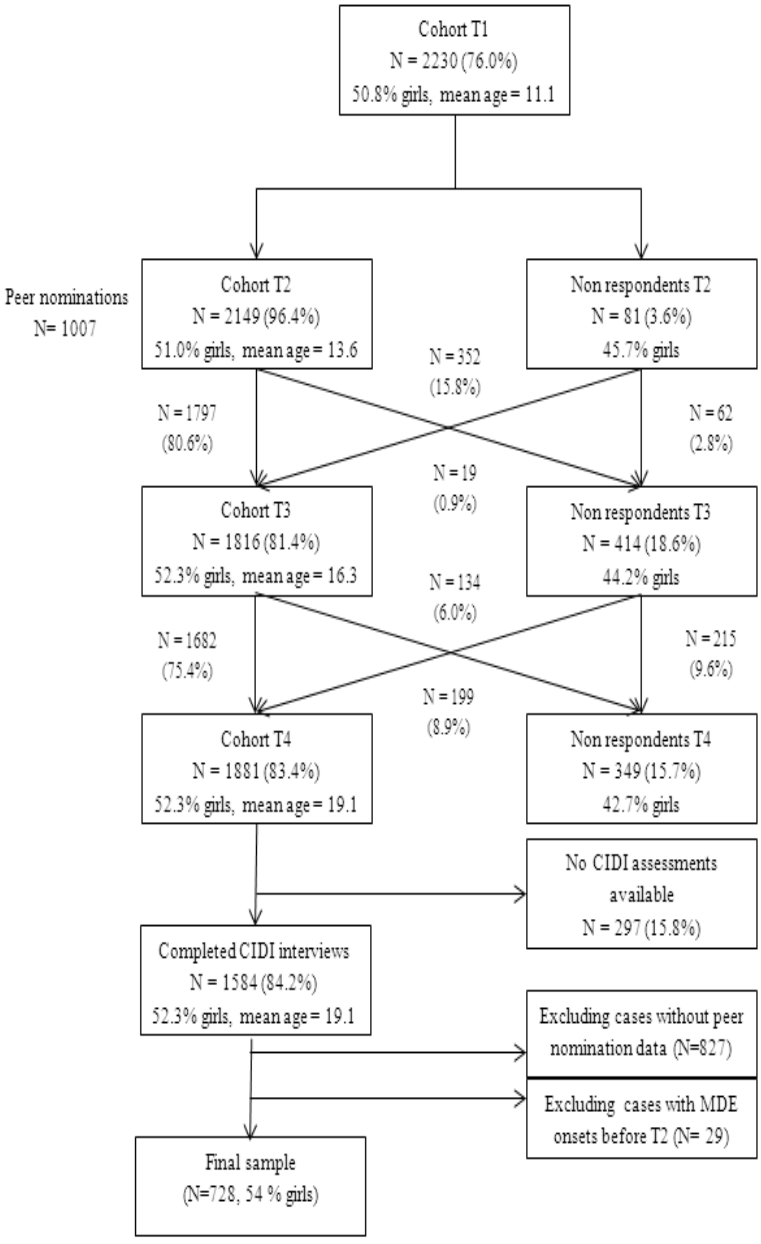
Time[#]	ADHD symptoms[*]	
	B (HR)	
	I	II
0	0.77 (2.16)	0.69 (1.99)
1	0.62 (1.86)	0.56 (1.75)
2	0.47 (1.60)	0.43 (1.54)
3	0.32 (1.38)	0.30 (1.35)
4	0.17 (1.19)	0.17 (1.19)
5	0.02 (1.02)	0.04 (1.04)
6	-0.12 (0.89)	-0.09 (0.91)

[#] Time in years after T2
[*] I = Not controlling for dislike or victimisation; II = Controlling for both dislike and victimisation

Table 5.4 Gender differences in Cox regression estimates of the effect of ADHD symptoms on depression onset before and after adjusting for peer dislike and victimisation

Covariate	**Girls**			**Boys**		
	B (SE)	p	HR	B (SE)	p	HR
Model 1						
ADHD	0.80 (0.19)	<0.001	2.22	0.64 (0.42)	0.12	1.90
ADHD*time	-0.18 (0.07)	0.013	0.84	-0.08 (0.13)	0.51	0.92
Model 2						
ADHD	0.72 (0.19)	<0.001	2.06	0.64 (0.38)	0.13	1.90
ADHD*time	-0.17 (0.07)	0.01	0.84	-0.09 (0.12)	0.50	0.92
Peer dislike	0.30 (0.10)	0.004	1.34	0.20 (0.17)	0.29	1.23
Model 3						
ADHD	0.77 (0.19)	<0.001	2.15	0.68 (0.45)	0.13	1.97
ADHD*time	-0.17 (0.07)	0.02	0.84	-0.09 (0.13)	0.48	0.91
Victimisation	0.17 (0.24)	0.49	1.18	0.69 (0.26)	0.009	1.95
Victimisation*time	-0.07 (0.10)	0.52	0.94	-0.41 (0.21)	0.05	0.67
Model 4						
ADHD	0.72 (0.19)	<0.001	2.05	0.68 (0.45)	0.13	1.97
ADHD*time	-0.16 (0.07)	0.02	0.85	-0.10 (0.14)	0.45	0.90
Peer dislike	0.33 (0.11)	0.003	1.38	0.25 (0.21)	0.24	1.28
Victimisation	0.02 (0.26)	0.95	1.02	0.58 (0.28)	0.04	1.79
Victimisation*time	-0.07 (0.11)	0.51	0.93	-0.43 (0.21)	0.04	0.65

Figure 5.1 Flowchart of participants at each wave with mean ages (in years)



CHAPTER 6

Peer problems and depressive outcomes in children with ADHD: a review and literature synthesis of developmental pathways and pathway differences based on ADHD-subtype and gender

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ABSTRACT

This review aims to provide a mechanistic model that explains the developmental progression from ADHD to peer problems and further on to depression. To this end we provide a synthesis of two separate bodies of literature on: the association of ADHD with peer problems and the association of peer problems with depression. Results indicate that apart from the symptoms of ADHD, peer difficulties also arise due to behaviour problems, anxiety, cognitive deficits, social skill deficits, and positive illusory biases. Friendship difficulties, negative peer assessments, and victimisation are the common peer difficulties faced by children with ADHD and these are likely to increase the risk for depression. The pathways from ADHD to peer problems and further on to depression differ amongst the three subtypes of ADHD, and the two genders. Results also show that particular subgroups of children with ADHD are at a greater risk for developing peer problems and depression. These subgroups include children who develop additional disruptive-aggressive behaviour problems, children with the ADHD-inattentive subtype, girls, and children with persistent ADHD. We conclude that peer relationship difficulties play a role in the ADHD- depression relationship. Recognition of the pathways that lead to peer problems and further on to depression, can assist in early diagnosis and development of newer therapeutic interventions.

Keywords: Attention Deficit Hyperactivity Disorder (ADHD); Depression; Peer problems; Children; Adolescents

INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD), a common neurodevelopmental problem (American Psychiatric Association, 2013), is often associated with comorbid depression (Angold, Costello, & Erkanli, 1999; Chronis-Tuscano et al., 2010; Jensen, Shervette, Xenakis, & Richters, 1993). The development of comorbid depression is influenced by many factors, one such important factor being problematic peer relationships. It is not yet understood through which pathways peer problems may develop in children with ADHD and further give rise to depression. This review aims to provide a mechanistic model that explains the developmental progression from ADHD to peer problems and further on to depression.

Peer problems are more common and severe in ADHD than in any other psychiatric illness (Gresham, MacMillan, Bocian, Ward, & Forness, 1998b; Wheeler & Carlson, 1994). The chance of encountering peer problems remains high throughout childhood and adolescence in those with ADHD (Hinshaw, 2002). Once developed, these problems are pervasive (Bagwell, Molina, Pelham Jr, & Hoza, 2001) and continue even after ADHD itself may have ceased (Bagwell et al., 2001; Kolko & Pardini, 2010). Moreover, they are worse in those whose ADHD persists into adolescence than those whose symptoms remit during childhood (Bagwell et al., 2001; Biederman, Mick, & Faraone, 1998b; St Pourcain et al., 2011).

Literature outside the context of ADHD has shown that peer problems lead to several negative outcomes in the long term (Patterson & Capaldi, 1990), the commonest being depression (Fauber, Forehand, Long, Burke, & Faust, 1987; Lefkowitz & Tesiny, 1985). Being part of a social group and feeling related to others is a basic emotional requirement, which if unfulfilled leads to depression (Baumeister & Leary, 1995). Apart from a direct effect on depression, peer problems can induce the development of depressogenic cognitions (Gibb & Alloy, 2006; Gibb et al., 2006; Gibb & Abela, 2008), and a tendency to blame oneself for the peer relationship difficulties (Barchia & Bussey, 2010; Sinclair et al., 2012), which in turn increase the risk for depression (Abramson, Metalsky, & Alloy, 1989). Not only can peer problems cause depression, depression also furthers peer problems, and hence the two factors may mutually reinforce each other, resulting in a maladaptive spiral (McLaughlin & Nolen-Hoeksema, 2012; Reijntjes, Kamphuis, Prinzie, & Telch, 2010).

Thus far, nine studies have assessed the role of peer problems in the ADHD-depression relationship (Becker, McBurnett, Hinshaw, & Pfiffner, 2013; Drabick, Gadow, & Sprafkin, 2006; Humphrey, Storch, & Geffken, 2007; Humphreys et al., 2013; McQuade et al., 2014; Mikami & Hinshaw, 2003; Mrug et al., 2012; Ostrander, Crystal, & August, 2006; Roy, Hartman, Veenstra, & Oldehinkel, 2015) (see Table 6.1 for summary). Results show that peer relationship problems are likely to increase the risk for depressive outcomes in children with ADHD (Humphrey et al., 2007; Humphreys et al., 2013; Ostrander et al., 2006; Roy et al., 2015). Furthermore, these relationships were found to be moderated by gender. According to two studies, girls with ADHD were more likely to develop depression as a result of peer problems than boys (Becker et al., 2013; Mikami & Hinshaw, 2003). Contrary to this, Drabick et al. (2006) reported that social problems predicted depressive outcomes in boys, but not girls with ADHD. According to McQuade et al. (2014), self-perceived social competence moderated the association between ADHD and depression. Lastly, Mrug et al. (2012) did not find a relationship of peer problems with depressive outcomes; they reported that peer rejection in ADHD predicted global impairment but not depressive outcomes in specific. Overall thus, eight of the nine available studies (Becker et al., 2013; Drabick et al., 2006; Humphrey et al., 2007; Humphreys et al., 2013; McQuade et al., 2014; A. Y. Mikami & Hinshaw, 2003; Ostrander et al., 2006; Roy et al., 2015) suggest that peer difficulties play a major role in the ADHD-depression relationship.

The above-mentioned studies draw attention to the importance of peer problems in children with ADHD and the consequent risk for depressive outcomes. Nine studies are, however, not sufficient for drawing detailed insights into the numerous ways in which peer problems may link the ADHD-depression relationship. In addition, the varying study designs (retrospective, cross-sectional and prospective), sample characteristics, and models (tested prediction, mediation, moderation) add to the difficulty of reviewing and summarising this evidence. Here we review two separate bodies of literature; the first concerning the development of peer problems in children with ADHD, and the second on the development of depressive symptoms in children and adolescents facing peer problems. Results from these two research areas are described and include findings on the development of peer problems in children with ADHD, the types of peer problems associated with ADHD, and the development of depression from peer problems. In addition, we present results on possible variations that may occur in these pathways due to differences in ADHD-subtype or gender. This review concludes with a proposed model that may explain the step-wise progression from ADHD to peer problems and further to depression.

METHODS

We conducted two separate literature searches: first, on the association of ADHD with peer problems, and second, on the association of peer problems with depression. The searches were conducted using the PubMed database for English language studies up to 03-03-2015. For the first literature search (association of ADHD with peer problems), the search terms included all possible variants of 'Attention Deficit Hyperactivity Disorder', 'social problems', 'social behaviour', 'peer', 'friends', 'bullying', and 'interpersonal relations'. For the second literature search (depressive outcomes of peer problems), the search terms included 'social problems', 'social behaviour', 'peer', 'friends', 'bullying', 'interpersonal relations', 'depressive disorder', 'depression', and their possible variants. The terms 'social problems' and 'social behaviour' were operationalized broadly in order to be comprehensive. We included only studies on peer relationship problems; family or teacher relationship difficulties, school adjustment and academic problems, anti-social delinquent behaviour, or other adjustment problems were not considered. In addition, the search was restricted to only epidemiological studies.

The following inclusion criteria were applied to all studies retrieved from the search: (1) English language; (2) participants between 0-18 years of age; and (3) variables on peer relationship problems. Using these criteria and the above-mentioned search terms, titles and abstracts of relevant studies were selected.

In the next step, full texts of the eligible studies were screened to include only those relevant. For abstracts retrieved in the first search the selection criteria were: (1) inclusion of cross-sectional or longitudinal studies on the association of ADHD with (subsequent) peer problems; and (2) exclusion of prospective studies on the development of ADHD as a consequence of peer problems. Selection criteria for abstracts retrieved in the second search were: (1) inclusion of studies on only those peer problem variables that were ascertained as being associated with ADHD in the first part of the review; (2) cross-sectional or longitudinal studies on the association of peer problems with (subsequent) depression; and (3) no prospective studies on the development of peer problems as a consequence of depression. In the last step, the references listed in all relevant studies were checked for additional literature.

RESULTS

Literature reviews were conducted using the criteria described above. A total of 3177 studies were retrieved using the search criteria; 971 on the association of ADHD with peer problems, and 2206 on the association of peer problems with depression. After inspecting the titles and abstracts of the retrieved studies on peer problems and ADHD, 102 were selected for further scrutiny. After a thorough scrutiny of the entire text, 56 were considered relevant to this review and hence included. Reference lists of these studies revealed an additional 11 relevant studies that were also included in this review. Of the 2206 articles retrieved on the association of peer problems with depression, 163 were selected based on screening of titles and abstracts. At the next stage, full texts of these studies were scrutinized using the criteria described above and a total of 82 articles were included. Based on reference lists of these 82 studies, another 14 studies were found relevant to this review and included. In sum, a total of 163 studies were reviewed and included (Please see Appendix 6 for an overview of the included studies).

The below-described findings are divided into five sections, and *all* studies are discussed in one or more of these sections according to their relevance. First, we report the possible pathways through which peer relationship problems may arise in children with ADHD. Second, we describe the specific peer problems associated with ADHD. Third, we report results on the pathways from these peer problems to depression. Fourth, we present results on differences among ADHD-subtypes in these pathways; and fifth, we report on possible gender differences.

Development of peer problems in children with ADHD

This section includes results from thirty-seven studies and presents the factors and pathways that may lead to peer problems. Included studies focus on the associations of ADHD diagnosis/ADHD symptoms (thirteen), behaviour problems (ten), cognitive functioning (nine), social skill deficits (eleven) and/or positive illusory bias (six) with peer problems. A majority of these included DSM diagnoses of ADHD (twenty-four studies) while the remainder included assessments of ADHD symptoms using parent (two studies), teacher (five studies), or a combination of parent, self or teacher reports (six studies).

A diagnosis of ADHD is a risk factor for peer relationship difficulties (Bagwell et al., 2001; Erhardt & Hinshaw, 1994; B. Hoza et al., 2005). Studies in both normative and clinical samples have revealed that inattentive, hyperactive, and impulsive symptoms predict concurrent as

well as future peer problems (Bellanti & Bierman, 2000; Connors, Connolly, & Toplak, 2012; Diamantopoulou, Henricsson, & Rydell, 2005; Diamantopoulou, Rydell, Thorell, & Bohlin, 2007; Lee, Lahey, Owens, & Hinshaw, 2008; Schwartz, McFadyen-Ketchum, Dodge, Pettit, & Bates, 1999; St Pourcain et al., 2011; Stormshak, Bierman, Bruschi, Dodge, & Coie, 1999). Of the three symptom domains, inattention is a particularly strong predictor of later peer problems, regardless of past peer difficulties (Connors et al., 2012). A sluggish cognitive tempo, common in children with ADHD and inattention symptoms, also gives rise to peer difficulties (Becker, 2014).

ADHD is frequently comorbid with social behaviour problems, i.e. disruptive and aggressive behaviours (Andrade & Tannock, 2013; Erhardt & Hinshaw, 1994; Frankel & Feinberg, 2002; Murray- Close et al., 2010; E. Taylor, Chadwick, Heptinstall, & Danckaerts, 1996; Zalecki & Hinshaw, 2004), as well as anxiety (Roy, Oldehinkel, Verhulst, Ormel & Hartman, 2015). As reported by Bellanti & Bierman (2000), inattention, in particular, is strongly associated with socially aggressive behaviours. Both behaviour problems and anxiety are well-known risk factors for peer relationship problems (Erhardt & Hinshaw, 1994; Schwartz et al., 1999; Sciberras et al., 2014; Taylor et al., 1996; Zalecki & Hinshaw, 2004) and both lead to a low self-perceived social competence in children with ADHD (Bagwell et al., 2001). Social behaviour problems predict immediate peer difficulties even in new and unfamiliar settings (Mrug, Hoza, Pelham, Gnagy, & Greiner, 2007). Further, the relationships of behaviour problems and ADHD symptoms with peer difficulties may depend on classroom composition. Stormshak et al. (1999), report that children with hyperactive, impulsive, or inattentive symptoms always face peer difficulties, even in classrooms where these symptoms are normative. In contrast, children with disruptive and aggressive behaviours do not necessarily face peer problems, especially in classrooms where such behaviours are common (Stormshak et al., 1999).

ADHD is associated with difficulties in regulating emotions and cognitive functioning (Biederman et al., 2004; Sjowall & Thorell, 2014). Emotion regulation problems, especially difficulties in regulating anger, increase the risk for peer problems in children with ADHD (Sjowall & Thorell, 2014). Cognitive difficulties, in general, lead to problematic peer relations (Bellanti & Bierman, 2000; Semrud- Clikeman, Walkowiak, Wilkinson, & Minne, 2010; Wilson, 2003), but their role in the ADHD-peer problems relationship is not straightforward. Three studies revealed an association of cognitive difficulties with peer problems in children with ADHD (Andrade, Brodeur, Waschbusch, Stewart, & McGee, 2009; Chiang & Gau, 2014; Fine, Semrud-Clikeman, Butcher, &

Walkowiak, 2008). According to Chiang & Gau (2014), working memory problems and planning difficulties lead to peer problems in children with ADHD. Andrade et al. (2009) found that sustained but not selective attention problems predicted peer problems, also after controlling for hyperactive behaviour. In a study by Rinsky and Hinshaw (2011), response inhibition and planning difficulties predicted long-term peer difficulties, regardless of ADHD status. In contrast Biederman et al. (2004), in a study on parent-rated peer outcomes in children with ADHD, reported no association of cognitive deficits with peer problems. Likewise, Wåhlstedt, Thorell, and Bohlin (2008) reported that ADHD symptoms predicted peer problems independent of cognitive deficits in their study.

Social skill deficits, often seen in children with ADHD, may underlie the peer relationship problems faced by them (Andrade & Tannock, 2013; Gresham, MacMillan, Bocian, Ward, & Forness, 1998a; Y. Lin, Lai, & Gau, 2012; Murray-Close et al., 2010; Wheeler Maedgen & Carlson, 2000). Social skill deficits may arise from developmental delays in children with ADHD (Deane & Young, 2014; Murray-Close et al., 2010). Inattention symptoms, in particular, predict poor social abilities (Bellanti & Bierman, 2000), and poor social abilities in turn hinder social interactions (Taylor et al., 1996). Furthermore, children with ADHD show a reduced ability to understand social situations and solve problematic social situations, which further threatens their peer standing (Wheeler Maedgen & Carlson, 2000). Social skill deficits may also lead to the development of aggressive and disruptive behaviour problems (Rosen et al., 2014). According to a study by Biederman et al. (1998b), social functioning worsens with time in children and adolescents with persistent ADHD. The authors speculate that the increasing complexity of adolescent social interactions is particularly challenging for those with persistent ADHD, due to their lack of social skills (Biederman et al., 1998b). Social skill deficits are not only a cause of peer relationship problems but can also result from these problems, leading to vicious circles of peer functioning difficulties (Murray-Close et al., 2010). Prosocial abilities may have a beneficial influence on peer relationship outcomes in ADHD; there is some evidence that engaging in prosocial behaviours increases positive friendship ratings of children with ADHD (Erhardt & Hinshaw, 1994).

Compared to others, children with ADHD are more likely to have a high opinion of their peer standing (Hoza, Pelham, Milich, Pillow, & McBride, 1993; Murray-Close et al., 2010; Smith, Pelham Jr, Gnagy, Molina, & Evans, 2000). This discrepancy between actual and self-assessed social desirability is termed positive illusory bias. Doubts persist on the existence of such a bias in children with ADHD (Gresham, MacMillan, Bocian, Ward, & Forness, 1998a), and there is

evidence suggesting that ADHD medications improve the ability to provide accurate self-assessments of social standing (Smith et al., 2000). Proponents of the theory suggest that children with ADHD lack insights into their actual social functioning and overestimate their peer standing (B. Hoza et al., 1993; Murray-Close et al., 2010; Smith et al., 2000). This leads to inappropriate social conduct such as brash, dominating, and aggressive behaviour (Hoza, Murray-Close, Arnold, Hinshaw, & Hechtman, 2010) which in turn increases negative peer appraisals and peer problems (Murray-Close et al., 2010). One study found that actual self-competence, rather than the positive illusory bias, was associated with peer problems in girls with ADHD (Swanson, Owens, & Hinshaw, 2012).

Types of peer problems faced by children with ADHD

This section includes results from twenty-two studies that describe the types of peer problems that may be faced by children with ADHD. Broadly, these problems can be classified as: friendship difficulties (twelve studies), negative assessments by peers (nine studies), and victimisation (seven studies). Twelve studies included DSM diagnoses of ADHD while the remainder included ADHD symptoms assessed with parent- (two), teacher (three), or a combination of parent-, teacher, and/or self-reports (seven).

Of the ten studies on friendship difficulties, three included sociometric assessments and two included observations of friend interactions. The remaining studies included teacher- (one study), self- (four studies) or parent- and self-reported (one study) assessments of friendships. Results show that children with ADHD have difficulties interacting with peers (Hubbard & Newcomb, 1991), and consequently have fewer friends than other children (Blachman & Hinshaw, 2002; Deane & Young, 2014; Taanila, Hurtig, Miettunen, Ebeling, & Moilanen, 2009; Taylor et al., 1996). The few friendships that these children may enjoy are marred by negative relationship features such as conflicts and dissatisfaction, which ultimately reduce the quality of the friendships (Blachman & Hinshaw, 2002; Normand et al., 2011; Normand et al., 2013). In addition, children with ADHD are likely to affiliate with other maladjusted children (Elkins, Malone, Keyes, Iacono, & McGue, 2011; Hinshaw & Melnick, 1995; Marshal, Molina, & Pelham Jr, 2003; Normand et al., 2011; Normand et al., 2013; Taylor et al., 1996) and form peer groups that indulge in unconventional activities such as alcohol and drug abuse (Bagwell et al., 2001; Lacourse et al., 2006; Marshal et al., 2003).

Six of the nine studies on negative peer assessments included sociometric measures, of which four studies included additional assessments from parents, teachers, self-ratings or observations of social interactions. The remaining three studies evaluated negative peer assessments through a combination of teacher- , and self- , or teacher- and parent-reports. Peer evaluations of children with ADHD suggest that they face rejection (Efron et al., 2014; Hinshaw & Melnick, 1995; Hinshaw, 2002; Mikami & Hinshaw, 2006; Pardini & Fite, 2010), have a low status in their classrooms (Elkins et al., 2011; Hinshaw, 2002), are disliked by peers instantly and rated negatively, even in new peer settings (Erhardt & Hinshaw, 1994). Especially, popular peers are likely to rate children with ADHD negatively Hoza et al., 2005). Treatments for ADHD do not seem to moderate negative assessments by peers (Hoza et al., 2005). Children with ADHD have an intact ability to assess others (Hoza et al., 2005); they have been found to give similar reasons for liking or rejecting peers as children without ADHD (Hinshaw & Melnick, 1995). Nevertheless, children with ADHD rate others with ADHD slightly better than comparison children do (Hinshaw & Melnick, 1995).

Peer difficulties of children with ADHD include problems of being victimised by bullies (Connors et al., 2012; Deane & Young, 2014; Elkins et al., 2011; Runions, 2014). From all studies retrieved, we gather that victimisation was studied less often than friendship problems and negative peer assessments: only six retrieved studies focussed on victimisation, of which two used peer-nominated assessments, four included self-reports of victimisation and one assessed victimisation with teacher- reports. Victimisation is predicted by inattention symptoms (Moura, Cruz, & Quevedo, 2011), and early symptoms of ADHD (Schwartz et al., 1999). The relationship of ADHD with victimisation is mediated by peer rejection, and moderated by friendships (Cardoos & Hinshaw, 2011; Schwartz et al., 1999). There is also some evidence to suggest that children with ADHD may bully other children (Ismail, Jaafar, Sidi, Midin, & Shah, 2014).

Progression to depression from peer problems

This section includes results from ninety studies on the associations of peer difficulties with depression. Studies included pertain to only those peer problem variables that were ascertained as being associated with ADHD in the first part of the review (excluded peer problems were: being a bully-victim, being a victim or perpetrator of physical/sexual violence in the classroom context, peer victimisation based on racial differences, cyberbullying). A majority of the studies (seventy-three) included self-reported depressive symptoms, of which twelve additionally included parent-

or teacher-reported depression while eight included assessments of anxiety symptoms additionally. The remaining sixteen studies included either DSM/ICD diagnoses of depression (six), teacher-reported depressive symptoms (four), parent- and teacher-reports of depression (one), peer-nominated depression (one), depressogenic cognitions (one), or self-reported loneliness (four).

Fourteen of the retrieved studies focussed on associations of friendship difficulties with depression. Results indicate that a lack of friends and a poor quality of friendships lead to depressive outcomes (Barchia & Bussey, 2010; Brendgen, Lamarche, Wanner, & Vitaro, 2010; Cole, Martin, Powers, & Truglio, 1996; Goodyer & Altham, 1991; Goodyer, Herbert, Tamplin, Secher, & Pearson, 1997; Goodyer, Wright, & Altham, 1990; Goodyer, Wright, & Altham, 1989; Goodyer, Wright, & Altham, 1990; Hill, Pettit, Lewinsohn, Seeley, & Klein, 2014; Lin et al., 2008; Meland, Rydning, Lobben, Breidablik, & Ekeland, 2010; Pelkonen, Marttunen, & Aro, 2003; Schwartz, Gorman, Duong, & Nakamoto, 2008). A poor choice of peers, such as friendships with aggressive peers, also predicts depressive outcomes (Mrug, Hoza, & Bukowski, 2004). Depressive symptoms either develop directly from a lack of friends or from the negative peer assessments and victimisation that follow a lack of friendship networks (Ciairano, Rabaglietti, Roggero, Bonino, & Beyers, 2007; Juvonen, Graham, & Schuster, 2003; Oldehinkel, Rosmalen, Veenstra, Dijkstra, & Ormel, 2007). In combination with other peer problems, friendship difficulties exacerbate depressive outcomes (Bukowski, Laursen, & Hoza, 2010b; Hodges, Boivin, Vitaro, & Bukowski, 1999). Furthermore, friendship difficulties hinder effective coping and recovery from depression (Bond et al., 2007; Goodyer, Germany, Gowrusankur, & Altham, 1991; Meland et al., 2010). The effects of friendship difficulties on outcomes may be timing dependent; poor friendships during prepuberty lead to anxious-depressed symptoms while post-pubertal friendship problems lead only to depression (Goodyer et al., 1989).

