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## The development of depression in children and adolescents with ADHD

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## **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.<sup>6</sup> 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

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<sup>6</sup> 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 et 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 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'.<sup>7</sup> 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

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<sup>7</sup> 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 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.