Twenty-eight studies assessed the relationships of negative peer assessments with depression. These studies reveal that negative peer assessments, which include peer rejection and a low peer standing, predict concurrent and future depressive symptoms (Auerbach, Bigda-Peyton, Eberhart, Webb, & Ho, 2011; Boivin, Poulin, & Vitaro, 1994; Boivin, Hymel, & Bukowski, 1995; Bukowski, Laursen, & Hoza, 2010a; Chen, Huang, Wang, & Chang, 2012; Comiskey et al., 2012; Kornienko & Santos, 2014; Ladd, 2006; MacPhee & Andrews, 2006; Nolan, Flynn, & Garber, 2003; Oldehinkel et al., 2007; Panak & Garber, 1992; Patterson & Stoolmiller, 1991; Pedersen,

Vitaro, Barker, & Borge, 2007; Rueger, Malecki, & Demaray, 2010; Shochet, Smith, Furlong, & Homel, 2011; Sontag, Graber, & Clemans, 2011). Negative peer assessments reduce self-esteem and create loneliness, both of which lead to depression (Asher & Wheeler, 1985; L. Bond et al., 2007; Buhs & Ladd, 2001; Fontaine et al., 2009; Qualter et al., 2010; Qualter, Brown, Munn, & Rotenberg, 2010). In addition, negative assessments can bring about depression by producing depressogenic cognitions (Braet, Van Vlierberghe, Vandevivere, Theuwis, & Bosmans, 2013; Prinstein & Aikins, 2004), increasing interpersonal stress and conflicts (Auerbach et al., 2011; Mercer & DeRosier, 2008), or impairing cognitive abilities such as reward processing (Casement et al., 2014). The relationship of negative peer assessments and depression is moderated by friendships (Bukowski et al., 2010b) and low friendship valuing (Martin, Cole, Clausen, Logan, & Strosher, 2003).

Thirty of the studies retrieved focused on the association of victimisation with depressogenic cognitions and depressive outcomes (Abada, Hou, & Ram, 2008; Barchia & Bussey, 2010; L. Bond et al., 2007; L. Bond, Carlin, Thomas, Rubin, & Patton, 2001; Braet et al., 2013; Desjardins & Leadbeater, 2011; Fekkes, Pijpers, & Verloove-Vanhorick, 2004; Fekkes, Pijpers, Fredriks, Vogels, & Verloove- Vanhorick, 2006; Fleming & Jacobsen, 2009; Gibb, Stone, & Crossett, 2012; Hanley & Gibb, 2011; Kaltiala-Heino, Fröjd, & Marttunen, 2010; Kumpulainen, Räsänen, & Henttonen, 1999; McLaughlin, Hatzenbuehler, & Hilt, 2009; Meland et al., 2010; Rothon, Head, Klineberg, & Stansfeld, 2011; Saluja et al., 2004; Sinclair et al., 2012; Snyder et al., 2003; Sourander, Helstelä, Helenius, & Piha, 2000; Storch & Masia-Warner, 2004; H. Sweeting, Young, West, & Der, 2006; Turner, Finkelhor, & Ormrod, 2010). Although incidents of victimisation decline with age (Kumpulainen et al., 1999), the risk for depressive outcomes does not decline concurrent to this age-related drop in victimisation (Rudolph, Troop-Gordon, Hessel, & Schmidt, 2011). Victimised children are likely to develop anxiety problems (Juvonen, Graham, & Schuster, 2003; Kochenderfer-Ladd & Skinner, 2002; Sourander, Helstela, Helenius, & Piha, 2000; Storch & Masia-Warner, 2004), a low-self-esteem (Hawker & Boulton, 2000; Sapouna & Wolke, 2013) and emotion regulation difficulties (McLaughlin, Hatzenbuehler, & Hilt, 2009), which in turn can lead to depressive outcomes. In addition, victimised children face greater difficulties in peer interaction and friendship formation than other children (Juvonen et al., 2003; Snyder et al., 2003), which add to the risk for depression. Victimisation also mediates paths from depression to further peer problems, especially at mid-adolescence (Sweeting, Young, West, & Der, 2006) thereby ensuring the

continuity of peer difficulties and further depressive problems (Hoglund & Chisholm, 2014; Kochel, Ladd, & Rudolph, 2012).

In addition to the above-mentioned peer problems, poor social competence (Blechman, McEnroe, Carella, & Audette, 1986; Cole, 1990; Crick, Ostrov, & Werner, 2006; Fauber et al., 1987; Pedersen et al., 2007; Ross, Shochet, & Bellair, 2010; Rubin, Hymel, & Mills, 1989; Gregory et al., 2007; Kistner, David-Ferdon, Repper, & Joiner Jr, 2006; Lee, Hankin, & Mermelstein, 2010; Zimmer-Gembeck, Hunter, Waters, & Pronk, 2009) and social behaviour problems (Fite, Rubens, Preddy, Raine, & Pardini, 2014; Hoglund & Chisholm, 2014; Kamper & Ostrov, 2013; Morgan, Shaw, & Forbes, 2013; Yang, Chen, & Wang, 2014) also predict depression. Further, one study found that a discrepancy in social-skills appraisals by children (high) and their parents (low) also predicts depression (Taylor & Wood, 2013).

Differences among ADHD subtypes in development of peer problems

Amongst the three subtypes of ADHD, the inattentive form (ADHD-I) is the most common followed by, respectively, the combined subtype (ADHD-C) and the hyperactive/impulsive subtype (ADHD-H/I). Studies on subtype differences in peer problems mostly focus on the two more prevalent forms, that is, ADHD-I and ADHD-C. In total, thirteen studies provided information on subtype differences, with eleven studies including DSM-III-R or DSM-IV diagnoses of ADHD and two studies with teacher- or parent- reported ADHD symptoms. Three of the eleven studies reported that children with ADHD-I and ADHD-C have similar social skill deficits (Bauermeister et al., 2005; Hinshaw, Owens, Sami, & Fargeon, 2006; Hodgens, Cole, & Boldizar, 2000). Despite their similar social skills (Efron et al., 2014), the subtypes differ in their social behaviours. While ADHD-C is typically associated with aggressive behaviours, withdrawn and passive behaviours are more common to ADHD-I (Wheeler Maedgen & Carlson, 2000). Children with ADHD-I have difficulties interpreting social cues (Fine et al., 2008), are less likely to initiate social contact and are less assertive in their interactions than children with ADHD-C (Bauermeister et al., 2005). According to Wan Ismail et al. (2014), children with hyperactive or inattentive symptoms, but not with ADHD-combined type, are likely to be bullies.

Differences between these two subtypes in the amount of peer problems faced are less clear-cut. While five studies demonstrated fewer peer problems in children with ADHD-I subtype (Hinshaw, 2002; Hinshaw et al., 2006; Kolko & Pardini, 2010; Pardini & Fite, 2010; Wheeler

Maedgen & Carlson, 2000), two others reported no differences between children with ADHD-I and ADHD-C (Hodgens et al., 2000; Riley et al., 2008), and one reported a trend towards more peer problems in those with ADHD-I (Owens, Hinshaw, Lee, & Lahey, 2009).

Other differences between ADHD-C and ADHD-I relate to the onset of peer problems. Due to their aggressive behaviours, children with ADHD-C are rejected immediately in new peer settings (Hodgens et al., 2000). Children with ADHD-I, on the other hand, only face rejection after longer periods of interactions (Blachman & Hinshaw, 2002; Hodgens et al., 2000). Maintaining a long-term consistent friendship relationship is also difficult for children with ADHD-I, while for those with ADHD-C, difficulties are present especially during initial stages of friendship formation (Hinshaw, 2002).

Gender differences in risk of peer problems and depressive outcomes

Eleven studies retrieved provided information on gender differences in pathways from ADHD to peer problems, of which six included DSM diagnoses and five parent- or teacher-reported ADHD symptoms. Results show that both boys and girls with ADHD have similar social skill deficits (Bellanti & Bierman, 2000; Greene et al., 2001; Hoza, Mrug et al., 2005). Nevertheless, gender differences exist in the peer problems faced by children with ADHD. Girls seem to be more likely to face problems of negative peer assessments, victimisation (one study reported no gender differences in the association of ADHD with victimisation [Runions, 2014]) and a poor quality of friendships (Berry, Shaywitz, & Shaywitz, 1985; Elkins et al., 2011; Schwartz et al., 1999; Young, Chadwick, Heptinstall, Taylor, & Sonuga-Barke, 2005; Young, Heptinstall, Sonuga-Barke, Chadwick, & Taylor, 2005), while boys are more likely to lack friends or associate with deviant peer groups (Elkins et al., 2011; Taanila et al., 2009). The friendship difficulties of boys are often attributed to their aggressive behaviours (Carlson, Tamm, & Gaub, 1997).

Information on gender differences in pathways from peer problems to depression was provided by twenty-five studies. Of these, twenty-three focussed on depressive symptoms and two on sadness and depressogenic cognitions. For ease of discussion we first present results from the twelve studies on gender differences in the effects of friendship difficulties and negative assessments. In general, girls are more sensitive to peers' appraisals than boys are (Cole, 1991; Cole, Martin, & Powers, 1997; Paquette & Underwood, 1999) and develop depressogenic cognitions in response to peer problems more easily (Cole, 1990). Girls are also more likely to face

interpersonal stresses and more vulnerable to their negative effects (Hankin, Mermelstein, & Roesch, 2007; Prinstein & Aikins, 2004). Studies on gender differences in negative peer assessments have consistently shown that, girls are more susceptible to depression following peer rejection than boys (Cole, 1991; Hankin et al., 2007; Moksnes, Espnes, & Haugan, 2013; Oldehinkel et al., 2007; Reijntjes, Stegge, & Meerum Terwogt, 2006; Shochet et al., 2011), although the coping skills used to deal with rejection are the same for both genders (Reijntjes et al., 2006). The effects of gender on the pathways from rejection to depression may be further complicated by pubertal influences; Sontag et al. (2011) in their study found that early puberty in girls and late puberty in boys worsened depressive outcomes following rejection. MacPhee and Andrews (2006) found evidence for greater depression in boys following peer problems; low popularity predicted depression in boys but not in girls.

Thirteen studies retrieved provided information on gender differences in pathways from victimisation to depression, with mixed findings. Of the thirteen studies, one found that both genders are equally susceptible to victimisation (Rothon et al., 2011), a second one that girls are less likely to be victimised than boys (Fleming & Jacobsen, 2009), and a third one that girls are more susceptible to victimisation than boys (Moore et al., 2014). An age related reduction in victimisation has been reported in girls but not in boys (Kumpulainen et al., 1999). Following victimisation, girls are more likely to develop aggressive behaviours, which can aggravate peer problems (Rudolph et al., 2011). Girls, as compared to boys, are likely to utilize peer support to cope with the victimisation (Hunter, Boyle, & Warden, 2004; Kochenderfer-Ladd & Skinner, 2002). Nevertheless, the risk of depressive outcomes following victimisation may or may not be worse for girls. While six studies report worse depressive outcomes in girls following victimisation (Abada et al., 2008; Fleming & Jacobsen, 2009; Paquette & Underwood, 1999; Rudolph et al., 2011; Sapouna & Wolke, 2013; Stange, Hamilton, Abramson, & Alloy, 2014), two other studies found a greater depressive risk in boys facing victimisation (Rothon et al., 2011; Sinclair et al., 2012). Further differences between boys and girls relate to the type of victimisation commonly faced. Girls are more likely to face relational victimisation while boys may be more susceptible to physical victimisation (Crick & Nelson, 2002; Sinclair et al., 2012). We found only one study on gender differences that accounted for the type of victimisation. According to Desjardins and Leadbeater (2011), the severity of depressive outcomes following relational victimisation is similar in both girls and boys.

DISCUSSION

Peer relationship problems in ADHD can be ascribed to the symptoms of ADHD, presence of additional behaviour problems, anxiety, cognitive dysfunction, social skill deficits, or a positive illusory bias. These factors may give rise to peer problems through at least two pathways. First, social skills deficits (probably arising due to developmental delays) and cognitive deficits lead to difficulties in expressing socially appropriate behaviours and consequently to peer relationship problems. Second, the symptoms of ADHD lead to peer problems directly, bypassing the involvement of cognitive and social skill deficits (Figure 1). There is mixed evidence on the impact of cognitive deficits in children with ADHD, and two of the studies reviewed found that cognitive dysfunction did not necessarily lead to peer problems (Biederman et al., 2004; Wåhlstedt et al., 2008). In light of this information, we may say that the second pathway is more probable than the first.

We further postulate that disruptive and aggressive behaviours develop secondarily in the pathways described above and in Figure 1. Facing peer problems may, in the long term, prompt children to respond in disruptive and aggressive manners in order to either achieve prominence or avoid further social failures. Being predictors of peer problems themselves, these behaviours create a self-persisting cycle wherein ADHD symptoms initially set the cascade of events in motion. The role of ADHD symptoms in triggering this cycle of events is supported by Stormshak et al.'s (1999) study on peer acceptance of ADHD and behaviour problems. Results from this study suggest that disruptive and aggressive children do not face peer difficulties in classrooms where these behaviours are normative. In comparison, children with ADHD face peer difficulties even in classrooms that have a high proportion of affected children with ADHD. (Stormshak et al., 1999). Thus, ADHD symptoms seem to cause more aversion in peers than disruptive or aggressive behaviours, which makes these symptoms a likely initial trigger for peer problems. Because behaviour problems compound the peer difficulties faced in ADHD, their development, and consequent self-perpetuation warns steadily worsening peer relations.

We surmise that positive illusory bias, similar to behaviour problems, develops secondarily in the developmental pathways from ADHD to peer problems (Figure 1). The development of positive illusory bias is a self-protective mechanism for maintaining self-esteem when facing social defeat chronically (B. Hoza et al., 2010). This indicates that a positive illusory bias may develop when children experience repeated social failures, and may not feature in ADHD early on. Children with ADHD have an accurate understanding of social norms and expectations (Nijmeijer et al.,

2008). Positive illusory bias may thus be a natural outcome of the social and cognitive deficits in ADHD combined with an intact knowledge of social norms. That is, children with ADHD may attempt to perform according to the social rules, but be hampered by deficits in social skill and cognition. These children therefore assess their social standing positively without realising their inability to interact pro-socially. The development of positive illusory bias in turn may further enhance the peer-relationship problems.

The two pathways described above lead to friendship difficulties, negative peer assessments, and victimisation in children with ADHD (Figure 1). Based on the reviewed literature, we postulate that negative peer assessments increase gradually over time. According to (Hoza et al., 2005), popular classmates are more likely to rate children with ADHD negatively than less popular ones. Other classmates may emulate the opinions of their popular peers and start rejecting children with ADHD as well. It is conceivable that, over time, more and more classmates assess children with ADHD negatively, resulting in an increase in problematic relationships. Furthermore, negative assessments and the resulting lack of support from popular classmates turn children with ADHD into potential victims of bullying, because these conditions give bullies an easy target. Negative assessments by other peers only increase the chances of victimisation. We therefore propose that problems of negative assessments feature in the peer relationships of children with ADHD first, followed by victimisation, which builds up later (Figure 6.1). This temporal order is supported by a study conducted by Schwartz et al. (1999), who found that pathways to victimisation in ADHD were mediated by peer rejection.

The reviewed results suggest that assessments of classmates made by children with and without ADHD are similar, in that children with ADHD also prefer popular classmates to those rejected and with a low status (Hoza et al., 2005). Nevertheless, peer groups of children with ADHD are composed of classmates with peer problems themselves or otherwise maladjusted classmates. As explained by Hoza et al. (2005), with time and after many unsuccessful attempts to form friendships with non-rejected peers, children with ADHD are compelled to approach other similarly rejected classmates despite disliking them. This lack of choice could explain the higher conflicts and lower dissatisfaction in the friendships of children with ADHD (Blachman & Hinshaw, 2002).

Peer problems that develop in children with ADHD may lead to depressive outcomes, probably through development of a low self-esteem, loneliness, depressogenic attribution styles, emotion regulation problems, interpersonal stresses, anxiety, and deficient reward processing

abilities. The reviewed studies revealed a strong relationship of negative peer assessments and victimisation with depressive outcomes. Friendship difficulties such as a lack of friends and a poor quality of friendships also increase the risk for depression, but we found no evidence that deviant peer group affiliation leads to depression. Possibly affiliating with peers provides protective benefits against depression, even if these peers are deviant. Further, social skill deficits and problems in social behaviours may directly give rise to depression, bypassing the involvement of peer relationship problems. There is also mixed evidence for associations between a positive illusory bias and depression. Positive illusory bias may prevent depression by protecting against low self-esteem. In line with this, Steca et al. (2014) reported that a high self-perceived social competence protects against depression. Contrary to this, results from Casement et al. (2014) showed that discrepancies in social competence reports between parents (low competence) and their children (high competence) predict depressive outcomes.

There are reasons to assume that friendship difficulties increase with age, and that their relative role in the pathways to depression, as compared to negative assessments and victimisation, increases with time. First, since both negative assessments and victimisation lead to difficulties in friendships (Juvonen et al., 2003) eventually problems in friendships will increase with time. Second, friendship difficulties impede remission from depression (Barchia & Bussey, 2010; Bond et al., 2007; Goodyer et al., 1991; Meland et al., 2010), prolonging the duration of depression and increasing the probability of additional peer difficulties. Third, with increasing age, children attach greater importance to friendships (Cole et al., 1996). This growing salience is likely to increase the depression risk in case of friendship difficulties with age.

In the pathways from ADHD to peer problems and further to depression, the secondary development of disruptive and aggressive behaviours may flag worsening of prognosis. Over and above the risk associated with ADHD, these behaviours increase depression risk both directly and indirectly, through further enhancing peer problems (Wilson, 2003). In contrast to disruptive-aggressive behaviours, the secondary development of positive illusory bias may not necessarily lead to a worse prognosis. As discussed above, positive illusory bias may increase the risk for peer difficulties but may also protect from depression (Hoza et al., 2010).

Results on ADHD-subtype differences and peer problems were mixed. While some studies reported higher peer difficulties in children with ADHD-C, others reported greater problems in children with ADHD-I. These differences may be better understood if we consider peer interactions

in the long term. Children with ADHD-C are likely to face problems immediately at initial peer encounters (Hodgens et al., 2000). Thus, initially, ADHD-C will be associated with worse peer problems than ADHD-I. Withdrawn behaviours, common to ADHD-I (Bauermeister et al., 2005), are not perceived as a threat immediately but may start to annoy peers in the long term. Accustomed to the passivity of children with ADHD-I, peers may also reduce their interaction attempts. Eventually peer problems in ADHD-I may increase, reaching similar levels as ADHD-C. We speculate that, with increasing age, the peer problems of ADHD-I may supersede those of ADHD-C for the following three reasons. First, while passivity in ADHD-I leads to social disconnection, the assertive nature of children with ADHD-C may attract attention from peers, particularly during adolescence. This could reduce chances of social isolation in those with ADHD-C. Second, the social isolation in ADHD-I may increase susceptibility to victimisation, worsening peer problems. Third, symptoms of ADHD-C remit with increasing age, while symptoms of ADHD-I remain stable over time (Hart, Lahey, Loeber, Applegate, & Frick, 1995; Hinshaw et al., 2006). Persistence of ADHD is associated with worse peer problems. Continuity of ADHD-I may consequently lead to greater problems in peer relationships over time.

Results from the reviewed studies suggest that girls with ADHD face more peer relationship problems than boys. Girls with ADHD are less hostile and more relationship-oriented and consequently more likely to make friends than boys with ADHD (Arnold, 1996; de Boo & Prins, 2007). Nevertheless, friendships of girls with ADHD are often dissatisfactory and marked with conflicts (Young et al., 2005). Therefore, even though girls with ADHD may have more friends than boys, they are not necessarily better off in the friendship domain. Additionally, symptoms of ADHD are considered gender inappropriate in girls, and peers assess them more harshly than they assess boys (Diamantopoulou et al., 2005; Kerr, Lambert, Stattin, & Klackenberg-Larsson, 1994). This gender-bias in peer assessments may explain why girls have more peer problems than boys despite their similar social skills.

Gender differences exist in the pathways from peer problems to depression as well. With the exception of one study (MacPhee & Andrews, 2006), the reviewed results show that negative peer assessments are more likely to be associated with depression in girls than in boys, with low popularity as the only exception to this rule. This exceptional role of low popularity suggests gender differences in sensitivity to type of peer assessments. Peer problems leading to depression are more likely to be affection-related in girls, and achievement-related in boys (Kornienko & Santos, 2014;

Moksnes et al., 2013; Oldehinkel et al., 2007). Thus, girls may be affected by isolating negative peer appraisals such as rejection, while boys may be affected more by peer problems that indicate social failure such as popularity.

This review indicates pathways through which peer problems may develop in children with ADHD and further increase the risk for depression, in an attempt to extend the knowledge yielded by previous studies on the association of peer problems with depression in children with ADHD (Becker et al., 2013; Drabick et al., 2006; Humphrey et al., 2007; Humphreys et al., 2013; McQuade et al., 2014; Mikami & Hinshaw, 2003; Ostrander et al., 2006; Roy et al., 2015) (See Table 1). Results from the current review extend this knowledge and suggest that, besides the peer problems identified by these previous studies (negative peer assessments, victimisation and low social competence), a lack of friends and a poor quality of friendships may also be involved in the development of depression. Additional new findings that emerged relate to the increased susceptibility for depression in particular groups of children with ADHD. First, children developing disruptive-aggressive behaviours may be at a greater risk for depression. Second, the risk for depression may increase with age in children with the ADHD-I subtype. Third, girls with ADHD are more likely to be depressed following peer problems than boys with ADHD. Fourth, continuation of ADHD leads to worse depression by allowing a greater time-period for development and progression of peer difficulties. Persistence of ADHD can also lead to the development of disruptive and aggressive behaviours in response to peer problems, which further reinforce the paths to depression.

Clinical Implications

Improvements in the peer relations of children with ADHD may prevent future depression. However, interventions aimed at improving peer functioning have been largely unsuccessful (Barkley, 2004; de Boo & Prins, 2007). Medications only marginally improve peer functioning (Bagwell et al., 2001; Molina et al., 2009; Nijmeijer et al., 2008) and cannot normalize the peer relationships (Hubbard & Newcomb, 1991). The absence of reliable and effective interventions points to the pressing need for newer therapies. Newer interventions can focus on and benefit from exploiting protective factors that offset the peer problem-depression relationship. The effects of peer problems on depression are attenuated by friendships, modifications in social behaviours, and academic or sport achievements (Barchia & Bussey, 2010; Bond et al., 2007; Ladd, 2006; Martin et al., 2003; Meland et al., 2010). Accordingly, building friendships (Barchia & Bussey, 2010; Bond et

al., 2007; Meland et al., 2010; Mikami, 2010; Nijmeijer et al., 2008), modification of behaviour to a more pro-social and helpful manner of interacting with peers (Mrug et al., 2007; Stormshak et al., 1999), and improvements in academics and sports (Blechman et al., 1986; Cole, 1990; Cole, 1991) can be potential intervention tactics.

So far, attempts at increasing friendships in ADHD have been effective to some extent (Hoza, Mrug, Pelham, Greiner, & Gnagy, 2003; Mikami, 2010). Hoza et al. (2003) found that pairing up of non- affected peers and children with ADHD improved peer functioning. Similarly, medications have been found to improve friendship choices and self-appraisals of social behaviours (Smith et al., 2000). Thus, friendship-based interventions such as buddy-pairing (Hoza et al., 2003; Mikami, 2010; Nijmeijer et al., 2008) can complement the effect of medications. The combination of friendship-based interventions with medications can be made more effective by providing interventions for modifying social behaviour. Additionally, children with ADHD may be encouraged to participate and excel in sports and academics to add to the effects of these interventions.

Efforts towards developing sensitive school and community environments that are positive towards children with ADHD can aid in reducing peer problems. Despite receiving therapy that induce a reduction in ADHD symptoms, peer difficulties continue and social networks of children with ADHD do not resemble that of other normative children (Nijmeijer et al., 2008). Therefore, a different tactic that makes school and community environments conducive for these children may have a better effect than the tried and tested social interventions. Early research in this line has already shown promising results: in a recently conducted randomised trial, training classmates to interact positively towards children with ADHD improved peer relations by a far greater margin than that achievable by the existing social training interventions alone (Mikami et al., 2013). Recent evidence also suggests that peer problems can be attenuated by increasing parent and teacher involvement during peer interactions (Mikami, Jia, & Na, 2014).

Recommendations for future research

A number of gaps exist in our understanding of pathways from ADHD to depression through peer problems. First, it is still not entirely clear why children with ADHD develop a particular type of peer functioning difficulty. Differences in ADHD-subtype, gender and age all partly explain the propensity for developing one peer problem over the other, but very few studies have directly compared the three broad categories of peer problems regarding their predictive factors. It is also

not known to what extent children with ADHD may develop multiple peer problems. Second, the relationship of socially aggressive behaviours with bullying has not been adequately assessed. Only one study reported on bullying behaviours in children with ADHD (Ismail et al., 2014). It is possible that incidents of bullying reflect social aggression, particularly reactive aggression and self-defence against victimisation. Further research is needed to understand the specific type of aggressive behaviours associated with ADHD and their relationship to bullying. Third, most studies assessed depressive outcomes of peer problems in adolescents. Specific to children with ADHD, depression may begin much earlier in childhood (Roy et al., 2014b). Fourth, recent studies have recognised the impact of internet usage on children and adolescents' peer functioning. Cyber-bullying in particular has been reported to predict depression (Elgar et al., 2014; Gámez-Guadix, Orue, Smith & Calvete, 2013). Currently, it is not known if cyber-bullying is also common amongst children with ADHD, and if such incidents influence the development of depression.

Conclusion

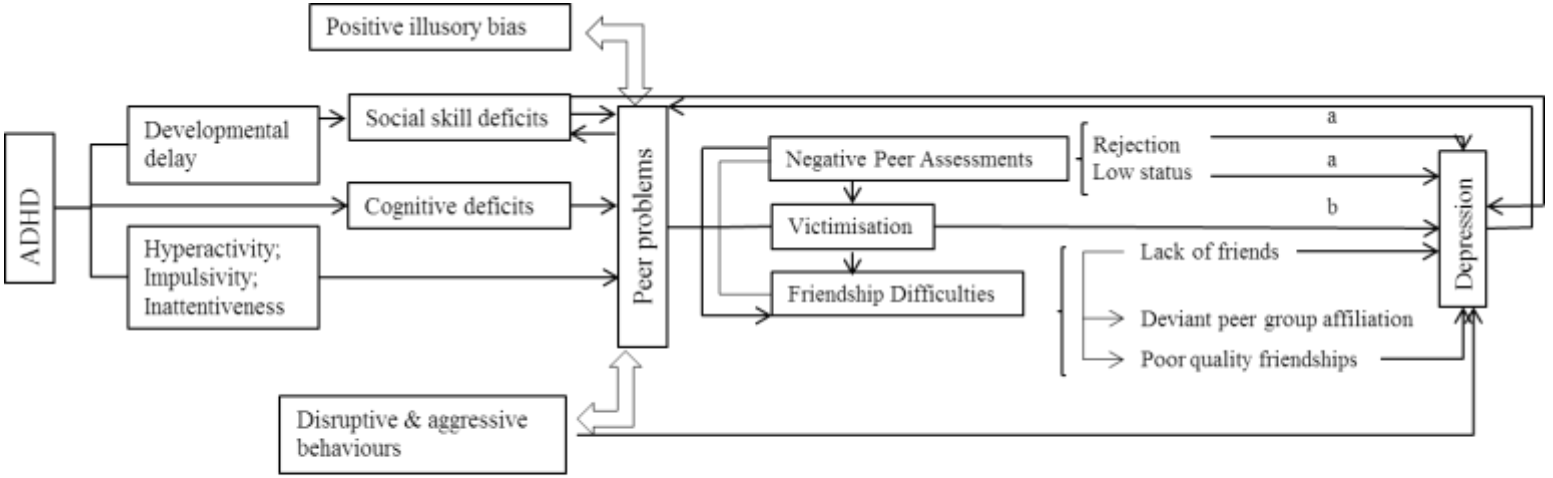
This review illustrates possible paths through which peer problems may arise in children with ADHD and further lead to depression. The pathways described in this review may not be the only mechanisms at work. Nevertheless, their cognizance can expedite early diagnosis and prevent development of depression. In describing the development of depression, we demonstrate lacunae in our knowledge and set the stage for further empirical work. We emphasize the need for further research on the developmental mechanisms of peer problems and depression in children with ADHD. In sum, knowledge from such studies shall assist in predicting impairments early on and may be utilised for development of newer intervention techniques against depression.

Table 6.1 Studies examining the association of peer problems with depressive outcomes in children with ADHD: summary table

Study	Broad aims	Study design	Participant characteristics	Key findings
Becker et al. (2013)	Determined the moderating effects of gender on the pathways from peer functioning problems to internalising disorders in children with ADHD-inattentive subtype	Cross-sectional	188 children with a diagnosis of ADHD (110 boys, 78 girls) aged 7-11 years	Peer functioning problems were more strongly associated with internalising problems in girls than boys
Drabick et al. (2006)	Examined psychosocial risk factors for depression in ADHD	Prospective	248 boys with ADHD aged 6-10 years	Social problems predicted depression in ADHD
Humphrey et al. (2007)	Examined correlation of peer victimisation with psychosocial adjustment in ADHD	Retrospective	91 boys and 25 girls with ADHD aged 4-18 years	Peer victimisation in children with ADHD was positively correlated with depression
Humphreys et al. (2013)	Determined the mediating effects of peer relationships in pathways from ADHD to depression	Cross-sectional (Study and prospective (Study	Study 1: 230 participants (163 boys, 67 girls), including children with (n=120) and without ADHD aged 5-10 years at baseline	Peer functioning problems were concurrently and prospectively associated with depression in children with ADHD
McQuade et al. (2012)	Examined moderating effects of ADHD diagnosis and peer status in the longitudinal relation between self-perceived social acceptance and changes in adjustment	Prospective	182 boys and 42 girls with ADHD compared to 94 and 29 girls without aged 8-13 years	Self-perceived social competence moderated the relationship of ADHD and depression
Mikami and Hinshaw (2003)	Examined effects of peer rejection on anxious/depressed behaviour in girls with ADHD	Short-term prospective with a follow-up period weeks	91 girls with ADHD compared to 58 girls ADHD, aged 6-13 years	Peer rejection was related to higher depressed anxious behaviour in girls with ADHD
Mrug et al.	Examined effects of peer	Prospective	362 participants (both	Peer rejection in ADHD

Study	Broad aims	Study design	Participant	Key findings
(2012)	rejection and lack of dyadic friendships on long-term emotional and behavioural problems in ADHD		genders) with ADHD aged 7-18 years	predicted global impairment but not depressive outcomes specifically. Dyadic friendships did not attenuate effects of peer rejection
Ostrander et al. (2006)	Examined mediation of depression in ADHD by parent, teacher and self-reported social competence	Cross-sectional	148 participants (both genders) with ADHD and controls aged 6-12 years	Depression was mediated self and others' appraisals self-competence
Roy et al. (2015)	Determined mediating effects of peer problems in pathways from ADHD to depression	Prospective	728 participants (335 boys, 393 girls) aged 11-19 years	Peer dislike and victimisation increased risk for depression in children with ADHD, especially girls

Figure 6.1 Postulated pathways from ADHD to the development of depression through peer problems



a. low self-esteem, loneliness, depressogenic cognitions, interpersonal stress, impaired reward processing
b. low self esteem, emotion regulation problems, anxiety

CHAPTER 7

General discussion

A significant proportion of individuals with ADHD eventually develop depression, the reasons for and pathways to which remain largely unknown. Prior research has long established that the association of ADHD with depression is not merely artefactual of psychiatric assessments, but a true association (Biederman, Newcorn, & Sprich, 1991). Nevertheless, large gaps yet remain in our understanding of the ADHD-depression relationship. Broadly, this encompasses a lack of clarity on the nature of the ADHD-depression association; is ADHD-depression a separate, yet unidentified disorder in itself or is depression a sequel of ADHD? If the latter is true, then what are the mechanisms through which depression develops in some individuals with ADHD?

I took a dual approach in this dissertation to examine the above-mentioned questions: First, to examine if ADHD with depression may constitute a separate disorder, I characterised adolescents with ADHD plus comorbid depression and assessed differences between adolescents with and without comorbid depression, as well as adolescents with depression alone. That is, if ADHD with depression is a unique disorder, then individuals with this condition should have specific characteristics that qualitatively differentiate them from individuals with either ADHD or depression alone. To assess this, two characteristics were selected for study – cognition and family functioning characteristics – and were examined in adolescents with ADHD both prior to and after the development of comorbid depression, as well as in adolescents with ADHD or depression only, or none of these disorders. Second, assuming that depression is a comorbid sequel of ADHD, I studied factors that could lead to a development of depression in children and adolescents with ADHD. Two specific candidate factors were selected for this assessment owing to their recognized associations with both ADHD and depressive disorders: comorbid anxiety or disruptive behaviour problems, and peer difficulties. Understanding the extent to which these factors contributed to the pathways between ADHD and depression provided an impression of the processes linking the two disorders. The goals of this thesis were thus twofold: a) characterisation of children and adolescents with ADHD and comorbid depression, as compared to those with only one of these disorders, and; b) identification of pathways that lead to a development of depression in children and adolescents with ADHD.

Apart from the main aim of gaining insights into the nature of the ADHD-depression association, this thesis addressed a few other issues raised in previous studies. First, researchers have stressed the importance of studying the ADHD-depression relationship in community samples (Daviss, 2008; Daviss, Diler, & Birmaher, 2009; Meinzer et al., 2013). Clinical sample-based studies are ubiquitous in the existing literature, and these mostly include extreme cases of ADHD with severe problems (Levy & Hay, 2003; Seymour et al., 2014). Community sample-based studies are required to develop a more comprehensive and nuanced picture of the ADHD-depression relationship. Second, examination of subthreshold ADHD symptoms in relation to development of depression has been put forth as an important area for detailed study (Bussing, Mason, Bell, Porter, & Garvan, 2010; Marcus & Barry, 2011; Nikolas & Burt, 2010; Sonuga-Barke, 2005). Third, although previous research has indicated that peak comorbid depression occurs around late-adolescence to young adulthood amongst individuals with ADHD (Meinzer et al., 2015), a majority of the existing studies on comorbid depression focus on early to mid-childhood participants, which misclassifies individuals likely to develop depression in future as non-depressed. This thesis considered all of the above-mentioned issues by conducting the studies in a large prospective population-based sample, including adolescents with subthreshold ADHD symptoms, and choosing a sample with an age range of early adolescence to young adulthood.

Results, in short, showed that both subthreshold and a full diagnosis of ADHD were associated with an increased risk for depression, and that additional mental health problems and poor social environments influenced the risk for depression. A comparison of adolescents with ADHD plus depression versus those with ADHD or depression only yielded no convincing evidence for uniquely differentiating characteristics. These and other results are further elaborated in the upcoming paragraphs.

Summary of findings: Part I

As mentioned in the previous section, a first aim of this thesis was to examine if ADHD-depression represents a separate disorder. To classify ADHD-depression as a separate disorder, evidence from a variety of studies are needed. These include studies to assess if, and to what extent, cases with ADHD-depression differ from cases with only ADHD or only depression in terms of presentation, course and outcomes. In this thesis the validity of ADHD-depression as a

disorder was examined by characterization of participants with this condition to assess if individuals with the combined condition differed qualitatively from either individuals with ADHD or depression alone. Two particular characteristics were selected for study: cognition and family functioning. Chapter 2 deals with the differences amongst adolescents with and without ADHD or depression in cognitive function. Cognitive function in six domains (processing speed, response time variability, focussed attention, working memory maintenance, response inhibition and cognitive flexibility) was assessed twice, at mean ages of 11 and 19 years. Participants were divided into groups of adolescents with ADHD plus depression, only ADHD, only depression, and neither ADHD nor depression. Retrospective self-reported symptoms were used to diagnose both ADHD and depression. Depression was defined as any major depressive episodes (MDE), minor depressive episodes, or dysthymia between the ages of 11 and 19 years. Using these criteria, more than one-third of adolescents with ADHD were found to have or have had an onset of depression in the past eight years.

At age 11, self-reported ADHD symptom severity was comparable in the two ADHD groups and higher than that in the depressed only and control groups. Self-reported depressive symptom severity was comparable for adolescents with only ADHD, ADHD plus depression and only depression and higher than that for the controls at this time-point. This pattern of results shows that there were no a-priori differences in symptom levels between adolescents with ADHD only or depression only and adolescents with ADHD and a future onset of depression. Results also showed that adolescents with only ADHD had poorer response time variability performance at age 11 than adolescents with only depression and controls. In contrast to this, response time variability of adolescents with ADHD and future depression did not differ significantly from that of adolescents with only depression and controls. The response time variability performance of the ADHD plus depression group fell approximately in-between the group with only ADHD and the group with only depression. Nevertheless, a direct comparison of the two ADHD subgroups showed no significant response time variability differences. This pattern of scores suggests that adolescents with ADHD who do and do not develop a depression do not differ strongly in their cognitive characteristics prior to the development of depression.

Between ages 11 and 19 years, self-reported ADHD symptomatology in the ADHD only group remained more or less stable, while it increased in the ADHD with depression group.

Confirming the group assignments that we made based on the CIDI, depressive symptoms showed an increase in the ADHD with depression group, but not in the ADHD only group. Response time variability of the ADHD only group improved with time, and by the age of 19, no differences were found between adolescents with only ADHD and controls anymore. In short, the stable ADHD symptom profile of this group coincided with an improvement in cognitive performance. No changes in response time variability occurred between ages 11 and 19 for the ADHD with depression group.

Group comparisons of self-reported symptoms scores at age 19 showed that adolescents with ADHD plus depression had higher ADHD as well as depressive symptomatology than adolescents with only ADHD, only depression and controls. At this time point, the ADHD with depression subgroup also showed poor working memory maintenance in comparison to the depressed only and control group. The ADHD only group did not differ from the depressed only and control group in working memory maintenance performance. Unlike at age 11, no 'in-between' performance pattern was seen at age 19: the ADHD only group performed much better than the ADHD plus depression group and only slightly worse than the depressed only and control group. When tested directly, the difference in working memory performance between adolescents with ADHD only and adolescents with ADHD plus depression did not reach statistical significance, which could be related to the small group sizes.

An increase in working memory maintenance problems amongst adolescents with ADHD and depression, as compared to the control and depressed only groups, was paralleled by an increase in ADHD and depressive symptomatology. It could be speculated, firstly, that the increase in depressive symptoms led to poor working memory maintenance in this group. However, depressive symptoms in the depression only group too showed an increase between the ages of 11 and 19 years, but this rise was not accompanied by working memory problems. Possibly, the working memory problems led to the development of depression amongst adolescents with ADHD, and not the other way around. Conversely, the increasing ADHD symptomatology may have influenced the development of both depression and working memory maintenance problems. Concurrent associations between ADHD symptoms and depression have been described in chapter 5 (see 'Summary of findings: Part II' for further details). Secondly thus, it is plausible that a high ADHD symptomatology is associated with the development of

depression as well as working memory maintenance difficulties. Thirdly, although depressive symptoms increased in both depressed only and ADHD plus depression groups, by late adolescence the depressive symptoms of the combined group were higher than that of the depressed only group. It is therefore also possible that the combined burden of having very high ADHD and depressive symptomatology triggered working memory maintenance problems. Further research must be conducted to assess the directions of associations between ADHD, depression and functioning problems.

Chapter 3 describes differences in family functioning between adolescents with and without ADHD and depression (i.e., the same four groups as in chapter 2). Information on family functioning characteristics was available for both the population and the clinical cohort at four time-points between early adolescence and young adulthood, allowing an in-depth assessment of change in family functioning patterns. Results showed that, in early adolescence, family functioning was worse in the ADHD, depression, and ADHD plus depression groups than in healthy controls. Between early adolescence and young adulthood, the family functioning of adolescents with depression (either with or without ADHD) worsened, while the family functioning of adolescents with only ADHD improved.

At all time-points, adolescents with both ADHD and depression had the poorest family functioning characteristics. In contrast, family functioning of the ADHD only group improved with time and was comparable to that of controls by age 19. Symptoms of ADHD also improved with time in the ADHD only group, while it increased in the combined group. Family functioning of ADHD plus depression worsened with time, and the impairments noted by age 19 may reflect the additive effects of both disorders. It should be noted that comparisons of family functioning characteristics between the ADHD plus depression and ADHD only groups did not reveal any significant differences. This lack of significant group differences may be a consequence of small group sizes, but could also signal a lack of support for the hypothesis that ADHD plus depression shows unique characteristics that are clearly different from ADHD and depression only and thereby constitutes a new disorder type.

Summary of findings: Part II

A second aim of this thesis was to understand the mechanisms through which depression may develop in children and adolescents with ADHD. For this, I examined the mediating effects of anxiety and disruptive behaviours (i.e., conduct and oppositional defiant disorders) on pathways from ADHD to depression in chapter 4. Of the entire sample, 4% and 18% of adolescents received a diagnosis of ADHD and subthreshold ADHD, respectively. Diagnoses of MDE differed between these adolescents. While more than a third of adolescents with ADHD had one or more lifetime episodes of MDE, only a quarter of adolescents with subthreshold ADHD had an MDE diagnosis. For adolescents with no history of ADHD, the number of cases with MDE dropped to one-seventh. Hence, the risk of developing an MDE amongst participants with subthreshold ADHD was halfway between that for adolescents with no ADHD and adolescents with a full ADHD diagnosis. The association of ADHD with MDE showed a dose response relationship: changes in diagnostic status from no ADHD to subthreshold ADHD or from subthreshold ADHD to full ADHD were both associated with an 89% increase in risk of developing depression. Thus, the association of ADHD with depression represented a continuum.

Further details emerged when analysing group differences in anxiety and disruptive behaviour problems. Approximately one-third of the subthreshold ADHD group and half of the ADHD group suffered from one or more episodes of anxiety disorders. In contrast, only a quarter of participants without ADHD had an anxiety disorder by the age of 19 years. Rates of disruptive behaviour problems (i.e., conduct or oppositional defiant disorder) were higher in the ADHD and subthreshold ADHD groups than in the no ADHD group as well: while one-fifth of the subthreshold group and half of the ADHD group reported disruptive behaviour problems, only one-tenth of those in the no ADHD group suffered from disruptive problems. Thus, a full diagnosis of ADHD was associated with the highest risk of co-occurring mental health problems. Subthreshold ADHD had a worse comorbidity profile than no ADHD, but lower rates of comorbidities than a full diagnosis of ADHD. These results also highlight the high rates of comorbidities amongst children and adolescents with ADHD, and support previous research showing that ADHD without comorbidities may be exceptions in practice. While high comorbidity estimates for adolescents with ADHD are usually based on clinically referred samples, results from chapter 4 show that this holds true for the general population as well.

The development of ADHD always preceded the development of depression, showing that pathways ran from ADHD to depression but not the other way round. Similar findings emerged when accounting for the mediating effects of anxiety and disruptive behaviours. Both anxiety and disruptive problems usually developed after the onset of ADHD but prior to the onset of depression. Results also revealed that symptoms of ADHD were present at the time of depression onsets. Moreover, in both the ADHD and the subthreshold ADHD groups, participants with co-occurring anxiety and disruptive disorders continued experiencing these comorbid symptoms concurrent to depressive onsets. In short, the development of (subthreshold) ADHD seems to be followed by a spiralling descent into further negative outcomes that culminate in depression, with no remission from symptoms of pre-existing mental health problems.

Anxiety mediated 14% and disruptive problems 22% of the pathway from ADHD to depression. Hence, the risk attributed by disruptive problems was greater than that attributed by anxiety. Together, anxiety and disruptive behaviour problems mediated 32% of the risk for depression. An examination of the individual anxiety (separation anxiety, simple phobia, social phobia, specific phobia, panic disorder, agoraphobia and generalized anxiety disorder) and disruptive behaviour (oppositional defiant and conduct disorders) problems showed mediating effects on the ADHD-depression pathways that were comparable to the aggregated anxiety and disruptive effects.

Although one-tenth of the boys with ADHD (either a full diagnosis or subthreshold symptoms) developed major depressive episodes and approximately a quarter of the girls with ADHD, the risk for depression attributable to ADHD was higher in boys. That is, ADHD had stronger effects on the risk for depression in boys than girls. Effects of anxiety and disruptive behaviours on the pathways to depression were comparable in boys and girls. Thus, for both genders the development of additional anxiety or disruptive problems lends a risk for future depression, with a higher risk being attributed by disruptive behaviours.

The effects of peer problems on the pathways to depression were examined in chapter 5. Peer problems were extensively measured during wave 2, when TRAILS participants were 14, by means of peer nominations. ADHD was operationalized as a continuous symptom measure, based on parent-, teacher- and self-reports assessed at 14 years of age, and lifetime diagnoses of

MDE at the age of 19. Results showed that an increase in ADHD symptomatology of one standard deviation doubled the risk of concurrent depression. This excess risk for depression reduced with time and was nullified six years after the initial assessments. The reduction in risk for depression may be related to transitory state effects, i.e., if ADHD remits, so does the risk for depression. It is also likely that adolescents most susceptible to the depressogenic effects of ADHD develop an MDE early on. This leaves a group of increasingly resilient individuals, in whom ADHD may not lend a risk for depression, over time. In short, the concurrent associations of ADHD and depression were stronger than prospective associations.

The associations between ADHD symptoms and depressive diagnoses were further explained by considering the role of peer problems. Specifically, chapter 5 examined the effects of peer nominated victimisation and dislike ratings on the pathways from ADHD to depression. Results showed only weak associations of ADHD with peer dislike and victimisation. Of the two peer problems, concurrent peer dislike was more strongly associated with ADHD symptoms than victimisation. Effects of peer dislike and victimisation on the pathways to depression were weaker than that of anxiety and disruptive problems (chapter 4). Dislike mediated 4% and victimisation 3% of the risk for depression. Together they mediated 7% of the effects of ADHD on MDE, indicating that the effects of the two peer problems were non-overlapping. The pathways through peer dislike and victimisation were unchanged after including the effects of co-occurring anxiety or disruptive behaviour problems. In short, apart from the 32% mediation through anxiety and disruptive problems (chapter 4), a further 7% of the effects of ADHD on depression could be explained by peer problems.

Results from several studies corroborate the development of peer problems in children with ADHD. However, the developmental pathways from ADHD to peer problems and further on to depression have not yet been delineated well. To fill this knowledge gap, a literature review was conducted that included studies on the associations of, on the one hand, ADHD with peer problems, and, the other hand, peer problems with depression. Information from these studies was used to build a conceptual model of the developmental progression from ADHD to depression through peer problems. This qualitative review on the effects of peer relationships in children with ADHD and the risk for future depression attributed by these problems is described in chapter 6.

Results from the reviewed studies showed that long-term presence of ADHD, in particular inattention symptoms, strongly predicts a risk for concurrent and prospective depression. The longer the ADHD symptoms continue, the greater is the risk for depressive outcomes. The studies reviewed point to multiple pathways from ADHD to the development of peer problems; ADHD triggers the development of peer problems through a variety of cascading paths. For example, symptoms of hyperactivity, impulsivity and inattention may give rise to peer difficulties directly, but ADHD may also lead to cognitive and social skill deficits, which in turn lead to peer problems. Peer problems in children and adolescents with ADHD could lead to a positive illusory bias of their social abilities and peer status (a self-protection mechanism to prevent the development of a low self-esteem in the face of repeated social failures) and disruptive behaviours (in retaliation to social defeat). Both positive illusory biases and disruptive behaviours trigger further peer problems. These paths culminate in the development of peer problems of peer rejection, low peer status, victimisation, lack of friendships, poor quality friendships and deviant peer group affiliation.

Comparable to the existence of multiple paths from ADHD to peer problems, the development of depression from peer problems also occurs through various paths, as evidenced by studies included in the review. In addition to direct pathways between peer problems and the development of depression, peer problems can give rise to intermediary problems which in turn increase the risk for depression. For example, victimisation can lead to the development of low self-esteem, emotion regulation problems or anxiety, all of which in turn increase the risk for depression. Peer rejection and low status additionally give rise to depressogenic cognitions, interpersonal stress and impairments in reward processing abilities, which again lead to depression.

The reviewed studies in chapter 6 pointed towards gender and ADHD-subtype differences in pathways through peer problems to depression. In general, girls were reported to have a higher likelihood of peer problems. More specifically, girls with ADHD were more likely to face dissatisfactory and conflicting friendships than boys with ADHD. Girls also showed a higher likelihood of developing depression following peer problems such as rejection. In contrast to these consistently reported gender-differences in peer rejection and friendships, results on gender differences in pathways to victimisation and through that to depression were

heterogeneous. While some studies reported no gender differences in the risk for victimisation in children with ADHD, others reported a greater likelihood of victimisation in either girls or boys. Furthermore, some studies on the development of depression following victimisation reported such effects in boys and others in girls. Similarly, results on subtype differences in these pathways showed wide heterogeneity: while some studies reported greater propensity for peer problems in ADHD-combined subtype, others found greater peer problems in the inattentive subtypes. This heterogeneity could be related to the time of assessment of peer problems: while children with ADHD-combined subtype are more likely to face immediate rejection in new peer groups, children with ADHD-inattentive subtype are more likely to face peer problems in the long term (as a result of their withdrawn behaviours which leads to social isolation).

ADHD and depression: general remarks

A few impressions of the ADHD-depression association can be gathered from the results from my thesis discussed above and findings from previous research. Prior studies indicate that 10% of the children (Blackman, Ostrander & Herman 2005), 30-40% of the adolescents (Daviss et al., 2009; Elia, Ambrosini & Berrettini 2008; Souza, Pinheiro, Denardin, Mattos, & Rohde, 2004), and 30-50% of the adults with ADHD develop depression (Kooij et al., 2012; Sobanski, 2006). The results presented in this dissertation showed comparable rates of depression among adolescents with ADHD. Up to 37% of the participants with ADHD reported having at least one episode of a depressive disorder by late adolescence (mean age 19 years).

Currently, the majority of the studies on ADHD are based on clinical samples. An early meta-analytic review reported that children with ADHD have a 5-6 times higher likelihood of developing depression than children with no ADHD (Angold, Costello, & Erkanli, 1999). Results from this thesis show that individuals with ADHD symptoms in the general population too show higher rates of depressive problems and are 2-3 times more likely than comparison adolescents to develop major depressive episodes. Further, it was found that subthreshold ADHD symptoms increased the risk for depression as well. In short, the risk for depression in ADHD is significant, exists in cases sampled from the general population that have fewer complications than clinically-referred samples, and affects a sizable proportion of adolescents with ADHD, thereby requiring further scientific investigation and clinical attention.

The analyses in chapter 5 revealed that parent and teacher-reported ADHD symptoms were associated with a high risk for concurrent – as opposed to future – depressive problems. Results from chapter 4 also showed that symptoms of ADHD were present at the time of depression onsets. Taken together, these results highlight that continuation of ADHD symptoms has a poor prognosis as it leads to a continued risk for depression. A high risk for depression due to ADHD persistence is supported by the review of studies in chapter 6.

Previous researchers have suggested that the risk for depression amongst individuals with ADHD increases with age, such that a peak incidence of depression occurs at late adolescence or young adulthood (Meinzer et al., 2015; McGough et al., 2005). Consistent with these findings, analyses in chapters 2 and 4 showed that the number of depressive symptoms as well as the risk for depression increased with age in adolescents with ADHD. This probably reflects a general age-related increase in depression risk during adolescence (Hankin et al., 1998; Oldehinkel, Wittchen, & Schuster, 1999). Indeed, a decline in depression risk beyond adulthood has been found amongst individuals with ADHD in a similar manner as amongst individuals without ADHD (Bramham et al., 2012; McGough et al., 2005; Meinzer et al., 2013). However, the risk for depression amongst individuals with ADHD is always higher than in the general population. It is important to note that ADHD symptoms increased concurrent to the increasing depressive symptomatology in the CIDI diagnosed depression groups. If ADHD symptoms do lead to a high concurrent risk for depression, as argued above, it is possible that the increasing depression risk during adolescence is due to increasing ADHD symptomatology. The opposite may be true too, i.e., increasing depressive symptoms worsen ADHD symptomatology. In addition, it is likely that the increased depression risk reflects the effects of the negative sequelae of ADHD. That is, development of depression in individuals with ADHD may occur due to direct effects of concurrent ADHD symptoms, but also to negative consequences of past ADHD symptoms, including early depressive symptoms. However, considering that the prospective association of ADHD symptoms and depression weakens when the time lag increases (chapter 5), it seems likely that ADHD symptoms increase in only a minority of the adolescents, and that negative sequelae, if any, occur and exert their influence relatively soon after the onset of ADHD.

The direct effects of ADHD on risk for depression have implications for the age of onset of depressive symptoms. As ADHD has an early onset, the risk for depression should already be

high at childhood. Although age-related increases in depression mean that a sizable proportion of individuals with ADHD develop depression only at adolescence, the *relative* risk for depressive symptoms is probably highest at childhood. This is concerning, as a diagnosis of depression at childhood may be difficult to establish. Moreover, presence of depression in childhood may complicate clinical decision making and initiation of interventions by masking symptoms of ADHD.

Results from chapters 2 and 3 show that individuals with ADHD improve in their functioning with time. Those developing additional depression showed impairments in family and cognitive function. It seems thus that escaping the development of depression is associated with a better prognosis and that ADHD without additional depression is associated with functioning improvements during adolescence. Such a time-dependent improvement could be related to an attenuation of ADHD symptomatology (Miranda, Colomer, Fernández, Presentación, & Roselló, 2015). It is known that ADHD symptoms may reduce with age. However, we did not find that ADHD symptoms attenuated in concert with functioning improvement. The apparent stability in ADHD symptomatology may be related to the use of self-reports, in contrast to previous studies which used observer ratings of ADHD.[6] It is also likely that adolescents with only ADHD adapted to their surrounding circumstances, thereby showing improved functioning over time, irrespective of symptom attenuation. Conversely, adolescents developing additional depression may have faced greater difficulties in adapting to their symptoms and circumstances leading to functioning difficulties. The latter reasoning is perhaps the most likely, as previous studies have shown cognitive improvements with age in children with ADHD, irrespective of symptom improvements (McAuley, Crosbie, Charach, & Schachar, 2013).

Characteristics of individuals with ADHD and depression

A second aim of thesis was to characterize adolescents with ADHD and depression to understand if ADHD-depression constitutes a separate disorder. To achieve this, I explored differences among adolescents with ADHD plus depression, only ADHD, only depression, and none of the

[6] Note that parent and teacher rated ADHD symptoms also did attenuate with time (see supplementary material 3, chapter 2). These symptom ratings though were derived from Child Behavior Checklist and the Teacher's Report Form, neither of which have been used often in conjunction with assessment of ADHD symptoms

two disorders, with regard to cognitive and family functioning characteristics. Evidence for a separate disorder type may be delivered if characteristics of adolescents with ADHD and depression are not explainable by the presence of either disorder alone. That is, (a) characteristics of ADHD-depression must be unique and not resembling that of either ADHD or depression alone, or; (b) characteristics of ADHD-depression must deviate from characteristics of ADHD only and depression only in a manner that is not explainable as the additive effects of each of the disorders.

Analysis of cognitive characteristics in chapter 2 showed that response time variability of adolescents with ADHD plus depression, prior to the development of depression, fell in-between that of the ADHD only and depressed only groups. The ADHD only group had poorer response variability performance and higher ADHD symptomatology than the ADHD with future depression group. In short, at age 11, ADHD-depression did not differ much from either ADHD alone or depression alone and the poorer response variability of ADHD only participants (than ADHD plus depression participants) may have been attributable to their higher ADHD symptoms. At age 19 though, working memory maintenance impairments in the ADHD-depression group was higher than the ADHD-only and depressed only groups, and in a non-additive fashion, providing some evidence for unique characteristics of the combined condition. It must be kept in mind that no statistically significant cognitive differences were found on direct comparisons of the ADHD only group to the ADHD-depression group. This lack of statistically significant differences may be due to the relatively small sample size of the study. Conversely, it is also possible that no substantial differences exist between individuals with ADHD with and those without a comorbid depression.

Family functioning characteristics of adolescents with ADHD plus depression, only ADHD and only depression were comparable and poorer than that of the normative adolescents (chapter 3). Although participants with ADHD plus depression had the highest impairments in family functioning, no statistical differences could be found between the combined condition and either ADHD or depression alone. A comparison of effect sizes showed that functioning impairments in the combined group at late adolescence had an additive pattern. Functioning impairments of this group were higher than the ADHD only group and only slightly higher than the depressed only group. Again, it seems that evidence is lacking to support a unique and

unexpected characteristic of ADHD plus depression, attributable neither to the presence of ADHD nor of depression, and which is necessary to classify it as a new disorder type.

It has been argued that evidence for ADHD plus depression being a separate disorder may emerge when gender differences are considered (Biederman et al., 1999; Meinzer et al., 2014; Mick, Biederman, Santangelo, & Wypij, 2003). Previous research has shown that girls with ADHD are more likely to suffer from depression than boys with ADHD, as evidenced by a study estimating that about 17% girls (aged 6 to 18 years) with ADHD developed major depression, as opposed to 1% of age-matched healthy controls (Biederman et al., 1999). According to the authors, this could point to a unique characteristic of ADHD with comorbid depression as opposed to ADHD alone – it tends to affect girls more often. Indeed, girls with ADHD are also more prone to have emotion regulation problems, greater peer problems, poorer coping strategies and a lower self-esteem than boys with ADHD; problems that are highly likely to increase the risk for depression (Biederman et al., 1999; Meinzer et al., 2014; Mick et al., 2003). However, this argument is tenuous, as gender differences in the risk for depression and depressogenic factors, such as poor emotion regulation and peer problems, are also seen in healthy, typically developing adolescents. Another postulated reason to account for gender differences when considering ADHD plus depression as a separate disorder is that parents of girls with ADHD plus depression are more likely to have ADHD-depression themselves than parents of girls with either ADHD or depression alone (Meinzer et al., 2014; Mick et al., 2003), while such a familial aggregation of ADHD and depression may be uncommon in boys (Meinzer at al., 2014). The authors suggest that at least in girls, therefore, ADHD plus -depression may be considered a separate disorder. Again, this argument seems invalid: a higher familial prevalence of ADHD plus depression when children suffer from these two disorders is to be expected as family members are more likely to have a genetic liability for symptoms of both these disorders, regardless of whether or not they should be considered a separate entity. Furthermore, the gender differences reported in the previous studies, i.e., lack of familial aggregation in boys with ADHD-depression, might well be due to a lack of power to find familial aggregation, given that numbers of boys with ADHD and depression are smaller than girls with ADHD and depression.

In this thesis, I found that pathways to depression through peer problems were more likely to occur in girls than boys. Thus, it may be said that some gender-differences exist in the

mechanisms through which depression develops in adolescents with ADHD. Nevertheless, this pattern of higher peer problems and subsequent depression among girls is common in normative adolescent development as well. Results in this thesis also found no gender differences in mediating pathways through comorbid anxiety and disruptive behaviours. Thus, once again, results from my studies do not support the notion that the combination of ADHD and depression is qualitatively unique when considering gender-based differences.

To sum up, results from chapter 3 did not indicate that the family functioning of adolescents with the combined condition of ADHD-depression is more impaired than the additive effects of either disorder alone. Results from chapter 2 showed some evidence to suggest that cognitive characteristics of ADHD-depression may differ qualitatively from ADHD or depression alone. Nevertheless, statistically significant differences amongst ADHD plus depression and ADHD only groups were not found. That said, the studies may have been underpowered to provide conclusive and statistically significant differences.

In short, I found little evidence to support the hypothesis that ADHD-depression constitutes a separate disorder. It needs to be emphasized again that I studied relatively small groups of children with ADHD and depression and only ADHD. More detailed investigations into characterizing ADHD plus depression in larger groups may deliver conclusive evidence in future to support the existence of a separate disorder. Further research must also establish if etiologic factors involved in the development of ADHD with depression, including genetic risks and pathophysiologic mechanisms, differ from that of ADHD and depression alone. Likewise, ADHD-depression may be considered a separate disorder if treatment responses or prognosis of affected individuals differs from that of individuals with either disorder alone. Till then, it may be prudent to say that the development of depression in children and adolescents with ADHD is a comorbid occurrence and not a separate disorder.

Although ADHD plus depression may not constitute a separate disorder, it is important to keep in mind that the added burden of depression in adolescents with ADHD does worsen functioning: my results showed that, whereas cognitive and family functioning of adolescents with only ADHD tended to improve over time, these functions seemed to deteriorate over the course of adolescence for adolescents with ADHD who developed depression as well. Thus, the

development of depression is to be viewed with caution and carefully monitored so as to prevent further impairments in outcomes among individuals with ADHD.

Mediators of pathways from ADHD to depression

ADHD by itself contributes to a risk for depression. Apart from continuing ADHD symptoms, the development of a number of negative correlates further increases the risk for depressive outcomes. In this thesis, I explored the role of two groups of negative correlates – anxiety and disruptive behaviour problems, and peer difficulties – in the pathways from ADHD to depression. Results showed that ADHD led to the development of anxiety/disruptive behaviours as well as peer difficulties, which in turn increased the risk for depression.

It is likely that the age at which these negative correlates develop relates to the risk for depression. Two previous studies on in older adolescents with ADHD found no evidence to suggest that anxiety problems (Meinzer et al., 2013) or ODD (Meinzer et al., 2015) mediated the pathway to depression. Both studies included older adolescents at a mean age of 17 years. Several onsets of anxiety and ODD may have been missed out by this time-point and therefore their effects on depressive outcomes may not have been captured. In contrast, studies in this thesis included younger participants in whom early effects of anxiety or disruptive problems may have been detected. For peer problems too, early rejection and victimisation showed an effect on depression. In short, it is likely that an early development of negative sequelae attribute a higher risk for depression than late development of the same problems.

The finding that comorbidities and peer problems in childhood and early adolescence affect pathways to depression is not surprising. Childhood and early adolescence are time-periods marked by rapid cognitive development and significant changes in mental capabilities. Further, the transition from childhood to adolescence marks a period of important adaptive changes and the acquisition of new abilities, such as more complex social and executive functioning skills. A slight disturbance in these time periods could mean shifting the normal developmental trajectories into maladaptive and deviant paths. Otherwise stated, development of comorbidities or peer problems during childhood or early adolescence burdens the normal developmental pathways and may lead to the development of additional problems, in this case depression, by skewing or delaying these processes.

Developmental maturation remains substantial after early adolescence, when the transition from adolescence to adulthood requires learning of new skills, such as social interactions in the workplace. This too is a susceptible period and altered development in the earlier transitioning phase (from childhood to adolescence) may have effects on this later transition from adolescence into adulthood. Thus, negative sequelae of ADHD may affect outcomes later in life on account of maladaptive developmental pathways between adolescence and adulthood. Effects of ADHD and its negative correlates on this second susceptible period must be examined in future studies.

Amongst all factors studied, comorbid disruptive behaviours emerged as the strongest predictor of future depressive risk, in both genders. Such strong effects on the risk for depression are concerning, given the high rates of comorbid disruptive problems in children with ADHD. On the other hand, it may be of advantage that disruptive behaviours attribute a higher risk for depression than anxiety or peer problems; because disruptive problems are generally more easily detectable by parents and teachers than anxiety or peer problems. It follows that a large proportion of children at depressive risk because of disruptive problems can be identified early and provided therapy. It should be noted further that comorbid disruptive problems must be considered seriously in boys as much as in girls: contrary to what is often assumed, the results presented in this thesis indicate that the effect of disruptive problems on depression in children with ADHD is equally strong in both sexes, and not more so in girls. Results also showed that the risk attributed by disruptive behaviours was equally strong for conduct and oppositional defiant disorder. This is interesting, as it suggests that the mechanisms through which depression develops may be comparable for both disorders.

Factors other than those included in this thesis have been studied previously in the context of developmental pathways to depression. Emotion regulation (Seymour et al., 2012; Seymour et al., 2014; Steinberg & Drabick, 2015); stressful life events (Antshel et al., 2013; Biederman et al., 2013; Daviss & Diller, 2014; Garcia et al., 2012; Semeijn et al., 2015); low self-esteem (Quinn & Madhoo, 2014); reward responsivity problems (Meinzer, Pettit, Leventhal, & Hill, 2012); maladaptive parenting styles (Deault, 2010; Wehmeier, Schacht, & Barkley, 2010); and ADHD medication such as amphetamine, atomoxetine and pemoline (Jerrel et al., 2015) have all been designated as important mediators of the pathways to depression. It is

important to emphasize that the effects of each of these mediators on the pathways to depression do not add up. For example, while emotion regulation has been reported to mediate 40-100% of the effects of ADHD on depression (Seymour et al., 2012), I found that anxiety and disruptive problems mediated 32% (chapter 4) and peer problems 7% (chapter 5) of this pathway. That is, almost 100% of the effects of ADHD on depression may seem to be explained when studying mediators in piecemeal, but obviously they are not independent. Rather, several pathways exist to the development of depression, many of which may be simultaneously seen in any affected individual at a given time-point. In addition, each of these mediating factors may lead to the development of additional negative sequelae and so generate a complex landscape of multiple interrelated depressogenic processes. Further, it is to be noted that not all individuals with ADHD develop depression. It is possible that certain protective factors may avert the effects of negative sequelae, preventing the development of depression. Finally, the negative sequelae may lead to the development of many poor outcomes, and the likelihood of such an outcome being depression is again dependent on the interaction of multiple risk and protective factors.

The multifactorial complexity, described above, shows that ADHD, as much as a disorder, may too be considered a risk factor for poor overall mental health. Thus with a diagnosis of ADHD, the affected individual's mental health status is not decisively established, but rather constantly evolving and clinicians must be alert to possible future changes. The presence of multiple pathways from ADHD to poor overall mental health, and the presence of inter-individual differences in these pathways also points to a need to revise our current definition of ADHD. That is, a child with multiple negative sequelae and in a negative trajectory may be considered in an advanced stage of the disorder compared to a child with fewer negative sequelae. The ADHD definition, in future, may incorporate the presence of such 'disorder stages'.[7] Treatments for these groups would, naturally, be adapted to the disorder stage: treatment protocols for advanced stages may incorporate a combination of therapies and which are intensive compared to treatments for early stages. Defining disorder stages may also spur further studies into the presence of subclasses of ADHD, which group individuals according to their propensity to proceed to an advanced stage of the disorder. Defining ADHD as a risk factor

[7] Note that the DSM-5 classifies ADHD into 'mild', 'moderate' or 'severe', depending on the number of symptoms present and functioning levels. This, however, excludes the recognition of negative sequelae and evolution of disorder trajectories.

for poor health, and inclusion of negative sequelae, inter-individual heterogeneity and disorder stages into the ADHD definition could add nuance to our understanding of this disorder; current practices involve establishment of an ADHD diagnosis, determination of subtype and assessment of functioning impairments. A change in assessment criteria to include the above-mentioned points would streamline research and generate information on individualised ADHD trajectories. A more comprehensive picture of ADHD may be gained when accounting for multiple sources of heterogeneity in trajectories and outcomes of ADHD. Moreover, discrepancies in current literature may be a result of inter-individual trajectory and disorder stage differences, which may be resolved through systematic recognition of such variance.

Ultimately, the development of multiple negative sequelae questions the validity of the ADHD construct as a diagnostic entity. Considering the wide variety of trajectories from ADHD to additional mental health and functioning problems, and the extensive inter-individual differences in such pathways, should ADHD be assigned a diagnostic class which depends on fulfilment of a rigid set of symptom criteria? What are the consequences of such rigidity for incipient cases of ADHD who miss classification but nevertheless develop maladaptations on account of subthreshold symptoms, which may snowball into functioning difficulties and a poor quality of life? In light of such questions, it may be prudent to revise our criteria for assessments of ADHD. More likely than not, the rigid classification systems employed lead to force-fitting of a diagnostic definition to an individual, when in fact the diagnosis as well as therapy may need to be tailored to each affected individual's unique trajectory.

Conclusions

Several explanations exist for the co-occurrence of ADHD and depression, and just one mechanism cannot explain this phenomenon; especially because each of the purported explanations explain some but not all of the ADHD-depression co-occurrence. First, part of why only some individuals with ADHD develop depression is related to the age of assessment. Comparable to non-affected individuals, the peak incidence of depression in individuals with ADHD occurs at late adolescence and young adulthood (Bramham et al., 2012; Meinzer et al., 2013). Before or after this time point the risks for depression exist, and are higher than in the general population, but these are of a lesser intensity than the depressive risks at late adolescence. That is, the absolute risk of depression in individuals with ADHD shows an age-

related pattern. The relative risk of depression in individuals with ADHD as compared to those with no ADHD though, does not vary with time in a similar way. As a result, studies on children with ADHD will show fewer cases with additional depression than studies among adolescents with ADHD, but the relative risk of depression is higher during childhood. Second, previous studies have shown that ADHD and depression share common vulnerabilities, such as genetic risks involving genes controlling the dopaminergic system (Cole, Ball, Martin, Scourfield, & McGuffin, 2009; Neuman et al., 2001), dysfunctional parent-child relationships (Meinzer et al., 2014; Ostrander & Herman, 2006), and reward responsivity (Meinzer et al., 2012), which may explain the co-occurrence of ADHD and depression. Third, the development of ADHD predisposes to a susceptibility for depression. The pathways discussed in this thesis – ADHD symptoms leading to a risk for depression directly, and indirectly through the development of other sequelae – may reflect some of the mechanisms through which ADHD and depression may be linked. It is quite likely that multiple other, yet undiscovered, factors are at work that may tip over an individual into a worsening trajectory. Regardless of the presence of negative sequelae, not all adolescents with ADHD develop depression. This implies that there are factors that protect individuals from an impaired trajectory and deteriorating outcomes. In short, ADHD is associated with a negative spiral of events, the eventual outcome of which may be depression in some individuals.

The possibility of ADHD-depression being a separate disorder requires further examination. Studies included in this thesis showed only some qualitative differences in cognitive, but not family functioning characteristics, between adolescents with ADHD plus depression, only ADHD and only depression. A noteworthy reason for this lack of differences could be small group sizes. However, the estimates, regardless of their statistical significance, did not consistently point to the presence of stronger than the additive effects of ADHD and depression only in the combined condition. Prior to the depression onsets, ADHD only, depression only and ADHD with future depression groups did not differ in their family or cognitive function. After the development of depression, poor family functions of the combined group could be explained by the additive effect of both depression and ADHD. Only cognitive function of the combined group at late adolescence was impaired in a non-additive fashion, but adolescents with the combined condition did not show any unique characteristic that was present in neither the depressed only nor the ADHD only group. Based on this, I am inclined to conclude

that ADHD-depression may not constitute a separate disorder type and that depression is more likely a consequence of ADHD and its correlates and sequelae. The subdivision of '*ADHD with other co-occurring sequelae*' into separate disorder types has been suggested not only for comorbid depression but other problems as well. For example, ADHD with emotion regulation problems (Shaw, Stringaris, Nigg & Leibenluft, 2014; Steinberg et al., 2015) and ADHD with sluggish cognitive tempo (McBurnett, Pfiffner, & Frick, 2001; Bauermeister, Barkley, Bauermeister, Martinez, & McBurnett, 2012) have both been suggested to be separate disorders, while the evidence for such a separation is lacking or weak at best.

Instead of creating separate disorder types ADHD and depression could better be approached as dimensional constructs (Wesselhoeft, Sørensen, Heiervang, & Bilenberg, 2013). Especially as the creation of a separate ADHD-depression disorder type does not add to the existing clinical management protocols, it is warranted to question and critically examine the need to do so (Coghill & Sonuga-Barke, 2012). Therapeutic decisions are dictated by the clinical presentation, regardless of the creation of a new diagnostic construct, and other considerations such as efficacy, adherence, and side effects. In case of individuals presenting with ADHD and depression, the treatment strategy would stay the same, whether or not ADHD-depression is classified as a disorder. As mentioned in a previous section though, defining further ADHD subtypes or new disorder classifications would assist in streamlining the research process. That is, more detailed information on the heterogeneous nature of ADHD can be derived by recognising that subtle differences in subgroups of ADHD may exist.

Taxometric studies (Frazier, Youngstrom, & Naugle, 2007; Haslam et al., 2006; Marcus et al., 2011) as well as results from this thesis support a dimensional nature of ADHD (as shown by a dose-response relationship of ADHD severity with depressive risk in chapter 4). A couple of genetic studies show that the heritability rates and patterns are comparable for individuals with a diagnosis of ADHD and subthreshold ADHD (Gjone, Stevenson, & Sundet, 1996; Coghill et al., 2012). The authors suggest that similar heritability patterns across the ADHD spectrum supports the dimensional nature of ADHD as etiological factors do not vary according to the specific cut-off criteria for diagnosis based on symptom counts. Previously, studies have also shown that subclinical levels of ADHD are sufficient to increase the risk for poor outcomes (Seymour et al., 2014; Bussing et.al., 2010; Keenan, Hipwell, Duax, Stouthamer-Loeber, & Loeber, 2004; Keenan et al., 2008), emphasising the dimensional nature of this disorder. Results from this

dissertation too showed associations between subthreshold ADHD and increasing depressive risk, which are very much in line with the dimensional concept of ADHD. Thus, although a matter of ongoing debate, the weight of evidence is increasingly suggesting that ADHD be viewed as a dimensional rather than categorical construct. In this context, and as discussed above, it may be futile to delineate ADHD-depression as a separate disorder.

Limitations

A couple of methodological considerations constrain the generalizability of these findings. First, as has been mentioned in all chapters, the reliance on self-reported retrospective assessments of ADHD may be considered unsound. However, and as explained in the individual chapters too, the best possible tool (interview) available for assessments of ADHD at or beyond 18 years of age was used. Second, as of now no studies exist on differences among ADHD subtypes in pathways to depression. Unfortunately, such an assessment could not be carried out in this thesis due to insufficient sample sizes. Third, due to power issues, the studies included in this thesis did not distinguish between individuals with and without a persistent diagnosis of ADHD. ADHD symptoms may attenuate over time, and about half of all affected children, in clinically referred samples, are no longer are eligible for a diagnosis of ADHD by late adolescence and early adulthood (Biederman, Mick, & Faraone, 2000; Faraone, Biederman, & Mick, 2006; Faraone et al., 2000; Mattingly, Culpepper, Babcock, &Arnold, 2015). Albeit the risks of depression are higher with persistence of ADHD, remitted individuals may too be liable to develop depression at a greater rate than in the general population. If such be the case, it signals a strong influence of common vulnerability factors and lasting effects of negative sequelae in the development of depression. Such hypothetical findings could also point to neural changes wrought by ADHD that produce depressogenic effects, and once triggered are independent of the continuation of ADHD, further adding to the evidence that depression is likely a comorbid outcome of ADHD. These and other possible effects of remission over persistence of ADHD on depressive outcomes were not explored in this thesis, but will hopefully be addressed in future research.

Clinical implications

Comorbid depression impairs outcomes and quality of life, but current treatment paradigms are not fully directed towards the management of depressive problems in children and adolescents

with ADHD. As seen in the qualitative review presented in chapter 6, a development of depression predicts further depressive problems in the future and is also associated with an problematic course of ADHD. It is thus very important to prevent the development of depression and thereby avoid a negative trajectory of outcomes.

ADHD symptoms pose a significant risk for the concurrent development of depression. A persistent course of ADHD is associated with a higher risk of depression than remittent ADHD symptoms (chapter 6). ADHD symptoms also predispose to the development of several negative sequelae, which in turn increase risk for future depressive problems. Fortunately, results show that an attenuation of ADHD symptomatology coincides with functioning improvements (as seen in cognitive and family function improvements in chapters 2 and 3). Taken together, the most optimum route to prevent comorbid depression may be an early and timely management of ADHD itself. Early interventions would also reduce the likelihood of negative sequelae, which, as discussed above, have stronger effects on the pathways to depression in childhood and early adolescence than late adolescence.

Close monitoring of children with ADHD is advisable in order to detect the development of negative sequelae early on. As discussed previously, the presence of disruptive behaviour problems in children with ADHD is, apart from being a problem on its own, a risk marker for depressive outcomes. Thus, disruptive behaviour problems may be routinely screened for in children with ADHD, and frequent follow-ups of children with ADHD may be advised for the timely detection of a deteriorating prognosis. These follow-ups should probably be most intensive in childhood and early adolescence, as these are particularly vulnerable time-periods with respect to the development of depression. Improvements in the ability to diagnose ADHD and to identify the development of comorbidities and other risk factors predicting a poor prognosis are also needed. This may include routine assessments for presence of risk factors in each child referred to the psychiatric clinic, and educating school personnel to assist in early reporting of ADHD symptoms. Amongst those diagnosed with ADHD, feedback may be requested at regular intervals from teachers and parents on the development of the child (in domains such as academic and social abilities). These strategies can assist in tracking the development of children with ADHD, and initiating preventive management as early as possible in cases with a significant risk for depression.

Future research

This thesis highlights some of the characteristics of the ADHD-depression relationship. Nevertheless, many gaps remain in our understanding of this association, and a few additional questions emerge from this dissertation. First and foremost, the available information to guide clinical decision making in individuals with ADHD and depression is very limited; further research is needed on the trajectories of individuals with ADHD subsequent to the development of depression (that is do what extent and time duration does deterioration in prognosis continue after the development of depression? Are there factors that may assist in improving these poor trajectories once depression has begun? If so, does there exist a critical time-period wherein such protective factors must be instated for the overall prognosis to improve?), and on therapeutic strategies for the management of ADHD once depression has already begun and is no longer preventable. Also, as discussed in a previous section, the transition from late adolescence into adulthood is a developmentally important period, which may be affected by the development of negative sequelae including depression. Effects of the negative correlates of ADHD on this sensitive time-period may only show up later in adulthood, making it important to conduct follow-up studies to assess late outcomes. Second, results from this dissertation show that the development of poor functional outcomes and correlates, such as anxiety, disruptive and peer problems, predispose to the development of depression only in some adolescents. Future research may unravel factors that thrust some individuals with ADHD into a negative trajectory producing negative correlates while others follow a more positive trajectory and show improved outcomes over time. Third, previous researchers have mostly studied ADHD using categorical definitions to define affected populations. Instead, as has been emphasised before, research may benefit from including dimensional assessments of ADHD in addition to categorical definitions (Polanczyk, 2014; Coghill et al., 2012). Fourth, differences in correlates of depression between remitted and persistent cases of ADHD may be studied in the future in order to better understand the ADHD-depression association. Fifth, results are unclear with regards to the direction of the associations between ADHD, depression and functioning impairments. Future studies may assess if increasing ADHD symptoms lead to functioning impairments or if the development of depression increases ADHD symptomatology and the increasing ADHD severity in turn leads to functioning impairments.

De ontwikkeling van depressie bij kinderen en adolescenten met ADHD

Samenvatting

10 tot 40% van de kinderen en adolescenten met ADHD (Attention Deficit Hyperactivity Disorder) ontwikkelen symptomen van depressie, die hun functioneren en kwaliteit van leven belemmeren, nog boven op de gevolgen van ADHD zelf. Ondanks dit hoge percentage depressieve klachten en de negatieve gevolgen hiervan, blijven veel vragen over het verband tussen ADHD en depressie onbeantwoord. Belangrijke vragen houden verband met de aard van deze relatie: gaat het om een comorbide verband of om een aparte stoornis? Daarnaast rijst de volgende vraag: welke factoren beïnvloeden de trajecten die leiden van ADHD tot de ontwikkeling van depressie?

Om bovenstaande problemen te onderzoeken, is voor een duale aanpak gekozen. Eerst heb ik adolescenten met ADHD plus depressie onderzocht om te bepalen of ADHD-depressie een aparte stoornis vormt. Als wordt aangetoond dat individuen met de gecombineerde aandoening unieke kenmerken hebben die hen differentiëren van gevallen van ADHD zonder depressie of depressie zonder ADHD, vormt dit gedeeltelijk bewijs voor ADHD-depressie als aparte stoornis. Daarom heb ik de verschillen op het vlak van cognitief functioneren (hoofdstuk 2) en van gezinsfunctioneren (hoofdstuk 3) onderzocht tussen enerzijds adolescenten met en zonder comorbide depressie, en anderzijds adolescenten met alleen depressie of zonder depressie noch ADHD. Om inzicht te krijgen in de ontwikkeling van depressie bij kinderen met ADHD, en ervan uitgaande dat depressie een comorbide gevolg van ADHD is, zijn ook de effecten van comorbide angst en ontwrichtend gedrag (hoofdstuk 2) evenals peerproblemen (hoofdstuk 3) op de trajecten van ADHD naar depressie onderzocht. Hoofdstuk 4 bevat een uitgebreider opinieonderzoek dat is uitgevoerd naar de trajecten van ADHD, via peerproblemen, naar depressie.

In hoofdstuk 2 worden verschillen in het cognitief functioneren van adolescenten met en zonder ADHD of depressie onderzocht op het gebied van verwerkingssnelheid, variabiliteit in responstijd, gerichte aandacht, werkgeheugenprestatie, responsinhibitie en cognitieve flexibiliteit bij een gemiddelde leeftijd van 11 en 19 jaar. De resultaten laten zien dat adolescenten met ADHD op 11-jarige leeftijd op variabiliteit in responstijd slechter scoren dan de controlegroepen. Het slecht cognitief functioneren van deelnemers met ADHD op 11-jarige leeftijd kan worden

toegeschreven aan de ernstigere ADHD-symptomen bij deze groep. Tussen de 11 en 19 jaar verbeterde de variabiliteit in responstijd bij de groep met alleen ADHD zodanig dat bij de 19-jarigen geen verschil meer bestond met adolescenten met alleen depressie of met de controlegroepen. De adolescenten met ADHD plus depressie lieten als 19-jarigen slechtere werkgeheugenprestaties zien dan de controlegroepen. Ondanks dat, op de leeftijd van 19, de geschatte werkgeheugenprestaties van de groep met ADHD plus depressie ook slechter waren dan de groep met alleen ADHD, was het verschil tussen de twee groepen statistisch gezien niet significant. De resultaten in hoofdstuk 2 leveren dan ook weinig bewijs op om ADHD-depressie als aparte stoornis aan te duiden.

Hoofdstuk 3 behandelt de verschillen in gezinsfunctioneren tussen adolescenten met ADHD plus depressie, met alleen ADHD, met alleen depressie en de controlegroepen, op vier momenten tussen vroege adolescentie en jongvolwassenheid. De resultaten tonen aan dat, gedurende hun adolescentie, deelnemers met ADHD plus depressie het slechtst functioneerden in het gezin. Adolescenten met ADHD plus depressie en met alleen depressie lieten tussen vroege adolescentie en jongvolwassenheid een verslechtering van het gezinsfunctioneren zien. Het gezinsfunctioneren van adolescenten met alleen ADHD verbeterde echter in deze periode. Het slechte gezinsfunctioneren als jongvolwassenen van adolescenten met ADHD plus depressie weerspiegelt waarschijnlijk de additieve effecten van beide stoornissen. Opnieuw wijzen de resultaten dus niet op unieke kenmerken van ADHD-depressie die het mogelijk maken de gecombineerde aandoening aan te merken als aparte stoornis.

In hoofdstuk 4 wordt het effect van comorbide angst en grensoverschrijdend gedrag in de trajecten van ADHD naar depressie onderzocht. Uit de resultaten blijkt dat het verband tussen ADHD en depressie een dosis-responsrelatie vertegenwoordigt: voor veranderingen in de diagnostische status van geen ADHD naar subdrempel ADHD, en van subdrempel ADHD naar volledige ADHD, gold een verhoogd risico van 89% op het ontwikkelen van een depressie. Voorts kampte een kwart van de deelnemers zonder ADHD, een derde van de deelnemers met subdrempel ADHD, en de helft van de deelnemers met volledige ADHD met een of meerdere periodes met angststoornissen. Ook de cijfers voor ontwrichtend gedrag (m.a.w. een antisociale of oppositioneel-opstandige gedragsstoornis) vielen hoger uit in de groepen met ADHD en subdrempel ADHD dan in de groep zonder ADHD. Een tiende van de groep zonder ADHD, een

vijfde van de groep met subdrempel ADHD, en de helft van de groep met volledige ADHD meldde ontwrichtend gedrag. Ook bleek dat angst 14% en ontwrichtend gedrag 22% van de trajecten van ADHD naar depressie beïnvloedt. De gevolgen van angst en ontwrichtend gedrag op ADHD-depressietrajecten overlapten niet. Daarnaast bleek dat de ontwikkeling van ADHD voorafging aan de ontwikkeling van depressie, en dat ontwrichtend gedrag een betere voorspeller was van depressie dan angst, bij zowel jongens als meisjes met ADHD. Hoofdstuk 4 focust op de hoge percentages comorbiditeiten bij kinderen met ADHD, en op het aanzienlijke risico op slechte resultaten bij subdrempel ADHD. Daarnaast focust dit hoofdstuk op het belang van het monitoren van comorbiditeiten, met name ontwrichtend gedrag, bij kinderen met ADHD om de ontwikkeling van depressie te voorkomen.

Hoofdstuk 5 bevat een studie naar peerproblemen bij adolescenten met ADHD en de gevolgen voor de ontwikkeling van depressie. Hieruit bleek dat enerzijds pesten en intimidatie en anderzijds een negatieve beoordeling door leeftijdsgenoten respectievelijk 3% en 4% van de trajecten van ADHD naar depressie beïnvloeden. De gevolgen van pesten en intimidatie en een negatieve beoordeling voor de trajecten naar depressie waren dus kleiner dan die van angst en ontwrichtend gedrag uit hoofdstuk 4. Het effect van deze twee peerproblemen op de trajecten van ADHD naar depressie overlapte niet, net zomin als de gevolgen van angst en ontwrichtend gedrag. De gevolgen van pesten en intimidatie en een negatieve beoordeling door leeftijdsgenoten bleven onveranderd na het toevoegen van co-existente angst en ontwrichtend gedrag. Dit laat zien dat, naast de 32% die beïnvloed wordt door angst en ontwrichtend gedrag (hoofdstuk 4), nog eens 7% kan worden verklaard door peerproblemen.

Hoofdstuk 6 bevat een studie naar de literatuur over de ontwikkeling van peerproblemen bij kinderen met ADHD, en over de ontwikkeling van depressie bij kinderen en adolescenten met peerproblemen. Op basis van de data uit deze studies is een conceptueel model ontwikkeld dat als doel heeft de trajecten van ADHD, via peerproblemen, naar depressie te verklaren. Dit hoofdstuk focust op het identificeren van factoren die leiden tot een verhoogd risico op depressie bij kinderen met ADHD, zoals symptomen van aandachtstekort en het langdurig aanhouden van ADHD. Ook laten de resultaten in dit hoofdstuk zien dat er meerdere trajecten mogelijk zijn van de ontwikkeling van ADHD naar de ontwikkeling van peerproblemen, en van deze problemen naar depressie.

Kortom, dit onderzoek wijst erop dat de ontwikkeling van ADHD of subdrempel ADHD een gevoeligheid voor depressie veroorzaakt. Er bestaan zowel directe als indirecte trajecten tussen de ontwikkeling van ADHD en de uiteindelijke ontwikkeling van depressie. Indirecte trajecten kunnen voortkomen uit de ontwikkeling van meerdere negatieve gevolgen van ADHD, waaronder (maar niet uitsluitend) comorbide angst, ontwrichtend gedrag en peerproblemen. Desalniettemin ontsnappen sommige kinderen met ADHD en met negatieve correlaten aan de ontwikkeling van depressie, wat suggereert dat er beschermende factoren bestaan die slechte resultaten voorkomen. ADHD wordt dus geassocieerd met een neerwaartse spiraal van gebeurtenissen, waarvan het resultaat bij sommige individuen depressie kan zijn.

De resultaten uit dit onderzoek ondersteunen de hypothese dat ADHD-depressie een aparte stoornis is niet: adolescenten met de gecombineerde aandoening beschikten niet over een uniek kenmerk dat niet aanwezig was bij de groep met alleen depressie of die met alleen ADHD. Het is waarschijnlijker dat depressie een gevolg is van ADHD en zijn correlaten. Bovendien wijst de dosis-responsrelatie tussen de ernst van ADHD en het risico op depressie op de dimensionele aard van ADHD. Dit suggereert dat een verschuiving van de bestaande categorische constructen naar dimensionele definities van ADHD gerechtvaardigd is. Daarnaast kan het vaststellen van aanvullende subtypes ADHD, of een nieuwe classificatie van stoornissen, de heterogeniteit van onderzoeksbevindingen reduceren, hoewel dit niet noodzakelijkerwijs bijdraagt aan het verbeteren van behandelingen. Bestaande therapeutische beslissingen voor individuen met ADHD plus depressie zijn gebaseerd op klinische presentaties, de doeltreffendheid van de behandeling, behandelingstrouw en bijverschijnselen, en hebben misschien maar weinig baat bij een aanvullende classificatie van stoornissen.

De klinische implicaties van dit onderzoek omvatten het belang van het regelmatig monitoren van kinderen met ADHD, zodat de negatieve gevolgen zo vroeg mogelijk worden opgemerkt. Belangrijker nog is dat kinderen met ADHD regelmatig gescreend worden op ontwrichtend gedrag. Om nauwkeurige monitoring te garanderen kan worden overwogen leerkrachten bij te scholen over ADHD, zodat ze in staat zijn om regelmatig uitgebreide feedback te geven. Dergelijke regelmatige feedback van docenten kan informatie opleveren over ontwikkelingen op academisch en sociaal vlak, die normaal gesproken niet beschikbaar is voor ouders en clinici. Daarnaast gaat de voorkeur uit naar intensieve follow-upbeoordelingen in de

kindertijd en vroege adolescentie, omdat in deze periodes het risico op de ontwikkeling van depressie groot is. De resultaten suggereren ook dat de beste route naar het voorkomen van depressie, het in een vroeg stadium en vroegtijdig aanpakken van ADHD zelf is.

De beperkingen van de onderzoeken in dit proefschrift zijn: (i) het gebruik van zelfbeoordeling achteraf om ADHD vast te stellen; (ii) het gebrek aan mogelijkheden om verschillen in subtypes ADHD te beoordelen in trajecten naar depressie; en (iii) onvoldoende steekproefomvang om verschillen tussen gevallen van verdwijnende en aanhoudende ADHD te beoordelen. De sterke punten van het onderzoek zijn o.a.: (i) het gebruik van een populatiesteekproef (in tegenstelling tot de meeste eerdere studies waarin onderzoek is gedaan naar klinische gevallen met een ernstige vorm van ADHD en die slecht functioneren); (ii) het onderzoeken van het risico op depressie bij adolescenten met subdrempel ADHD; en (iii) het onderzoeken van deelnemers tussen vroege adolescentie en jongvolwassenheid om de piekperiode waarin depressie zich ontwikkelt vast te stellen.

Al met al zijn er verschillende factoren die de ontwikkeling van depressie bij kinderen en adolescenten met ADHD beïnvloeden. Daarnaast is het huidige bewijs voor ADHD-depressie als aparte stoornis op zijn hoogst zwak, en zijn er meer studies nodig om deze hypothese tot in detail te onderzoeken. Belangrijk is echter dat de zoektocht naar een aparte stoornis betwistbaar is, omdat deze niet bijdraagt aan verbeteringen in de behandelingen. In plaats daarvan moet, zoals in dit proefschrift is uiteengezet, ADHD worden beschouwd als een dimensionele stoornis en niet als een categorisch construct.

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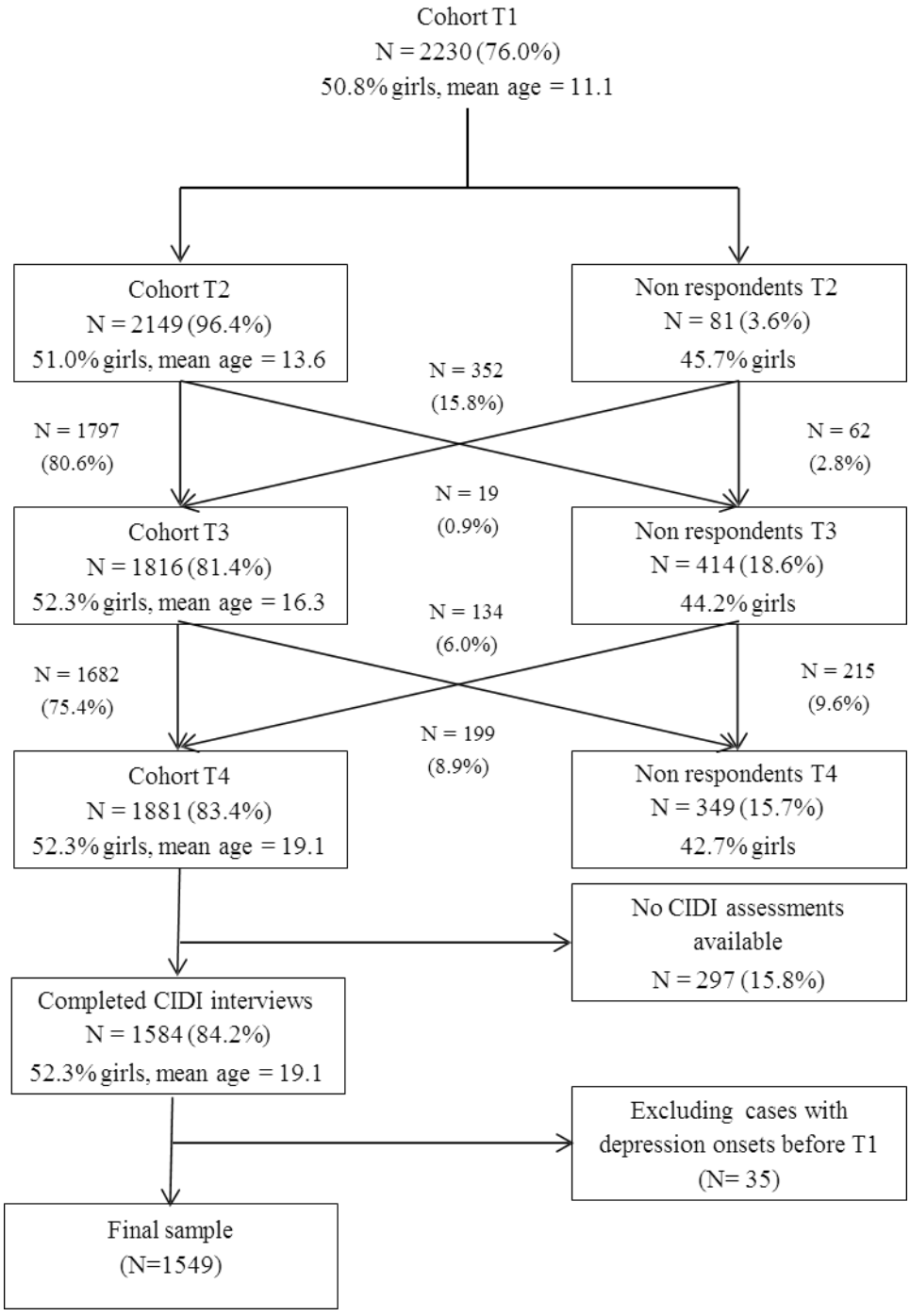
Appendix 1 Overview of the mean age and gender distributions of participants in the TRAILS sample



Appendix 2 The Amsterdam Neuropsychological Tasks (ANT): task descriptions

The Amsterdam Neuropsychological Tasks program (ANT) (De Sonneville 1999) is a computer aided assessment battery of response time tasks that allow for the systematic evaluation of cognitive capacities. The ANT has proven to be a sensitive and valid tool in non-referred (De Sonneville *et al* 2002, Groot *et al* 2004, Stins *et al* 2005) as well as referred samples of various clinical domains such as minor neurological dysfunction (de Sonneville *et al* 1993), attention deficit disorders (Hanisch *et al* 2004, Slaats-Willemse *et al* 2003), and autism-related disorders (Althaus *et al* 1996). For the present study, five subtasks from the ANT were selected and these are further described below:

1) Baseline speed task
   A white fixation cross is projected at the centre of the screen that changes into a white square at random time intervals (Fig. 1). Children are instructed to press a mouse button with their index finger as soon as the white cross is seen. The task consists of two parts, each with 10 practice trials and 32 test trials. The first part requires responses from the non-dominant hand and the second part responses from the dominant hand. The valid response window (VRW) ranges from 150-4000 milliseconds (ms). The post response interval (PRI) ranges from 500 to 2500 ms. The measure 'processing speed' is calculated as the mean reaction time (RT) over both the non-dominant and dominant hand responses.

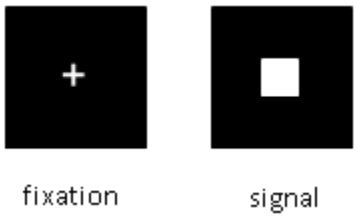
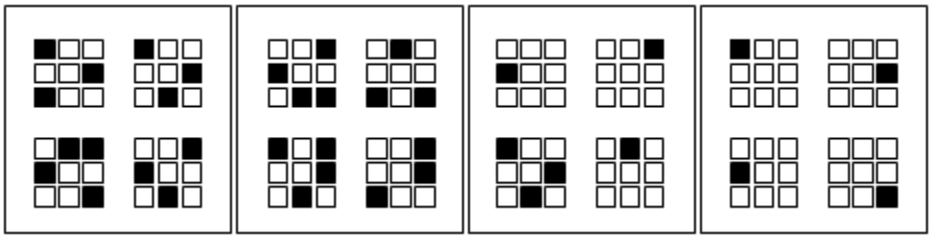


Fig. 1

2) Pattern recognition task
   Children are instructed to memorize a predefined target pattern following which they are asked to recognize this pattern from a display set containing four patterns. Patterns contained in half of the display sets appear dissimilar to the target and the other half contain patterns appearing similar to the target (Fig. 2). The task consists of 12 practice trials and 80 test trials. Of the 80 test trails, half require responses with the non-dominant hand and the other half require responses with the dominant hand. The VRW is 200-7000 ms and the PRI is 1200 ms. The measure 'focussed attention' is computed by subtracting the mean RT of the dissimilar trials from the similar trials.

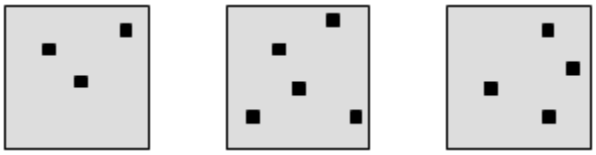

(Target pattern)



(Target similar) (Non-target similar) (Target dissimilar) (Non-target dissimilar)

Fig. 2

3) Sustained attention task
Six hundred dot patterns are successively presented on the screen in 50 series of 12 trials. Each series consists of four 3-, 4-, and 5-dot patterns, presented in a pseudo random sequence. Participants responded by pressing either the left or the right mouse button, depending on the stimulus. Responses to 4-dot patterns were made by pressing the mouse button with the dominant hand ('yes response') (Fig. 3). Responses to 3-, or 5-dot patterns were made by pressing the mouse button with the non-dominant hand ('no response'). Task assessments are preceded by 24 practice trials. The measure 'response time variability' is computed as the within-subject standard deviation (i.e. the variability) of the mean RT of the 50 series and is interpretable as a measure of response stability in continuous task performance.



Non target Non target Target

Fig. 3

4) Memory search task
Children are instructed to memorise one (part 1, 40 trials), two (part 2, 72 trials), and three (part 3, 96 trials) target consonant(s). Display sets are subsequently presented that consist of four consonants (Fig. 4). Display sets in half the trials contain the complete target set requiring a 'yes-response' (pressing mouse button by the dominant hand). In the other half, display sets contain none of the target letters or an incomplete target set, requiring a 'no-response' (pressing mouse button by non-dominant hand). Each task (part) is preceded by 12 practice trials. The VRW is 200-8000 ms and the PRI 1200 ms. The measure 'working memory maintenance' is computed by subtracting the mean RT of part 1 low working memory load) target trials from the mean RT of part 3 (high working memory maintenance load) target trials.

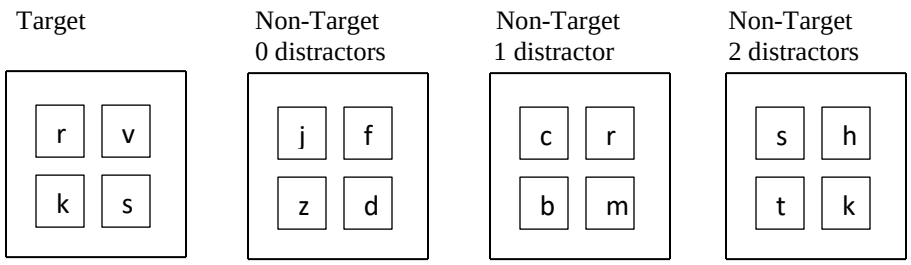


Fig. 4

5) Shifting set task

A horizontal bar is presented in the centre of the screen. In each trial, a coloured square moves across the bar randomly, to either to the left or to right (fig 5). The task consists of three parts. In part 1, children are instructed to copy the movement of a green coloured square (i.e. a green square moving to the left requires pressing the left mouse button, and a green square moving to the right requires pressing the right mouse button). In part 2, children are instructed to 'mirror' the direction of a red coloured square (i.e. a leftward moving red square requires pressing the right mouse button, and a rightward moving red button requires pressing the left mouse button). In part 3, the colour of the moving square randomly alternates between green and red. When the square is green, children are required to 'copy' its movement (i.e. responses as in part 1), and when the square is red, children are required to 'mirror' its movement (i.e. responses as in part 2). Parts 1 and 2 consist of 40 test trials each and are each preceded by 10 practice trials. Part 3 consists of 80 test trials, preceded by 16 practice trials. The VRW is 150 – 6000 ms and the PRI 250 ms. The measure 'response inhibition' is computed by subtracting the mean RT of part 1 from the mean RT of part 2. The measure 'cognitive flexibility' is computed by subtracting the mean RT of part 1 from the mean RT of part 3.

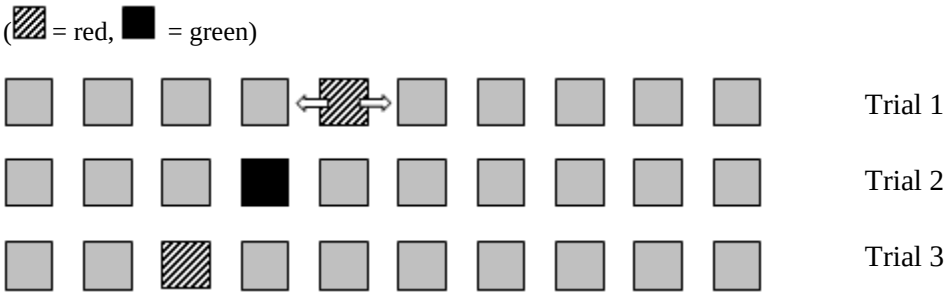


Fig. 5

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Appendix 3.1 Percentage of participants in each group receiving medications for ADHD or depression at the four time points

Groups	Dexamphetamine				Methylphenidate			
	T1	T2	T3	T4	T1	T2	T3	T4
A + D	0	0	0	4.7	0	4.7	0	38.1
A	0	0	0	2.8	5.7	0	8.6	20.0
D	0	0	0	0	0	8.5	1.1	2.1
C	0	0.2	0.1	0	0.4	5.2	0.2	1.5
	Atomoxetine				Venlafaxine			
	T1	T2	T3	T4	T1	T2	T3	T4
A + D	0	0	0	0	0	0	0	0
A	0	5.7	0	0	0	0	0	0
D	0	0	0	0	0	0	0	0.7
C	0	0	0	0	0	0	0	0
	Imipramine				Clomipramine			
	T1	T2	T3	T4	T1	T2	T3	T4
A + D	0	0	0	0	0	0	0	0
A	0	0	0	0	0	0	0	0
D	0	0	0	0	0	0.7	0	0
C	0.1	0	0	0	0	0.1	0	0
	Amitryptyline				Nortriptyline			
	T1	T2	T3	T4	T1	T2	T3	T4
A + D	0	0	0	0	0	0	0	0
A	0	0	0	0	0	0	0	0
D	0	0.7	0	0	0	0	0	0
C	0	0.1	0	0	0	0.2	0	0
	Fluoxetine				Citalopram			
	T1	T2	T3	T4	T1	T2	T3	T4
A + D	0	0	0	0	0	0	0	0
A	0	0	0	0	2.8	0	0	0
D	0	0	0.3	1.1	0	0	0	1.7
C	0	0	0	0	0	0.1	0	0.1
	Paroxetine				Sertraline			
	T1	T2	T3	T4	T1	T2	T3	T4
A + D	0	0	0	0	0	0	0	0
A	0	0	0	0	0	0	0	0
D	0	0	0.3	0.3	0	0	0	0
C	0	0.1	0	0	0	0	0	0.2
	Fluvoxetine				Moclobemide			
	T1	T2	T3	T4	T1	T2	T3	T4
A + D	0	0	0	0	0	0	0	0
A	0	0	0	0	0	0	0	0
D	0	0	0.3	0	0	0.7	0	0
C	0	0.1	0	0	0	0.1	0	0

Groups: A+D (ADHD with an onset of depression); A (only ADHD); D (only an onset of depression); C (comparison)
N = 1549

Appendix 3.2 Cognitive functioning differences between participants receiving and not receiving medications

	Baseline				
	Participants with medications RT - Mean (SD)	Participants without medications RT - Mean (SD)	t	df	p
Processing speed	289.1 (7.97)	331.6 (38.8)	1.89	330	.06
Focussed attention	1463.6 (457.5)	1473.6 (465.8)	.02	329	.99
Response time variability	2420.0 (810.0)	1747.0 (842.7)	-1.38	334	.17
Working memory maintenance	699.4 (60.8)	515.98 (274.6)	-1.21	332	.29
Response inhibition	178.3 (237.9)	249.6 (194.2)	.63	332	.53
Cognitive flexibility	572.3 (115.6)	648.7 (251.0)	.52	326	.61
	Follow-up				
	Participants with medications RT - Mean (SD)	Participants without medications RT - Mean (SD)	t	df	p
Processing speed	252.8 (26.5)	252.0 (24.2)	-.19	327	.85
Focussed attention	840.4 (310.8)	807.8 (259.0)	-.65	331	.51
Response time variability	877.8 (357.3)	880.3 (382.1)	.04	333	.97
Working memory maintenance	313.6 (183.6)	807.8 (259.0)	-1.79	335	.07
Response inhibition	226.8 (220.0)	207.4 (169.6)	-1.01	324	.31
Cognitive flexibility	403.0 (176.3)	373.1 (155.0)	-.19	327	.85

RT – Reaction time

Appendix 3.3 Standardized scores of self- (YSR and ASR), parent- (CBCL) and teacher-reported (TCP) ADHD symptoms in the four groups across the four assessment time-points

Assessment time points*	**Groups#**				**ANOVA**	
	A + D mean (SD)	**A** mean (SD)	**D** mean (SD)	**C** mean (SD)	**F**	**p**
T1						
YSR	0.45 (0.95)	0.86 (1.11)	0.16 (0.95)	-0.07 (0.99)	14.78	<.001
CBCL	0.78 (1.33)	1.15 (1.02)	0.06 (0.94)	-0.05 (0.98)	19.85	<.001
TCP	0.65 (1.25)	0.39 (1.23)	-0.02 (0.98)	-0.01 (0.98)	3.84	.009
T2						
YSR	0.95 (1.28)	0.94 (1.06)	0.16 (0.96)	-0.08 (0.97)	22.03	<.001
CBCL	0.99 (1.36)	1.13 (1.03)	0.23 (0.93)	-0.10 (0.96)	26.96	<.001
TCP	0.45 (1.17)	0.92 (1.24)	0.002 (0.96)	-0.03 (0.98)	7.89	<.001
T3						
YSR	0.99 (1.36)	1.13 (1.03)	0.23 (0.93)	-0.10 (0.96)	30.71	<.001
CBCL	1.21 (1.51)	1.49 (1.44)	0.10 (0.90)	-0.08 (0.94)	36.28	<.001
TCP	0.60 (0.80)	0.79 (1.19)	0.09 (0.99)	-0.05 (0.98)	6.46	<.001
T4						
ASR	1.98 (1.17)	1.18 (1.24)	0.43 (1.01)	-0.16 (0.89)	78.90	<.001

*ADHD symptoms were measured using Youth Self Reports (YSR), Child Behavior Checklists (CBCL) and Teacher's Checklist of Pathology (TCP) at the first (T1), second (T2), and third (T3) assessment waves. At the fourth wave (T4) ADHD symptoms were assessed using the Adult Self Reports (ASR)

A+D: ADHD with depression; A: only ADHD; D: only depression; C: comparisons

Appendix 3.4 Standardized scores of self- (YSR and ASR) and parent-reported (CBCL) depressive symptoms in the four groups across the four assessment time-points

Assessment time points*	**Groups#**				**ANOVA**	
	A + D Mean (SD)	**A** Mean (SD)	**D** Mean (SD)	**C** Mean (SD)	**F**	**p**
T1						
YSR	0.40 (0.94)	0.43 (1.23)	0.35 (1.10)	-0.10 (0.94)	19.80	<.001
CBCL	1.01 (1.30)	0.58 (1.20)	0.28 (1.14)	-0.09 (0.92)	20.76	<.001
T2						
YSR	0.32 (0.97)	0.27 (0.88)	0.57 (1.25)	-0.14 (0.87)	44.53	<.001
CBCL	1.08 (1.42)	0.29 (1.26)	0.38 (1.18)	-0.11 (0.90)	27.02	<.001
T3						
YSR	1.02 (1.53)	0.17 (0.94)	0.75 (1.24)	-0.19 (0.81)	79.26	<.001
CBCL	1.01 (1.43)	0.56 (1.16)	0.54 (1.34)	-0.14 (0.83)	40.05	<.001
T4						
ASR	1.55 (1.20)	0.37 (1.20)	0.79 (1.17)	-0.22 (0.80)	117.78	<.001

*Symptoms of depression were measured using Youth Self Reports (YSR) and Child Behaviour Checklists (CBCL) at the first (T1), second (T2), and third (T3) assessment waves and Adult Self Reports (ASR) at the fourth wave (T4)
A+D: ADHD with depression; A: only ADHD; D: only depression; C: comparisons

Appendix 4.1 Standardized scores of self- (YSR and ASR), parent- (CBCL) and teacher-reported (TRF) ADHD symptoms in the four groups across the four assessment time-points

Assessment time points*	**Groups#**			
	C Mean (SD)	**A** Mean (SD)	**D** Mean (SD)	**A + D** Mean (SD)
T1				
YSR	-0.09 (0.97)	0.83 (1.10)	0.15 (0.92)	0.72 (1.20)
CBCL	-0.08 (0.96)	1.02 (0.99)	0.02 (0.94)	1.15 (1.25)
TRF	-0.02 (0.98)	0.61 (1.18)	-0.02 (0.97)	0.39 (1.09)
T2				
YSR	-0.09 (0.96)	0.85 (1.07)	0.13 (0.94)	1.00 (1.18)
CBCL	-0.07 (0.95)	1.09 (1.10)	-0.01 (0.94)	1.18 (1.06)
TRF	-0.04 (0.97)	0.78 (1.12)	0.01 (0.98)	0.45 (1.06)
T3				
YSR	-0.11 (0.96)	0.95 (1.01)	0.19 (0.94)	0.96 (1.21)
CBCL	-0.10 (0.92)	1.22 (1.30)	0.07 (0.93)	1.34 (1.18)
TRF	-0.08 (0.96)	0.80 (1.18)	0.11 (1.02)	0.52 (0.93)
T4				
ASR	-0.17 (0.89)	1.06 (1.08)	0.40 (1.03)	1.53 (1.14)

*ADHD symptoms were measured using Youth Self Reports (YSR), Child Behaviour Checklists (CBCL) and Teacher Report Forms (TRF) at the first (T1), second (T2), and third (T3) assessment waves. At the fourth wave (T4) ADHD symptoms were assessed using the Adult Self Reports (ASR)

#C: comparisons; A: only ADHD; D: only depression; A+D: ADHD with depression

Appendix 4.2 Standardized scores of self- (YSR and ASR) and parent-reported (CBCL) depressive symptoms in the four groups across the four assessment time-points

Assessment time points	**Groups**			
	C Mean (SD)	**A** Mean (SD)	**D** Mean (SD)	**A + D** Mean (SD)
T1				
YSR	-0.10 (0.95)	0.46 (1.13)	0.30 (1.07)	0.39 (0.99)
CBCL	-0.10 (0.92)	0.60 (1.23)	0.21 (1.06)	1.10 (1.38)
T2				
YSR	-0.14 (0.88)	0.20 (0.91)	0.52 (1.24)	0.53 (1.12)
CBCL	-0.12 (0.90)	0.33 (1.15)	0.33 (1.14)	1.20 (1.42)
T3				
YSR	-0.19 (0.82)	0.11 (0.87)	0.72 (1.26)	0.86 (1.39)
CBCL	-0.15 (0.84)	0.38 (1.06)	0.47 (1.26)	1.36 (1.55)
T4				
ASR	-0.21 (0.81)	0.21 (1.03)	0.77 (1.18)	1.27 (1.17)

*Symptoms of depression were measured using Youth Self Reports (YSR) and Child Behaviour Checklists (CBCL) at the first (T1), second (T2), and third (T3) assessment waves and Adult Self Reports (ASR) at the fourth wave (T4)
C: comparisons; A: only ADHD; D: only depression; A+D: ADHD with depression

Appendix 5.1 Cox regression estimates of the effect of ADHD symptoms on depression onset before and after adjusting for peer dislike and victimisation and controlling for gender, disruptive behaviours and anxiety

Covariate	**B (SE)**	***p***	**Wald χ^2**	**Hazard Ratio**	**95% CI**
Model 1					
ADHD	0.54 (0.19)	0.005	8.03	1.72	1.18 to 2.49
ADHD*time	-0.12 (0.06)	0.065	3.40	0.89	0.79 to 1.01
Model 2					
ADHD	0.51 (0.19)	0.008	7.13	1.67	1.15 to 2.43
ADHD*time	-0.12 (0.06)	0.069	3.30	0.89	0.79 to 1.01
Peer dislike	0.20 (0.10)	0.038	4.31	1.22	1.01 to 1.47
Model 3					
ADHD	0.50 (0.19)	0.010	6.61	1.65	1.13 to 2.41
ADHD*time	-0.10 (0.06)	0.125	2.35	0.91	0.80 to 1.03
Victimisation	0.35 (0.14)	0.010	6.55	1.42	1.09 to 1.85
Victimisation*time	-0.16 (0.08)	0.032	4.59	0.85	0.73 to 0.99
Model 4					
ADHD	0.48 (0.19)	0.013	6.20	1.62	1.11 to 2.37
ADHD*time	-0.10 (0.06)	0.124	2.37	0.91	0.80 to 1.03
Peer dislike	0.21 (0.10)	0.039	4.24	1.24	1.01 to 1.52
Victimisation	0.27 (0.15)	0.066	3.39	1.31	0.98 to 1.75
Victimisation*time	-0.17 (0.08)	0.029	4.78	0.84	0.72 to 0.98

Appendix 5.2 Gender differences in Cox regression estimates of the effect of ADHD symptoms on depression onset before and after adjusting for peer dislike and victimisation and controlling for disruptive behaviours and anxiety

Covariate	**Girls**			**Boys**		
	B (SE)	p	HR	B (SE)	p	HR
Model 1						
ADHD	0.57 (0.22)	0.01	1.77	0.55 (0.40)	0.17	1.72
ADHD*time	-0.14 (0.07)	0.06	0.87	-0.09 (0.12)	0.48	0.92
Model 2						
ADHD	0.53 (0.22)	0.01	1.69	0.54 (0.41)	0.19	1.72
ADHD*time	-0.14 (0.08)	0.07	0.87	-0.09 (0.13)	0.46	0.91
Peer dislike	0.23 (0.12)	0.04	1.26	0.24 (0.18)	0.19	1.27
Model 3						
ADHD	0.52 (0.23)	0.02	1.68	0.58 (0.44)	0.19	1.79
ADHD*time	-0.13 (0.08)	0.10	0.88	-0.09 (0.13)	0.45	0.91
Victimisation	0.33 (0.24)	0.17	1.39	0.50 (0.19)	0.009	1.66
Victimisation*time	-0.10 (0.10)	0.32	0.90	-0.29 (0.14)	0.045	0.75
Model 4						
ADHD	0.49 (0.22)	0.02	1.63	0.57 (0.45)	0.20	1.77
ADHD*time	-0.12 (0.08)	0.12	0.89	-0.10 (0.13)	0.44	0.90
Peer dislike	0.23 (0.12)	0.06	1.26	0.27 (0.20)	0.18	1.31
Victimisation	0.25 (0.26)	0.34	1.28	0.43 (0.21)	0.04	1.53
Victimisation*time	-0.11 (0.11)	0.31	0.90	-0.30 (0.15)	0.04	0.74

Table II Overview of all included studies on the associations of ADHD with peer problems and of peer problems with depression

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
Abada et al. (2008)	To determine effects of victimisation on mental health of adolescents	Prospective	1742 children from a population based cohort aged 12-13 years at baseline and including both genders	Self-reports of verbal and physical victimisation	Symptoms of depression assessed with the self-reports (CES-D)	Harassment at school was associated with poor mental health and depression, especially in girls
Andrade et al. (2008)	To assess the relationship between social difficulties and sustained/selective attention in clinic-referred children with attention problems	Cross-sectional	101 participants (82 boys, 19 girls) aged 6 to 12 years including children with ADHD, attention problems, and neither ADHD nor attention problems	Teacher-reported social problems (CRS-Revised)	DSM-IV diagnoses of ADHD	Social problems were associated with both selective and sustained attention. Results were more robust for sustained attention
Andrade and Tannock (2013)	To determine associations of hyperactive-inattentive symptoms with peer problems and their mediators	Cross-sectional	Population-based sample of 500 children (245 boys, 255 girls) aged 6-9 years	Parent and teacher reports of social behaviours and peer problems (SDQ)	Parent and teacher rated symptoms of ADHD based on DSM-IV-TR criteria	Hyperactive and inattentive symptoms were associated with peer problems. Conduct problems and pro-social behaviours mediated these relationships
Asher and Wheeler (1985)	To compare loneliness in rejected and neglected children	Short-term prospective with follow-up at 1 week	200 children (89 girls, 111 boys) between third and sixth grade of school	Sociometric measures of peer acceptance, rejection and neglect	Symptoms of loneliness assessed by self-reports	Rejected children were more lonely than neglected children

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
Auerbach et al. (2010)	To assess the relationships between social support, stress and depressive outcomes in adolescents	Prospective	258 adolescents aged 12-18 years at baseline (110 boys, 148 girls)	Self-reported social support (SSSCA)	Self-reported symptoms of depression (CES-D)	Interpersonal stress mediates the relationship between social support and depressive symptoms
Bagwell et al. (2001)	To determine the association between childhood ADHD and peer-relationships in adolescence	Cross-sectional	211 participants (202 boys, 9 girls) aged 13-18 years including adolescents with (n=111) and without (n=100) ADHD	Self-reported peer acceptance, friendship, and characteristics of friends; parent-reported peer rejection (CBCL)	DSM-III-R or DSM-IV diagnoses of ADHD by parent and teacher reports (DBDRS; DISC)	Childhood ADHD predicts impairments in peer relations at adolescence
Barchia and Bussey (2010)	To determine factors that mediate the relationship between victimisation and depression	Prospective	1285 children (593 boys, 692 girls) with a mean age of 14.9 years at baseline	Self-reports of physical, verbal and relational victimisation	Symptoms of depression assessed with the CES-D	Rumination mediated the relationship between victimisation and depression
Bauermeister et al. (2005)	To distinguish between ADHD-C and ADHD-I	Cross-sectional	98 participants (58 boys, 40 girls) aged 6-11 years including children with ADHD-C (n=44), ADHD-I (n=25) and no ADHD (n=29)	Parent- and teacher-reported social skills	DSM-IV diagnoses of ADHD by parent and teacher reports (CBCL; DBDRS; TRF)	Children with ADHD-I were less assertive and less likely to initiate social contact than children with ADHD-C
Becker (2014)	To determine the role of sluggish cognitive tempo in pathways from ADHD to peer	Prospective	176 children (82 boys, 94 girls) with a mean age of 9.17 years	Teacher-reported peer relationships (VADTRS), peer preference (DSAS) and popularity	Teacher-rated symptoms of ADHD (VADTRS) based on DSM-IV criteria	Sluggish cognitive tempo in children with ADHD predicts peer functioning

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
	functioning problems			(ICS)		difficulties
Bellanti and Bierman (2000)	To determine the association of inattention with social behaviours and peer relations	Cross-sectional	387 children (195 boys, 192 girls) attending kindergarten	Peer nominations of dislike, aggression and prosocial behaviours; teacher-rated social behaviour (TRF)	Parent- and teacher-reported inattention (CBCL; TRF)	Inattention was associated with problems in social behaviour and peer difficulties
Berry et al. (1985)	To compare and differentiate between girls and boys with ADHD	Cross-sectional	228 participants (164 boys, 64 girls) aged 7-14 years including 134 clinic-referred children with ADHD and 94 children with no ADHD	Parent and teacher-reported social behaviour	DSM-III diagnoses of ADD with or without hyperactivity	Both girls and boys with ADHD showed peer problems and aggressive peer-interactions. Girls faced greater peer rejection than boys
Biederman et al. (1998)	To assess normalisation of functioning in clinic-referred boys with persistent ADHD	Prospective	166 boys aged 6-17 years with persistent (n=85), remittent (n=13) and no ADHD (n=68)	Parent and self-reported peer interactions, social behaviours, and social functioning (SAICA)	DSM-III-R diagnoses of ADHD	Social functioning worsened with time in persistent ADHD, irrespective of baseline social functioning
Biederman et al. (2004)	To determine the associations between executive dysfunction and functional outcomes in children with ADHD	Cross-sectional	484 clinic-referred children (224 boys, 260 girls) with (n=259) and without ADHD (n=225) (including both genders) aged 6-17 years	Maternal reports of social functioning (SAICA)	DSM-III-R diagnoses of ADHD based on maternal reports and interviews	In children with ADHD, no social functioning differences were found between those with and without executive dysfunction
Blachman and	To compare	Short-term	228 participants	Sociometric	DSM-IV diagnoses of	Girls with ADHD

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
Hinshaw (2002)	friendship patterns between girls with and without ADHD	prospective study with a follow-up period of 5 weeks	aged 6-12 years including 140 clinic-referred girls with ADHD and 88 comparison girls	measures of positive and negative peer regard, and friendship	ADHD based on parent and teacher reports (SNAP; DISC)	(esp. those with ADHD-C) had fewer friendships than girls without ADHD
Blechman et al. (1986)	To assess the relationships of social and academic competence with depression		169 children (82 boys, 87 girls) between third and sixth grade of school	Sociometric measures of peer status; self-reported social competence (HSPPC)	Symptoms of depression assessed with peer nominations and self-reports (CDI-Modified)	Happiness was higher in socially competent children than in academically competent children
Bogart et al. (2014)	To determine the prospective association of peer victimisation with mental health	Prospective	4297 children (2105 boys, 2192 girls) with a mean age of 11.1 years at baseline	Self-reported victimisation (PEQ)	Self-reported depressive symptoms based on DSM-IV criteria (DISC)	Both current and past victims of bullying were more likely to develop depressive symptoms than children not victimised
Boivin et al. (1995)	To assess the relationship of peer rejection, victimisation and social withdrawal with depression and loneliness in childhood	Prospective	567 children (279 boys, 288 girls) aged 9-12 years at baseline	Sociometric measures of victimisation and peer status; peer assessments of social behaviours	Self-reported depressive symptoms (CDI); symptoms of loneliness (LSDQ)	Feelings of loneliness in socially withdrawn children were mediated by victimisation and poor peer status. Loneliness in turn predicted depression
Boivin et al. (1994)	To assess depression in peer rejected children	Cross-sectional	214 children (104 boys, 110 girls) with a mean age of 9	Sociometric measures of peer status, rejection,	Assessment of depressive symptoms with self-reports	Both aggressive-rejected and withdrawn rejected

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
			years	neglect and social behaviours	(CDI; DDPCA; LSDQ)	children showed symptoms of depression
Bond et al. (2007)	To determine associations between social relationships and mental health in adolescents	Prospective	2400 children (1124 boys, 1276 girls) aged 13-14 years at baseline	Self-reports of social connectedness and victimisation	Depressive symptoms assessed using the CIS	Poor social relationships at school predicted mood problems
Bond et al. (2001)	To assess the relationship of victimisation with depressive symptoms in young adolescents	Prospective	2680 adolescents (including both boys and girls) aged 13 years at baseline	Self-reports of victimisation and social relations (Interview schedule for social interaction)	Self-reported depressive symptoms assessed with the revised CIS	Recurrent victimisation predicted depressive symptoms, especially in girls
Braet et al. (2013)	To assess the relationships of peer problems and depressogenic cognitions on depressive outcomes	Prospective	228 adolescents (147 boys, 81 girls) aged 12-18 years	Self and parent-reports of peer rejection and victimisation	DSM-IV based diagnoses of depression (SCID); self (YSR) and parent-reported (CBCL) depressive symptoms	Early life peer problems led to the development of depressogenic cognitions in late adolescence and further on to depression
Brendgen et al. (2010)	To understand the relationship of different friendship types with depressed mood	Prospective	201 children (93 boys, 108 girls) aged 11 at baseline	Peer nominated friendship ratings	Depressive symptoms assessed with the CDI	Compared to friendless adolescents, those with non-depressed friends were less depressed, whereas those with depressed friends were more depressed

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
Buhs and Ladd (2001)	To understand mediators of the relationship between peer rejection and emotional adjustment	Short-term prospective	399 children (202 boys, 197 girls) with a mean age of 5.5 years	Sociometric measures of peer acceptance, rejection and victimisation; behaviour observations	Assessment of loneliness (LSDQ)	Negative peer treatment and reduced classroom participation mediated the relationship between rejection and loneliness
Bukowski et al. (2010)	To assess if friendship moderates the relationship between peer problems and depression	Prospective	231 children (101 boys, 130 girls) in first-grade of school	Sociometric measures of peer avoidance, exclusion and friendship	Peer nominations of depression	Peer avoidance and exclusion was associated with depression. Friendship moderated these relationships
Cardoos and Hinshaw (2011)	To determine the moderating effects of friendship on pathways from behavioural problems and victimisation in girls with ADHD	Short-term prospective with follow-up at 1, 3 and 5 weeks	228 girls aged 6-12 years including those with (n=140) and without (n=88) ADHD	Sociometric measures of friendship and victimisation; parent reported social competence (CBCL)	DSM-IV diagnoses of ADHD based on parent and teacher reports (SNAP; CBCL; TRF; DISC)	Poor social competence predicted victimisation in girls with ADHD. Friendships reduced the risk for victimisation
Carlson et al. (1997)	To differentiate between girls and boys with disruptive behaviour problems	Cross-sectional	508 participants (362 boys, 146 girls) with a mean age of 7.83 years including children with ADHD-C (n=57), ODD (n=94), ADHD-C plus comorbid ODD	Teacher reports of social functioning	DSM-IV diagnoses of ADHD based on teacher reports (TRF)	Girls with disruptive behaviour problems faced greater peer difficulties than boys

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
			(n=103) and healthy controls (n=254)			
Casement et al. (2014)	To determine neural mechanisms underlying depressive symptoms in girls facing social stress	Prospective	120 girls aged 11-12 years at baseline	Self-reports of victimisation (PEQ)	Parent and self-reported depressive symptoms (K-SADS-E)	Early social stressors impaired reward processing and led to depressive symptoms
Chen et al. (2012)	To determine the relationships between peer relationships, aggression and depression	Prospective	1162 children (580 boys, 582 girls) aged 9-12 years at baseline	Sociometric measures of peer acceptance, rejection, friendship and social behaviours; Teacher rated social behaviours (TCRS)	Assessment of depressive symptoms with the CDI	Aggressive behaviours predicted poor peer relations and depression
Chiang and Gau (2014)	To assess the effects of executive functioning on peer problems in children with persistent ADHD	Cross-sectional	635 participants (525 boys, 110 girls) aged 8-18 years, including 511 clinic referred children with ADHD and 124 children with no ADHD	Parent reports of peer interactions and peer problems (SAICA)	DSM-IV diagnoses of ADHD based on parent and self-reports (K-SADS-E)	A diagnosis of ADHD was associated with peer problems. Deficits in working memory and planning abilities increased the risk of peer problems in children with ADHD
Ciairano et al. (2007)	To assess the patterns of friendships, psychological adjustment and	Prospective	622 adolescents (299 boys, 323 girls) aged 14-20 years	Self-reports and sociometric assessments of friendships, peer relations and self-	Self-reports of depressive symptoms	Reciprocal friendships protect from development of aggressive behaviours

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
	antisocial behaviour in adolescents			reported social behaviours		
Cole (1990)	To assess the relationship between social competence and depression in childhood	Cross-sectional	750 children (383 boys, 367 girls) in the fourth grade of school	Sociometric and teacher reported peer acceptance and rejection	Depressive symptoms assessed using the CDI; teacher rated depressive symptoms based on the DSM-III-R	Socially competent children were less depressed than those non-competent
Cole (1991)	To assess if depression is influenced by competency in social, academic, sport, physical attractiveness and conduct domains	Cross-sectional	1422 children (712 boys, 710 girls) with a mean age of 9.3 years	Sociometric measures of social competence	Symptoms of depression assessed with the CDI	Poor social competence was associated with symptoms of depression
Cole et al. (1996)	To assess causal relationships between social/academic competence and depression	Prospective	945 children (480 boys, 465 girls) aged 8.37-11.36 years	Self-reported (HSPPC), parent-reported and peer nominated measures of social competence	Assessment of depressive symptoms using the CDI-self and parent-reported; sociometric and teacher-reported measures of depressive symptoms	Poor social competence predicted depression, but depression did not predict poor social competence
Cole et al. (1997)	To assess the relationship between self-perceived competency and depression in children	Prospective	617 children aged 8-13 years including both boys and girls	Self-perceived social acceptance (HSPPC); sociometric measures of social status and competence	Depressive symptoms assessed with the CDI	Self-perceived social competence was associated with changes in depressive symptoms for both boys and girls
Comiskey et al.	To determine	Cross-sectional	552 children (276	Self-reports of	Depressive symptoms	Social support and

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
(2012)	epidemiological and socioeconomic factors associated with childhood depression		boys, 276 girls) aged 4-12 years	social support and peer relations (Kidscreen-27)	assessed with the CDI-short version	peer relations were predictors of childhood depression
Connors et al. (2012)	To determine the association between inattention and peer problems	Prospective	1532 children (758 boys, 774 girls) aged 10-11 years	Self-reports of victimisation and quality of peer relationship	Self and parent-reported inattention using a 3-item questionnaire (rated on a 3-point scale)	Inattention predicted victimisation and a poor quality of peer relationships
Crick and Nelson (2002)	To assess gender differences in victimisation by friends and its relationship to psychological adjustment	Cross-sectional	496 children (244 boys, 252 girls) between fourth and sixth grade of school	Sociometric measures of peer acceptance, rejection and friendship; Self-reports of victimisation and social anxiety (Franke and Hymel social anxiety scale)	Assessments of internalising problems with teacher (CBCL) and self-reports (Weinberger adjustment inventory-short form); self-reported symptoms of loneliness (AWLS)	Relational victimisation was more common in girls whereas physical victimisation was more common in boys. Both forms of victimisation were associated with internalising problems
Crick et al. (2006)	To assess the relationship between social aggression and psychological adjustment	Prospective	224 children (111 boys, 113 girls) in third and fourth grades of school	Crick et al. (2006)	To assess the relationship between social aggression and psychological adjustment	Prospective
de Moura et al. (2011)	To determine the prevalence of victimisation in school-age children	Cross-sectional	1075 students aged 6-18 years, including boys (n=566)and girls (n=509)	Self-reported victimisation	Symptoms of hyperactivity assessed with self and parent reports (SDQ)	Children with hyperactivity were likely to be victimised
Deane and Young	To assess adolescent	Retrospective	4 girls with ADHD	Interpretations of	Teacher and parent	Girls with ADHD

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
(2014)	functioning in girls with ADHD and conduct disorders (CD)		and comorbid CD and 4 girls with neither ADHD nor CD, aged 13-16 years	audio-taped interviews on social-skills, peer support and victimisation	rated symptoms of hyperactivity (Rutter questionnaires)	and CD faced victimisation and had poor peer support. These children also faced developmental barriers, coping abilities to which were poor
Desjardins and Leadbeater (2011)	To determine moderators of the associations between relational victimisation and depression	Prospective	540 adolescents (246 boys, 294 girls) between 12-19 years at baseline	Self-reported victimisation (SEQ) and peer emotional support (perceived social support from friends scale)	Assessment of depressive symptoms with self-reports (BCFPI)	Relational victimisation was associated with depressive symptoms. Emotional support from peers moderated this relationship
Diamantopoulou et al. (2005)	To determine the associations between ADHD symptoms and peer relations	Cross-sectional	Population-based sample of 635 children (321 boys, 314 girls) aged 12 years, including both boys and girls	Sociometric measures of social preference and peer status, self-reported loneliness, teacher-reported prosocial behaviour (Social initiative scale)	Teacher-rated ADHD symptoms based on DSM-IV criteria (ARS-IV)	ADHD symptoms were associated with peer dislike. Peers were more likely to tolerate ADHD symptoms in boys than girls
Diamantopoulou et al. (2007)	To determine the associations of ADHD symptoms and executive functioning with social adjustment	Prospective	Population-based sample of 112 children (50 boys, 62 girls) aged 8 years	Sociometric measures of peer preference	Parent and teacher rated ADHD symptoms based on DSM-IV criteria (ARS-IV)	ADHD symptoms predicted poor social functioning

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
Efron et al. (2014)	To compare peer function of children with and without ADHD and further assess gender and ADHD subtype differences in associations	Cross-sectional	391 participants (259 boys, 132 girls) aged 6-8 years including 179 children with ADHD (93 combined type, 64 inattentive type, and 22 hyperactive-impulsive type) and 212 children without ADHD	Parent and teacher reports of peer problems and social functioning (SDQ)	DSM-IV diagnoses of ADHD based on parent reports (DISC-IV)	Children with ADHD had more peer problems than those without ADHD. Parent but not teacher reported peer problems were higher in boys with ADHD than girls. Social functioning did not differ by subtype
Elkins et al. (2011)	To assess adjustment in children with ADHD and further determine gender differences	Cross-sectional	Population-based sample of 998 children (479 boys, 519 girls) aged 12 years with (n=253) and without (n=745) ADHD	Self-reported victimisation and popularity, teacher-reports of peer relationships	DSM-IV diagnoses of ADHD based on teacher reports, parent and/or child interviews (DISC–revised	Girls with ADHD-I had the poorest peer functioning
Erhardt and Hinshaw (1994)	To assess the influence of behaviours on peer outcomes in boys with and without ADHD	Short-term prospective with follow-up at 3 days	49 participants aged 6-12 years including clinic-referred boys with ADHD (n=25) and population drawn comparison boys (n=24)	Sociometric measures of friendship ratings and (social) behaviour observations	DSM-III-R diagnoses of ADHD based on parent reports (CASQ)	Boys with ADHD faced greater peer rejection than those without ADHD. Aggressive behaviour predicted negative peer nominations
Fauber et al. (1987)	To determine associations between social functioning and depressive	Cross-sectional	89 adolescents (39 boys, 50 girls) aged 11-15 years	Self (HSPPC) and teacher (Teacher's rating scale) reports of social	Assessment of depressive symptoms using CDI	Low teacher and self-reported social competence was associated with

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
	symptoms in adolescents			competence; Behaviour observations		depressive symptoms
Fekkes et al. (2004)	To determine the associations between involvement in bulying and depression	Cross-sectional	2766 children (1370 boys, 1384 girls, and 12 gender not known) aged 9-12 years	Self-reports of bullying and victimisation	Self-reported symptoms of depression (Short form depression questionnaire for children)	Victims and bully victims had higher chances of depression than children not involved in bullying
Fekkes et al. (2006)	To assess if victimisation precedes mental health problems or vice-versa	Prospective	1118 children aged 9-11 years including both genders	Self-reported bullying and victimisation (Olweus bully/victim questionnaire)	Self-reported symptoms of depression and anxiety (KIVPA and short depression inventory for children)	Victimisation increased risk for anxiety and depression. Symptoms of depression and anxiety in turn increased risk for being newly victimised
Fine et al. (2008)	To assess differences in social perception among typically developing children, children with ADHD, and children with autistic spectrum disorders (ASD)	Cross-sectional	Clinic referred children (N=86) with ADHD (n=30), ASD (n=37) and typically developing controls (n=19) aged 6 – 15 years, including both boys (n=59) and girls (n=27)	Assessments of child's perceptions of social situations using the CASP	DSM-IV diagnoses of ADHD (diagnoses were confirmed using the Behaviour Rating Scale for Children)	Symptoms of inattention were associated with poor interpretations of social interactions
Fite et al. (2014)	To assess the moderating effects of peer relationships	Prospective	289 adolescent boys with a mean age of 16 years	Self-reported peer rejections (YSR) and social	Self-reports of depressive symptoms (YSR, ASR)	Socially aggressive behaviours predicted

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
	in pathways from social aggression to depression amongst boys			behaviours (RPAQ)		depressive symptoms. These relationships were mediated by peer rejection
Fleming and Jacobsen (2009)	To determine the associations between bullying and depression in middle school students	Cross-sectional	8131 adolescents (3962 boys, 4084 girls) aged 13-15 years	Self-reports of bullying and victimisation	Self-reported measures of depressive symptoms	Boys were more likely to report victimisation, while girls were more likely to report depression following victimisation
Fontaine et al. (2009)	To assess the role of loneliness as a mediator of the relationship between social preference and depression	Prospective	585 kindergarten aged children (304 boys, 281 girls)	Sociometric measures of peer acceptance and rejection	Parent (CBCL), teacher (TRF), and self-reported (YSR) anxious/depressed symptoms; self-reports of loneliness (LSDQ)	Loneliness partly mediated the relationship between low social preference and anxious/depressed symptoms in adolescence
Frankel and Feinberg (2002)	To assess social problems in children with ADHD and oppositional defiant disorder (ODD) who were referred for friendship problems	Cross-sectional	95 children (77 boys, 18 girls) referred to the clinics for friendship problems aged 6-12 years including participants with ADHD (n=20), ODD (n=14), ADHD plus ODD (n=30), and neither	Parent reported measures of social skills	DSM-III-R diagnoses of ADHD	A diagnosis of ADHD was associated with high disruptive behaviour and low resistance to provocation

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
			ADHD nor ODD (n=31)			
Gibb et al. (2012)	To determine the relationship between victimisation and depressogenic inferential styles	Prospective	100 children (41 boys, 59 girls) aged 8-12 years at baseline	Self-reported peer victimisation (SEQ)	Self-reported depressive symptoms assessed with the CDI	Peer victimisation increased cognitive vulnerability to depression
Goodyer and Altham (1991)	To determine the relative contributions of friendship difficulties, family adversities and lifetime exit events to anxiety and depression	Cross-sectional	100 clinic referred children (including both boys and girls) and 100 age and gender matched controls	Self-reports of friendship; parent and teacher reported social competence	DSM-III based diagnoses of depression and anxiety	All three factors (friendship difficulties, family adversities and lifetime exit events) were associated with anxiety and depression
Goodyer et al. (1991)	To understand the influence of social relationships on developmental courses of depression	Prospective	49 participants (23 boys, 26 girls) including children with anxiety (n=21) and depression (n=28) with a mean age of 13.1 years at baseline	Parent reports of social competence and friendships	DSM-III based diagnoses of depression	Lack of friendships predicted poor recovery from depression
Goodyer at al. (1997)	To assess if any pattern of social characteristics predict depression	Short-term prospective with follow up at 36 weeks	68 clinic referred children (including both boys and girls) between 8-16 years of age	Self and parent reported friendships	DSM-III-R based diagnoses of depression with self and parent reports (K-SADS-E)	A lack of friendships predicted depression in children
Goodyer et al. (1989)	To assess peer relationships of children with	Cross-sectional	200 participants (98 boys, 102 girls) including clinic-	Self and parent reported friendship quality	Self-reported symptoms of depression	Pre-pubertal children with poor friendships showed

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
	depression		referred children with emotional disorders (n=100) aged 8-16 years as well as age and gender matched controls (n=100)			depressed-anxious symptoms while post-pubertal children with poor friendships showed only depressive symptoms
Goodyer et al. (1990a)	To assess the relationship of social achievements and friendship difficulties with depression	Cross-sectional	200 participants (98 boys, 102 girls) including clinic-referred children aged 7-16 years as well as age and gender matched controls (n=100)	Self-reports of friendship difficulties	Assessment of depression with self and parent reports (Rutter's A2 questionnaire)	Interactions between a lack of social achievement and friendship difficulties were associated with depression
Goodyer et al. (1990b)	To compare the effects of undesirable events and friendship quality on symptoms of depression	Cross-sectional	200 participants (98 boys, 102 girls) including clinic-referred children aged 7-16 years as well as age and gender matched controls (n=100)	Self and parent reported friendship quality	Assessment of depression with self and parent reports (Rutter's A2 questionnaire)	Undesirable events and friendship quality exerted independent effects on the risk for depression
Greene et al. (2001)	To assess social functioning in clinic referred girls with ADHD	Cross-sectional	Girls with (n=127) and without (n=114) ADHD. For some analyses a comparative sample of boys with (n=140) and without (n=120) ADHD was also included (N=501).	Parent reported measures of peer difficulties and social competence	DSM-III-R diagnoses based on parent interviews (K-SADS-E)	Girls with ADHD had a poorer social functioning than girls without ADHD. No differences in social impairments were found between girls and

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
						boys with ADHD
Gregory et al. (2007)	To determine associations among interpersonal cognitions, anxiety and depression	Cross-sectional	300 pairs of 8 year old twins (261 boys, 337 girls, and two children with unknown gender)	Self- and peer-reported perceptions of social support; Self-reported social behaviour (CESBQ)	Assessment of depressive symptoms with CDI and anxiety symptoms with the screen for childhood anxiety-related emotional disorders	Interpersonal cognitions were more strongly correlated with depression than with anxiety
Gresham et al. (1998)	To assess peer problems in children with inattention and/or hyperactivity symptoms and comorbid conduct problems	Prospective	231 students (133 boys, 98 girls) in the third grade including children with symptoms of hyperactivity and/or inattention plus comorbid conduct problems (n=25), internalising or externalising problems (n=105), and controls (n=101)	Peer nominated measures of friendship, social preference and social impact; teacher rated social skills and behaviours; self-reported loneliness; self-perceived social standing	Participant groups (with hyperactivity or inattention) were defined based on the problem behaviour subscale of the SSRS-teacher reports	Children with symptoms of inattention and/or hyperactivity along with comorbid conduct problems faced worse peer problems than children with other internalising or externalising symptoms
Hankin et al. (2007)	To determine sex differences in adolescent depression	Prospective	538 children (245 boys, 293 girls) aged 13-18 years	Self-reported social functioning and stressful peer interactions	Assessment of depressive symptoms with self (CDI) and parent reports (CES-D)	Girls showed higher depressive symptoms than boys. Gender differences in depression were due to higher stressful peer interactions in girls than in boys
Hanley and Gibb	To assess the impact	Prospective	448 children (188	Self-reported	Self-reported	Verbal

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
(2011)	of verbal victimisation on feelings of hopelessness		boys, 260 girls) with a mean age of 9.77 years at baseline	victimisation (Emotional abuse subscale of the childhood trauma questionnaire)	symptoms of depression (CDI) and feelings of hopelessness (Children's hopelessness scale)	victimisation predicted feelings of hopelessness independent of concurrent depression
Hill et al. (2014)	To determine factors that predict escalation of subthreshold depressive symptoms to major depressive disorders (MDD)	Prospective	424 adolescents (178 boys, 246 girls) aged 14-18 years at baseline	Self-reported peer support	Self-reported symptoms of depression (BDI) and DSM-III-R or DSM-IV diagnoses of depression with self-reports (K-SADS; SCID)	Poor friend support predicted the development of MDD. Amongst children with fewer friends, those with added anxiety were more likely to progress to MDD
Hinshaw and Melnick (1995)	To assess the mechanisms underlying peer problems in clinic-referred boys with ADHD	Short-term prospective with follow-up between 1 to 6 weeks	181 boys aged 6-12 years including clinic-referred participants with ADHD (n=101) and a population-drawn comparison sample without (n=80) ADHD	Sociometric assessments of peer acceptance and rejection; parent and teacher reports of peer status; observations of children's (social) behaviour	DSM-III-R diagnoses of ADHD based on parent reports (CBCL; CASQ) and interviews	Boys with ADHD were more likely to accept other children with ADHD as their peers. Amongst those with ADHD, aggressive behaviours predicted worse social outcomes
Hinshaw (2002)	To assess and compare peer problems in girls with ADHD-C, ADHD-C, and no ADHD	Short-term prospective with follow-up at 1, 3 and 5 weeks	228 girls aged 6-12 years with ADHD-C (n=93), ADHD-I (n=47) and no ADHD (n=88)	Sociometric measures of peer acceptance and rejection; investigator ratings of social	DSM-IV diagnoses of ADHD based on parent and teacher reports (SNAP; CBCL; TRF; DISC)	Girls with ADHD-I faced more social isolation but less rejection than those with ADHD-C

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
				behaviours; behaviour observations		
Hinshaw et al. (2006)	To assess long term impairments in adolescent girls with a childhood diagnosis of ADHD	Prospective	228 girls with (n=140) or without (n=88) ADHD aged 6-12 years at baseline	Parent and teacher reported social skills (SSRS; SRQ; DSPS) and self-reports of social relationships and social standing	DSM-IV diagnoses of ADHD based on parent and teacher reports (DISC; SNAP-IV; CBCL, TRF)	Girls with a childhood diagnosis of ADHD showed worse social functioning in adolescence than those without a childhood diagnosis of ADHD
Hodges et al. (1999)	To determine the relationships between victimisation, friendship and internalising or externalising behaviours	Prospective	393 children (188 boys, 205 girls) with a mean age of 11 years at baseline	Sociometric measures of victimisation and friendship	Teacher reported internalising and externalising problems (Rutter's children's behavioural questionnaire)	Victimisation predicted increases in internalising behaviours but only for children without a mutual best friendship
Hodgens et al. (2000)	To assess peer functioning differences among boys with ADHD-I, ADHD-C, and nonclinical controls	Cross-sectional	85 boys aged 8-11.5 years including clinic referred participants with ADHD-I (n=15), ADHD-C (n=15) and population drawn controls (n=55)	Sociometric measures of peer interactions; behaviour observations of play groups	DSM-III-R based assessments of ADHD symptoms using teacher reports (CBCL)	Boys with ADHD-I showed social withdrawal whereas boys with ADHD-C showed aggressive behaviours
Hoglund and	To assess the	Prospective	461 children (226	Sociometric	Self-reports of	Socially aggression

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
Chisholm (2014)	pathways from peer relationship problems and socially aggressive behaviours to internalising problems		boys, 235 girls) with a mean age of 6.87 years	measures of peer rejection, socially aggressive behaviours; self-reported victimisation	depressive and anxious symptoms (Behaviour assessment system)	led to anxious and depressed symptoms through the development of peer exclusion. Depression and
Hoza et al. (1993)	To compare self-perceptions of social functioning between boys with and without ADHD	Cross-sectional	Clinic referred boys with (n=27) ADHD and non-referred boys without ADHD (n=25) aged 8.5-13 years (N=52).	Self-reports of perceived social competence (HSPPC; Peer social attribution questionnaire)	DSM-III-R diagnoses of ADHD based on parent and teacher interviews (CRS; DBDRS)	Boys with ADHD had positive perceptions of their social functioning
Hoza et al. (2005a)	To assess and compare peer functioning in children receiving treatments for ADHD	Prospective	285 children with ADHD (226 boys, 59 girls) aged 7-10 years at baseline and 2232 classmates without ADHD (1771 boys, 461 girls)	Sociometric measures of peer preference, dislike, and friendship	DSM-IV based diagnoses of ADHD-combined type	No differences in social functioning were found among groups of children receiving medications, behavioral therapy, a combination of the two treatments, and community care
Hoza et al. (2005b)	To compare peers preferences and relationships of children with and without ADHD	Cross-sectional	165 children with ADHD (130 boys, 35 girls) aged 7-10 years and 1298 classmates (1026 boys, 272 girls) without ADHD. Total N=1463	Sociometric measures of peer preference, dislike and friendship	DSM-IV based diagnoses of ADHD-combined type	Those with ADHD disliked other children with ADHD while preferring popular classmates

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
Hoza et al. (2010)	To assess self-perceptions of social standing in children with ADHD	Prospective	513 children with ADHD aged 8-13 years and 284 comparison peers (including both genders)	Self and teacher-reports of peer acceptance (HSPPC)	DSM-IV based diagnoses of ADHD-combined type	Children without ADHD showed a greater decrease in social perception biases with age than children with ADHD.
Hubbard and Newcomb (1991)	To assess behaviours of medicated children with ADHD during initial interactions with a peer without ADHD	Cross-sectional	32 clinic referred boys with (n=8) and without (n=24) ADHD aged	Behaviour observations of children with ADHD and without ADHD in free play settings. Interactions of ADHD-normal and normal-normal pairs were assessed	DSM-III-R based assessments of ADHD using teacher and parent versions of the Conner's behaviours checklist	Interactions of ADHD-normal pairs were more solitary and less communicative than normal/normal pairs
Ismail et al. (2014)	To determine correlates of bullying behaviours	Cross-sectional	410 children (200 boys, 210 girls) aged 12 years	Self-reports of bullying behaviours	Symptoms of ADHD assessed with parent and teacher reports based on DSM-IV criteria (CRS)	Children with hyperactive and inattentive symptoms but not combined symptoms showed bullying behaviours
Juvonen et al. (2003)	To determine the psychological problems of bullies, victims and bully-victims	Cross-sectional	1985 children (893 boys, 1092 girls) with a mean age of 11.5 years	Sociometric measures of bullying and victimisation; teacher reports of peer popularity	Self-reported depression (CDI-short form), anxiety (SASA) and loneliness; Teacher reported internalising and externalising	Victimised children were more likely to be depressed, anxious and lonely than bullies. Of all three groups, bully-

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
					problems	victims showed worst adjustment
Kaltiala-Heino et al. (2010)	To understand if bullying predicts depression or vice-versa in adolescents	Prospective	2070 children (903 boys, 1167 girls) aged 15 years	Self-reports of bullying, victimisation and peer neglect	Assessment of depression with self-reports (BDI-short form)	Peer victimisation predicted depression in adolescents.
Kamper and Ostrov (2013)	To determine associations between social behaviours, friendships and depression	Prospective	776 children (391 boys, 385 girls) with a mean age of 10.42 years	Teacher reported behaviours of relational and physical bullying; self-reported friendship quality	Self-reports of depressive symptoms (CDI)	Negative friendship quality mediated the associations between peer aggression and depression
Kistner et al. (2006)	To assess the relationships between perceived peer acceptance and depressive symptoms	Prospective	667 children (304 boys, 363 girls) with a mean age of 9.42 years	Sociometric and self-reported measures of peer acceptance and social status; self-reports of perceived social competence (HSPPC)	Self-reported depressive symptoms (CDI)	Inaccurate perceptions of peer acceptance predicted depressive symptoms
Kochel et al. (2012)	To understand the associations between peer difficulties and depressive problems	Prospective	486 children (244 boys, 242 girls) with a mean age of 9.93 years	Sociometric measures of peer acceptance, rejection and victimisation; self and teacher reports of victimisation	Assessment of depressive symptoms with parent (CBCL) and teacher reports (TRF)	No evidence was found to suggest that peer difficulties increase risk for depression. Victimisation mediated the associations between depression and subsequent peer rejection

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
Kochenderfer-Ladd and Skinner (2002)	To assess the moderating effects of coping strategy on depressive outcomes in victimised children	Cross-sectional	356 children (179 boys, 177 girls) aged 9-10 years	Sociometric measures of peer acceptance and rejection; teacher-reported social problems (TRF)	Assessment of anxious-depressed symptoms with teacher reports (TRF); self-reported loneliness (LSDQ)	Victimisation was associated with anxious-depressed problems. Seeking social support protected victimised girls, but not boys, from peer problems
Kolko and Pardini (2010)	To assess the effects of pre-treatment ADHD symptoms on outcomes in children with CD and ODD	Prospective	177 children aged 6-12 years including both genders	Parent and teacher reported social problems (CBCL; TRF)	DSM-IV based assessments of ADHD symptoms and diagnoses using parent and child interviews (K-SADS)	Pre-treatment ADHD predicted ODD symptoms and social problems in children
Kornienko and Santos (2014)	To determine moderators of the relationship between friendship networks and depression	Prospective	367 children (189 boys, 178 girls) with a mean age of 11.9 years	Sociometric measures of friendship and popularity	Self-reported depressive symptoms (CDI)	In pathways from peer popularity to depression, fear of negative evaluation was a moderator for boys and a mediator for girls
Kumpulainen et al. (1999)	To assess the relationship between bullying and psychological problems	Prospective	1268 children (646 boys, 622 girls) with a mean age of 8.5 years at baseline	Parent and teacher reports of bullying and victimisation	Self-reported depressive symptoms (CDI)	Involvement in bullying declined with age. Victims had higher depressive problems than bullies or bully-victims
Lacourse et al. (2006)	To determine the childhood	Prospective	1037 kindergarten aged boys from low	Self-reports of peer group	Teacher rated hyperactivity	Hyperactivity in kindergarten boys

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
	behaviours that predict deviant peer group affiliations		socioeconomic neighbourhoods	characteristics and teacher-rated social behaviours (SBQ; prosocial behaviour questionnaire)	symptoms using the SBQ	predicted deviant peer group affiliations
Ladd (2006)	To assess relationships among peer difficulties, behaviour problems and psychological maladjustment	Prospective	399 children (206 boys, 193 girls) with a mean age of 5.62 years at baseline	Teacher (TRF, CBS) and self-reported measures of social behaviours; peer nominations and teacher reports of peer acceptance and rejection	Assessment of anxious-depressed symptoms with teacher reports (TRF, CBS)	Both social behaviour problems and peer difficulties increase risk for psychological maladjustment
Lee et al. (2008)	To assess long term adjustments in children with ADHD	Prospective	222 children with (n=96) and without (n=126) ADHD aged 4-6 years at baseline, including both boys (n=176) and girls (n=46)	Teacher-reported peer acceptance, peer rejection, neglect and social skills (DSPS; SSRS)	DSM-III-R diagnoses of ADHD based on parent reports (DISC)	Children with ADHD had a poor social adjustment at adolescence irrespective of improvements in ADHD symptomatology
Lee et al. (2010)	To assess the relationship of social interactions, social competence and cognitive styles with depression in adolescence	Prospective	350 adolescents (159 boys, 191 girls) with a mean age of 14.5 years	Self-reports of perceived social competence (HSPPC); self-reported peer relationships (Network of relationships inventory)	Assessment of depressive symptoms with self-reports (CDI)	The relationship between perceived social competence and depression was mediated by parent, but not peer, interaction problems
Lin et al. (2008)	To determine factors	Cross-sectional	9586 adolescents	Self-reports of peer	Assessment of	Poor peer

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
	associated with depression in adolescents		(4673 boys, 4913 girls) with a mean age of 14.7 years	relationships (Adolescent family and social life questionnaire)	depressive symptoms with self-reports (CES-D)	relationships were associated with depression
Lin et al. (2012)	To assess social adjustments in adolescents with ADHD and comorbid tic disorders	Cross-sectional	80 clinic referred children between the ages of 8 and 16 years with ADHD (n=40) and with ADHD plus comorbid tic disorders (n=40), and 40 typically developing age matched controls. Sample included both boys (n=114) and girls (n=6)	Self or parent reports of social functioning (SAICA)	DSM-IV diagnoses of ADHD	The presence of additional tic disorders in children with ADHD did not exacerbate social functioning difficulties
MacPhee and Andrews (2006)	To identify risk factors of early adolescent depression	Cross-sectional	2014 children aged 12-13 years and including both boys and girls	Self-reports of peer acceptance and rejection (Self-description questionnaire)	Assessment of depressive symptoms with self-reports (CES-D)	Poor peer relationships were associated with depressive symptoms
Maedgen and Carlson (2000)	To compare social functioning associated with the ADHD subtypes	Cross-sectional	A total of 47 children (33 boys, 14 girls) aged 8-11 years including those with ADHD-C (n=16), ADHD-I (n=14) and no ADHD (n=17)	Parent, teacher and self-rated rated social status, functioning, social knowledge (Children's assertiveness behaviour scale; DSPS) and	DSM-IV diagnoses of ADHD based on parent interviews	Children with ADHD-C showed aggressive behaviours whereas those with ADHD-I showed social passivity

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
				behaviour observations		
Marshal et al. (2003)	To assess the effects of deviant peer group affiliations on the risk for substance abuse in adolescents with childhood-diagnosed ADHD	Prospective	242 children with (n=142)and without (n=100) ADHD aged 13-18 years, including both genders	Self-reports of peer group characteristics	DSM-III-R or DSM-IV diagnoses of ADHD based on teacher and parent reports (DBDRS; IOWA Conners; SNAP)	Children with ADHD were more likely to affiliate with deviant peers than those without ADHD.
Martin et al. (2003)	To determine moderators of the relationship between peer popularity and depression	Prospective	63 children (39 boys, 24 girls) between the third and sixth grade of school, including subgroups of unpopular (n=25) and popular (n=38) participants	Sociometric measures of friendship and social competence	Assessment of depressive symptoms with self-reports (CDI)	Placing higher valuations on friendships predicted depressive symptoms in unpopular but not popular children
McLaughlin et al. (2009)	To assess if emotion dysregulation mediates the relationship of victimisation with depression	Prospective	1065 (545 boys, 520 girls) children aged 11-14 years	Self-reported victimisation	Self-reported measures of depressive (CDI) and anxiety symptoms (Multidimensional anxiety scale for children)	Emotional dysregulation mediated the relationship between victimisation (reputational and relational) and anxious-depressed symptoms
Meland et al. (2010)	To understand emotional characteristics and social integration of bullies and victims	Cross-sectional	1237 children (597 boys, 627 girls) aged 11-15 years	Self-reports of bullying and victimisation	Assessment of depressive and anxious symptoms with self-reports based on the WHO-	Victims reported greater depressive and anxiety problems than bullies and children

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
					Health behaviour in school aged children	not involved in bullying
Mercer and DeRosier (2008)	To assess the influences of teacher preference, peer rejection and aggressive behaviours on emotional adjustment in childhood	Prospective	1193 children (586 boys, 607 girls) in the third grade of school	Sociometric measures of peer acceptance, dislike and social aggression	Self-reports of loneliness (LSDQ), depressive (SMFQ), and anxiety symptoms (Social anxiety scale for children-revised)	Peer rejection predicted difficult relationships with teachers. Problematic student-teacher relationships were associated with loneliness and depression
Moksnes et al. (2013)	To determine the association of social stress with depression assess gender differences	Cross-sectional	1209 adolescents (586 boys, 617 girls, 6 gender unknown) aged 13-18 years	Self-reports of social relationships and peer status (adolescent stress questionnaire)	Self-reported symptoms of depression	Peer pressure related to school performance in boys and inter-personal relationship problems in girls led to depression
Moore et al. (2014)	To determine the concurrent and prospective associations of aggressive peer behaviours with mental health	Prospective	1590 adolescents aged 14 years at baseline and including both genders	Self-reports of bullying and victimisation	Self-reported depression (BDI) and anxious-depressed symptoms (YSR)	Boys were more likely to be perpetrators of peer aggression while girls were more likely to be victimised. Victimisation predicted anxious and depressive symptoms
Morgan et al.	To determine the	Prospective	160 boys aged 9-12	Observations of	Self-reported	Early social

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
(2013)	associations between peer interactions and depressive symptoms in boys		years	social behaviours; sociometric measures of pee acceptance and dislike; teacher-reported social behaviour (TRF)	depressive symptoms (CDI, K-SADS)	withdrawal in boys predicted depressive symptoms at pre-adolescence
Mikami and Hinshaw (2006)	To assess risk and protective factors of adjustments in girls with ADHD	Prospective	228 girls with (n=140) and without (n=88) ADHD, aged 6-13 years at baseline	Sociometric measures of peer rejection and liking; Teacher reports of social functioning (DSPS); parent reported popularity	DSM-IV diagnoses of ADHD based on teacher and parent reports (CBCL; TRF; SNAP-IV; DISC-IV)	Peer rejection in girls with ADHD predicted poor long term adjustments
Mrug et al. (2004)	To assess the relationship of social behaviours with internalising and externalising problems	Prospective	236 children (105 boys, 131 girls) between third and fifth grade of school	Sociometric and self-reported measures of friendship; peer nominations of social behaviour (Revised class play)	Self-reports of depressive symptoms (CDI) and loneliness (AWLS)	Self-reported friendships with aggressive peers was associated with depressive symptoms
Mrug et al. (2007)	To determine social behaviours of children with ADHD and their effects on peer status	Short term prospective with follow-up at 2, 5 and 8 weeks	268 children with ADHD aged 5-13 years (233 boys, 35 girls)	Sociometric measures of peer rejection and acceptance; observations of social behaviours	DSM-IV- diagnoses of ADHD based on parent and teacher reports and parent interviews (Disruptive behaviour disorder structured parent interview)	Increasing helpful behaviours and following activity rules improves peer status of children with ADHD
Murray-Close et al. (2010)	To understand the developmental processes leading to	Prospective	536 children with ADHD and 284 age matched population	Teacher and self-reported social competence; parent	DSM-IV based diagnoses of ADHD-combined type	Peer problems in children without ADHD may result

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
	peer problems in children with ADHD		controls (231 boys, 53 girls) aged 7-10 years at baseline. Total N=820	reports of social behaviour; teacher-reported social skills (SSRS) and peer status (DSAS)		from difficulties in negotiating developmental stages
Nolan et al. (2003)	To assess the relationship between peer rejection and depression in adolescents	Prospective	240 children (110 boys, 130 girls) with a mean age of 11.46 years at baseline	Assessments of peer rejection with self- (YSR, school hassles questionnaire), parent- (CBCL), and teacher-reports (TRF)	Assessment of depressive symptoms with self-reports (revised children's depression rating scale; CDI) and parent reports (CDI)	Rejection predicted depression in adolescents. No evidence was found to suggest that depression predicted rejection.
Normand et al. (2011)	To compare friendship relations of children with and without ADHD	Cross-sectional	133 clinic-referred participants (101 boys, 32 girls) aged 7-13 years including 87 children with ADHD and 46 children with no ADHD and 133 invited friends of the clinic-referred participants	Observations of social behaviours; peer and self-rated dyadic friendships; self-rated friendship satisfaction (FQM)	Parent and teacher reported symptoms of ADHD based on DSM-IV criteria (CARS)	Children with ADHD were likely to be friends with those who had oppositional symptoms or ADHD. Children with ADHD were more likely to be dissatisfied with their peer relationships more dominant in their interactions than other children
Normand et al. (2013)	To assess friendships of children with ADHD prospectively	Prospective	266 participants (101 boys, 165 girls) aged 7-13 years, including 133 clinic-referred	Sociometric assessments of friendships; Self-rated friendship	Parent and teacher reported symptoms of ADHD based on DSM-IV criteria	Symptoms of ADHD predicted poor friendship quality and

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
			children with and 133 children with no ADHD	quality and satisfaction (FQM)	(CARS)	dissatisfaction with friends
Oldehinkel et al. (2007)	To determine associations between social status and depressive problems	Cross-sectional	1046 adolescents (498 boys, 548 girls) with a mean age of 13.52 years	Sociometric measures of peer status (peer affection and achievement)	Assessment of depressive symptoms with self- (YSR) and parent-reports (CBCL) based on the DSM-IV criteria	Low achievement related peer status in boys and affection related peer status in girls was associated with depressive symptoms
Owens et al. (2009)	To assess social adjustments in adolescent girls with a childhood diagnosis of ADHD	Prospective	228 girls with (n=140) and without (n=88) ADHD aged 6-12 years at baseline	Teacher reports of social functioning (SSRS) and peer status (DSAS)	DSM-IV-TR diagnoses of ADHD based on parent interviews (DISC-IV)	Social functioning is poorer in adolescent girls with childhood diagnoses of ADHD than those without ADHD
Panak and Garber (1992)	To determine the associations between aggression, peer rejection and depression in children	Prospective	521 children between the third and fifth grade of school, and including both boys and girls	Sociometric and self-reported measures of peer acceptance and rejection (based on HSPPC); teacher reports of social behaviours (TRF)	Self-reports of depressive symptoms (CDI)	Peer rejection mediated the relationship between aggressive behaviours and depression
Pardini and Fite (2010)	To determine associations between symptoms of ADHD and psychosocial adjustment	Prospective	Population based sample of 1517 boys with a mean age of 10.7 years (SD=2.7)	Parent (CBCL) and teacher (TRF) reported social problems	Symptoms of ADHD assessed with parent interviews (DISC) based on DSM-III and DSM-III-R criteria	Symptoms of ADHD in boys predicted oppositional defiant behaviours, conduct problems

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
						and social difficulties
Paquette and Underwood (1999)	To explore gender differences in social behaviours	Cross-sectional	76 children (39 boys, 37 girls) with a mean age of 13.8 years	Self-reports of social competence (HSPPC) and social behaviours (SEQ)	Self-reported feelings of sadness	Girls with peer problems were more likely than boys to report low global self-worth
Patterson and Stoolmiller (1991)	To assess factors associated with depression in preadolescent boys	Cross-sectional	317 boys in either the fourth grade of school or aged 9-12 years	Teacher reports of peer relationships	Assessment of depressive symptoms with parent, teacher, observer and self-reports	Poor peer relations were associated with depressed mood in preadolescent boys
Pedersen et al. (2007)	To assess relationships between behaviours, peer rejection, friendships, loneliness and depression	Prospective	551 children (301 boys, 250 girls) aged 6-13 years	Sociometric measures of peer rejection and friendships; Parent reports of social withdrawal	Self-reports of depressive symptoms (CDI) and loneliness (LSDQ)	Behaviour problems in childhood led to peer rejection, a lack of friendships and ultimately depressive symptoms by adolescence
Pelkonen et al. (2003)	To assess factors in mid-adolescence that predict depression	Prospective	1648 adolescents (761 boys, 887 girls) aged 16 years at baseline	Self-reports of peer relationships and friendships	Assessment of depressive symptoms with self-reports (BDI-short version)	A lack of close friends predicted depression in late adolescence
Prinstein and Aikins (2004)	To assess the effects of peer rejection on depressive outcomes	Prospective	158 adolescents (61 boys, 97 girls) aged 15-17 years	Sociometric measures of peer acceptance and rejection; self-reported importance of peer status	Assessment of depressive symptoms with self-reports (CDI)	Peer rejected adolescents showed depressive symptoms; especially those who ascribed importance to peer

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
						status or had depressogenic attributional styles
Qualter et al. (2010)	To assess the effects of loneliness and social satisfaction with depression	Prospective	296 children (146 boys, 150 girls) aged 5 years at baseline	Sociometric measures of peer acceptance and rejection	Self-reports of depressive symptoms (DDPCA)	Peer -related loneliness but not peer acceptance predicted depression
Qualter et al. (2013)	To determine the trajectories of loneliness and their predictors and outcomes	Prospective	586 children aged 7-17 years and including both boys and girls	Sociometric measures of peer acceptance and rejection; observations of social behaviours	Self-reported symptoms of depression (CES-D), loneliness (Loneliness and aloneness scale for children and adolescents), and depressogenic cognitive styles	Low peer acceptance and negative cognitive styles were associated with high stable trajectories of loneliness. Both increasing and high stable trajectories of loneliness predicted depression
Reijntjes et al. (2006)	To determine coping and emotional functioning in peer rejected children	Cross-sectional	234 children (123 boys, 111 girls) aged 10-13 years	Assessment of responses to hypothetical peer rejection scenarios	Self-reported depressive symptoms (CDI); Self-reported sadness	Girls reported higher sadness in response to peer rejection than boys
Riley et al. (2008)	To assess functioning differences between children with ADHD-C and ADHD-H/I subtypes	Cross-sectional	102 clinic-referred participants (75 boys, 27 girls) aged 3-5 years, including children with ADHD-C (n=71) and ADHD-H/I	Parent and teacher reported social skills (SSRS); behaviour observations	DSM-IV diagnoses of ADHD by parent and teacher reports (CARS)	Social skills did not differ between the two ADHD subtypes

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
			(n=31)			
Rinsky and Hinshaw (2011)	To determine associations between executive and social functioning in girls with ADHD	Prospective	228 girls with (n=140) and without (n=88) ADHD aged 6-12 years at baseline	Teacher (Dishion social preference scale, TRF) and parent reports of social functioning (SSRS, CBCL, SRQ)	DSM-IV diagnoses of ADHD based on parent and teacher reports (SNAP – parent & teacher; CBCL; TRF; DISC)	Development of comorbidities mediated the relationship between executive functioning and social functioning problems in girls with ADHD
Rosen et al. (2014)	To determine the mediating effects of externalising behaviours on the relationships between social self-control and peer dislike in children with ADHD-combined type	Cross-sectional	1470 participants (1162 boys, 308 girls) aged 7-10 years including 172 children with ADHD-combined type and 1298 same-sex classmates without ADHD	Sociometric measures of peer acceptance and dislike; teacher reported social skills (SSRS)	DSM-IV based diagnoses of ADHD-combined type	Oppositional and defiant behaviours mediated pathways from poor social skills to peer problems in children with ADHD-combined type
Ross et al. (2010)	To determine the impact of social skills and school connectedness on depressive symptoms at preadolescence	Cross-sectional	127 children (43 boys, 84 girls) aged 10-13 years	Self-reported social skills	Self-reported depressive symptoms (CDI)	Both social skills and school connectedness explained the variance in depressive symptoms
Rothon et al. (2011)	To assess the effects of bullying on mental health	Prospective	2790 (1356 boys, 1434 girls) children aged 11-14 years at baseline	Self-reports of victimisation and social support (Multidimensional scale of perceived	Self-reported depressive symptoms (SMFQ)	Family support but not peer support protected victims from depressive symptoms

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
				social support)		
Rubin et al. (1989)	To assess long-term outcomes of social interactions and withdrawal	Prospective	111 children (55 boys, 56 girls) in kindergarten at baseline	Observations of social behaviours and peer interactions; Self-reported social competence (HSPPC); Teacher-reported social skills (TCRS)	Self-reported depressive symptoms (CDI) and loneliness (LSDQ)	Social withdrawal predicted symptoms of depression and loneliness
Rudolph et al. (2011)	To determine of peer victimisation predicts mental health problems	Prospective	433 children (195 boys, 238 girls) in second grade at baseline	Self- and teacher-reported victimisation (SEQ); teacher-reported social behaviours (CSBS)	Self-reports of depressive symptoms (SMFQ)	Victimisation predicted aggressive behaviours and symptoms of depression, especially in girls
Rueger et al. (2010)	To assess relationships between perceived parental, peer, and teacher support and psychological adjustment	Prospective	636 children (311 boys, 325 girls) between seventh and eighth grade of school	Self-reports of peer support (Child and adolescents social support scale)	Assessment of depressive symptoms with self- reports (Behavioural assessment scale for children)	Low social support on parent-, self- and peer-reports predicted depressive symptoms
Runions (2014)	To determine the associations of hyperactive symptoms and aggressive behaviours with victimisation	Prospective	1167 children (607 boys, 560 girls) aged 4-5 years at baseline	Teacher reported victimisation (SBQ)	Teacher ratings of hyperactive and impulsive symptoms (SBQ)	Poor teacher-child relationships mediated the association of hyperactive-aggressive behaviours with victimisation

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
St. Pourcain et al. (2011)	To determine the associations between social-communication deficits and hyperactive-inattentive symptoms	Prospective	Population based sample of 5383 children (2669 boys, 2714 girls) aged 4-17 years	Parent reported social-communication problems (Social communication disorder checklist)	Symptoms of ADHD assessed using parent reports (SDQ)	Children with persistent hyperactive-inattentive symptoms are likely to have social-communication deficits
Saluja et al. (2004)	To assess risk factors of depressive symptoms in young adolescents	Cross-sectional	9863 children (4715 boys, 5148 girls) aged 11-15 years	Self-reports of bullying and victimisation	Assessment of depression based on DSM-III-R criteria	Both bullies and victims showed depression than children not involved in bullying
Sapouna and Wolke (2013)	To determine moderators of the association between victimisation and depression	Prospective	3136 children (1521 boys, 1615 girls) aged 12-14 year	Self-reported measures of social support, friendships and victimisation	Self-reported symptoms of depression	The association between victimisation and depression was moderated by gender (male), high self-esteem, peer support, and friendships
Schwartz et al. (1999)	To assess relationships between hyperactive-impulsive behaviours and peer victimisation	Prospective	389 children aged 5-6 years including both boys and girls	Sociometric measures of peer acceptance, rejection and victimisation; teacher reported social problems (TRF)	Teacher reports of hyperactive impulsive behaviours (TRF)	Peer rejection mediated while friendship moderated the associations between behaviour problems and victimisation

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
Schwartz and Gorman (2008)	To assess the influence of social difficulties on depressive outcomes	Prospective	199 children (105 boys, 94 girls) with a mean age of 9.1 years	Sociometric measures of peer preference and friendships	Self-reported depressive symptoms (CDI)	The relationship between a lack of friends and depression was moderated by academic competence
Sciberras et al. (2014)	To determine peer functioning of children with ADHD and comorbid anxiety	Cross-sectional	370 clinic-referred (317 boys, 53 girls) children with ADHD aged 5-12 years	Parent and teacher reported peer problems (SDQ)	DSM-IV diagnoses of ADHD based on clinician and parent reports (ARS- IV)	Children with ADHD and comorbid anxiety showed greater peer problems than those without anxiety
Semrud-Clikeman et al. (2010)	To assess social perceptions and behaviours in children with neurodevelopmental disorders	Cross-sectional	342 participants (240 boys, 102 girls) including children with non-verbal learning disability or NLD (n=24), Asperger's syndrome or AS (n=52), ADHD-C (n=76), ADHD-I (n=77) and controls (n=113) aged 9-16.5 years	Parent reports of social skills (SSRS); self-perceived descriptions of social interactions (CASP)	DSM-IV diagnoses of ADHD by parent interviews	Children with ADHD had fewer social perception problems than those with AS or NLD. Attention problems predicted difficulties in understanding emotional cues
Shochet et al. (2011)	To assess the impact of school belonging on affective problems in adolescence	Prospective	504 children (277 boys, 227 girls) with a mean age of 13.3 years	Self-reported peer acceptance and rejection	Self-reported depressive symptoms (CDI)	Peer rejection was associated with depressive symptoms. In girls, rejection predicted

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
						future depressive symptoms
Sinclair et al. (2012)	To determine effects of victimisation on depressogenic cognitions	Prospective	478 children (237 boys, 241 girls) aged 8-14 years at baseline	Sociometric and self-reported measures of victimisation	Assessment of depressogenic cognitions with self-reports (Cognitive triad inventory for children-CTI-C; Children's automatic thoughts scale-CATS	Victimisation predicted increases in depressogenic cognitions, especially in girls
Sjöwall and Thorell (2014)	To assess mediators of functional impairments in children with ADHD	Cross-sectional	204 participants (92 boys, 112 girls) including 102 clinic-referred children with ADHD and 102 age and gender matched population-based controls	Parent and teacher rated peer preference and friendship (SDQ)	DSM-IV diagnoses of ADHD based on teacher and parent reports (ARS-IV; SDQ)	Problems in regulating emotions, especially anger, mediated the relationship of ADHD with low peer preference and friendship
Smith et al. (2000)	To assess reliability and validity of self-report measures by adolescents with ADHD	Short-term prospective with follow-ups over 8 weeks	36 adolescents with ADHD including both genders and with a mean age of 13.5 years	Behaviour observations; self-reported peer functioning and social behaviours; counsellor and teacher reports of social behaviours	DSM-III-R diagnoses of ADHD based on parent interviews and teacher reports (IOWA Conners; DBD)	Adolescents receiving treatment for ADHD provided valid self-reports of negative social behaviours
Snyder et al. (2003)	To assess effects of victimisation on social behaviour and depressive problems in children	Prospective	266 (134 boys, 132 girls) children aged 5-7 years	Observations of social behaviours and victimisation; parent (CBCL) and teacher (TRF)	Assessment of depressive symptoms with parent (CBCL), teacher (TRF), and self-reports	Victimisation was associated with increases in social behaviour and depressive

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
				reports of social behaviours	(Computer assisted child interview-CACI)	problems
Sontag et al. (2011)	To understand the effects of pubertal timing and peer stress on psychopathology	Cross-sectional	264 children (98 boys, 166 girls) with a mean age 12.4 years	Self-reported social behaviours (PEQ-revised; RPAQ), peer stress (Responses to stress questionnaire), and social desirability (Marlowe-Crowne social desirability scale)	Self-reported symptoms of anxiety and depression (YSR)	Peer stress was associated with symptoms of anxiety and depression. High peer stress in early maturing girls and late maturing boys increased aggressive behaviours
Sourander et al. (2000)	To determine factors associated with bullying and victimisation in childhood and adolescence	Prospective	580 children between 8-16 years of age and including both genders	Self-reported bullying and victimisation	Assessment of depressive symptoms with self-reports (CDI; YSR) and parent reports (CBCL)	Bullies were more likely to show aggressive social behaviours while victims had more depressed-anxious symptoms
Stange et al. (2014)	To assess gender differences in depression and cognitive responses following victimisation	Prospective	256 children (118 boys, 138 girls) with a mean age of 12.32 years	Self-reported peer victimisation (SEQ)	Self-reported symptoms of depression (CDI),	Stange et al. (2014)
Storch and Masia-Warner (2004)	To assess the effects of victimisation on social anxiety and loneliness in adolescent girls	Cross-sectional	561 female adolescents aged 13-17 years	Self-reports of victimisation (SEQ)	Self-reported anxiety (SASA) and loneliness (AWLS)	Victimisation predicted social anxiety and loneliness

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
Stormshak et al. (1999)	To assess relationships between behaviour problems and peer status in different classrooms	Cross-sectional	2985 children in the first-grade from 134 classrooms (including both genders)	Sociometric measures of peer acceptance and rejection; teacher ratings of social behaviours (Teacher observation of classroom adaptation-revised)	Teacher and peer rated hyperactive-inattentive behaviours	While acceptability of aggressive or withdrawn behaviours varied across classrooms, peer acceptability of hyperactive-inattentive behaviours was low in all classrooms
Swanson et al. (2012)	To assess self-perceptions of social competence in girls with ADHD	Prospective	228 participants including 140 girls with ADHD and 88 age-matched controls between 6-12 years of age at baseline	Self-reports of perceived social competence (HSPPC); sociometric measures, teacher ratings (DSPS) and parent reports of peer status	DSM-IV-TR diagnoses of ADHD based on parent interviews (DISC-IV)	Girls with ADHD showed 'illusory' and positive self-perceptions; self-ratings of social functions, however, were negative
Sweeting et al. (2006)	To determine the direction of the victimisation-depression relationship and assess possible gender differences	Prospective	2586 children (1339 boys, 1247 girls) aged 11 years at baseline	Self-reported victimisation	Assessment of depressive symptoms with self-reports	At early adolescence, victimisation predicted depression. At mid-adolescence depression increased risk for victimisation
Taanila et al. (2009)	To assess psychosocial functioning in	Cross-sectional	6475 participants (3222 boys, 3253 girls) aged 15-16	Self-reported measures of social functioning and	DSM-IV based assessments of ADHD symptoms by	Self-reported psychosocial wellbeing was poor

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
	adolescents with ADHD		years from a population-cohort, including children with (n=487) and without (n=5988) ADHD	social satisfaction	parent reports (strengths and weakness of ADHD symptoms and normal behaviour)	in adolescents with ADHD. Boys with ADHD reported a lack of friends
Taylor et al. (1996)	To assess the developmental risk associated with hyperactive behaviour	Prospective	98 boys from a community sample aged 6-7 years at baseline, including 18 boys with conduct problems, 30 with hyperactivity, 21 with both hyperactivity and conduct problems, and 29 controls	Parent and adolescent reported social behaviours and functioning	ICD-10 and DSM-III-R based assessments of hyperactivity-inattention using parent reports (Parental account of child and adolescent symptoms); teacher reports of hyperactivity-inattention (Rutter scale B)	Hyperactive behaviours were associated with an increased risk for social impairments
Taylor and Wood (2013)	To determine if discrepancies in self- and parent-appraisals of social functioning predict depression	Cross-sectional	3976 children (1913 boys, 2063 girls) with a mean age of 13. 43 years	Parent and self-reports of social skills (SDQ) and social functioning	Diagnoses of anxiety and/or depression based on ICD-10 using parent, teacher, and self-reports (Development and well-being assessment)	Children with a high self-appraised but low parent-appraised social skills were likely to develop anxiety and /or depression
Turner et al. (2010)	To determine effects of victimisation on depressive symptoms in adolescence	Prospective	523 children (246 boys, 277 girls) aged 11-18 years	Self-reported victimisation (Juvenile victimisation questionnaire)	Self-reported depressive symptoms (Trauma symptom checklist for children)	Victimisation increased the risk for depression. Low self-esteem mediated these relationships

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
						especially in girls
Wåhlstedt et al. (2008)	To assess the relationship of ADHD symptoms and executive dysfunction with socio-emotional impairments	Prospective	87 children from a community sample (42 boys, 45 girls) aged 4-6 years at baseline	Parent and teacher rated social competence (Prosocial orientation scale)	DSM-IV based assessments of ADHD symptoms using teacher ratings	Symptoms of ADHD predict poor social competence irrespective of cognitive dysfunction
Yang et al. (2010)	To assess the moderating effects of social support on depressive outcomes	Prospective	143 adolescents (71 boys, 72 girls) aged 14-18 years	Peer-reported social support	Assessment of depression with self-reports (CES-D; K-SADS-E)	Low social support following stressful events led to greater increases in depressive symptoms
Yang et al. (2014)	To determine if academic achievement moderates relationships between social difficulties and depression	Prospective	1171 children (591 boys, 580 girls), with a mean age of 9.33 years at baseline	Sociometric measures of social aggression, peer preference, peer dislike and victimisation; teacher-reported social competence; self-reported social competence and social satisfaction	Self-reported symptoms of depression (CDI) and loneliness	Socially aggressive behaviours predicted victimisation and low popularity. The relationship of social difficulties with depression and loneliness was moderated by academic achievement
Young et al. (2005a)	To assess peer problems in girls with hyperactive behaviours	Prospective	Population-based sample of 74 girls aged 6-7 years at baseline	Child interviews of peer relationships and functioning	Assessment of hyperactivity symptoms with teacher reports (Rutter scale B)	Hyperactive symptoms in childhood predicted poor peer functioning at adolescence

Study	Broad aims	Study design	Participant characteristics	Peer/social variables measured	ADHD/depression measures	Key findings
Young et al. (2005b)	To assess self-reported social functioning at adolescence in girls with ADHD	Prospective	Population cohort of 74 girls aged 6-7 years at baseline	Parent and self-reports of social adjustment, peer relationships and self-perceptions of functioning (SAICA)	Assessment of hyperactivity symptoms with teacher reports (Rutter scale B)	Childhood hyperactivity did not predict self-perceived social functioning difficulties
Zalecki and Hinshaw (2004)	To compare social behaviours and functioning amongst the ADHD subtypes	Short term prospective with follow-up at 1, 3 and 5 weeks	228 girls with ADHD-C (n=93), ADHD-I (n=47) and no ADHD (n=88), aged 6-12 years	Parent and teacher rated social behaviours (CSBS); behaviour observations; sociometric measures of peer acceptance and rejection; self-reports of peer regard	DSM-IV diagnoses of ADHD based on teacher and parent reports (CBCL; TRF; SNAP-IV; DISC-IV)	Girls with ADHD-C showed more socially aggressive behaviours than girls with ADHD-I. Aggressive behaviours were associated with a low peer status
Zimmer-Gembeck et al. (2009)	To assess the relationship between peer relations and depression	Prospective	308 children (145 boys, 163 girls) with a mean age of 11 years	Sociometric measures of peer acceptance and dislike; Self-reported social functioning (HSPPC)	Self-reported depressive symptoms (CDI)	Depression was both a predictor of and predicted by peer dislike

ADHD-C: ADHD-combined subtype; ADHD-H/I: ADHD-hyperactive/impulsive subtype; ADHD-I: ADHD-inattentive subtype; ARS: ADHD Rating Scale; ASD: Autism Spectrum Disorders; ASR: Adult Self-Reports; AWLS: Asher and Wheeler Loneliness Scale; BCFPI: Brief Child and Family Phone Interview; BDI: Beck's Depression Inventory; CARS: Conner's ADHD Rating Scale; CASP: Child and Adolescent Social Perception Measure; CASQ: Conners' Abbreviated Symptom Questionnaire; CBCL: Child Behaviour Checklist; CBS: Child Behaviour Scale; CD: Conduct Disorder; CDI: Children's Depression Inventory; CES-D: Centre for Epidemiologic Studies Depression Scale; CESBQ: Children's Expectations of Social Behaviour Questionnaire; CIS: Clinical Interview Schedule; CRS: Conners' Rating Scale; DBDRS: Disruptive Behaviour Disorders Rating Scale; DDPCA: Dimensions of Depression Profile for Children and Adolescents;DISC: Diagnostic Interview Schedule for Children; DSAS: Dishion Social Acceptance Scale; DSPS: Dishion Social Preference Scale; FQM: Friendship Qualities Measure; HSPPC: Harter's self-perceived peer competence; ICS:

interpersonal Competence Scale; K-SADS-E: Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiologic version; LSDQ: Loneliness and Social Dissatisfaction Questionnaire; ODD: Oppositional Defiant Disorder; PEQ: Peer Experience Questionnaire; RPAQ: Reactive-Proactive Aggression Questionnaire; SAICA: Social Adjustment Inventory for Children and Adolescents; SASA: Social Anxiety Scale for Adolescents; SBQ: Social Behaviour Questionnaire; SCID: Structured Clinical Interview for DSM Disorders; SDQ: Strengths and Difficulties Questionnaire; SEQ: Social Experiences Questionnaire; SMFQ: Short Moods and Feelings Questionnaire; SNAP: Swanson, Nolan, and Pelham ADHD rating scales; SRQ: Social Relationship Questionnaire; SSRS: Social Skills Rating System; SSSCA: Social Support Scale for Children and Adolescents; TCRS: Teacher-Child Rating Scale; TRF: Teacher Report Form; VADTRS: Vanderbilt ADHD Diagnostic Teacher Rating Scale