

**Symptoms of Attention Deficit Hyperactivity Disorder, Oppositional  
Defiant Disorder and Conduct Disorder in preschool children: comorbidity  
patterns, functional impairment and perinatal maternal risk factors**

*By*

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## SUMMARY

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most frequent and debilitating childhood disorders, in which comorbid behaviour disorders considerably worsen the prognosis. Early identification could promote prevention and intervention at an earlier stage, but there is also a need for more knowledge about the presentation of co-occurring patterns of Oppositional Defiant Disorder (ODD) compared to Conduct Disorder (CD), and how symptom patterns impact daily life function at an early stage. Sex differences are shown to vary with sample source, rater source, age and comorbid conditions. A better understanding of the observed sex-distributions of ADHD could benefit from a more systematic examination of the course and putative risk- and protective factors. Although ADHD has been found to be highly heritable, environmental risk and protective factors are also shown to be involved, including antenatal and postnatal maternal anxiety and/or depression. More knowledge is therefore needed from studies examining different types of exposure, time variation during gestation and postnatally, as well as various symptom dimensions or symptom clusters within the same study design.

The overall aim of this thesis was to provide more knowledge on young preschool children's symptom characteristics, clinical presentation and the risk factors associated with ADHD, ODD and CD. Participants were recruited from a prospective birth cohort, the Norwegian Mother and Child Cohort Study (MoBa), and clinically assessed in the preschool ADHD study, which took place when the children were 3.5 years old. Children who had scores above the 90<sup>th</sup> percentile on ADHD characteristics from the MoBa questionnaires at 36 months (n = 1048) were included in the first two studies, while a randomly selected control group (n = 147) was also included in the third study (n = 1195).

The first objective was to examine the co-occurrence patterns of ODD and/or CD in children with symptoms of ADHD (Study I). The assessment of DSM-IV-TR symptoms and functional impairment were based on parental ratings and a semi-structured psychiatric interview, "The Preschool Age Psychiatric Assessment" (PAPA). Among children with ADHD, concurrent ODD was present more often than CD (31% vs. 10%), but having ADHD gave an almost three times higher increase in the odds of CD compared with ODD. Among children with co-occurring CD, a greater proportion of children had the combined ADHD subtype and more severe inattentiveness than those with ODD. We discuss these important differences in co-occurring patterns of ODD compared to CD identified in these young preschool children with symptoms of ADHD.

The second objective was to investigate the impairment of ADHD by examining which functional domains were affected and how the impairment was related to ADHD subtype, symptom load, co-occurrence ODD and/or CD (Study II). Impairment was assessed in domains of family functioning, peer relationships, play, life quality and areas of learning. All domain scores of impairment were strongly inter-correlated, and added to a total score. Impairment was mainly reported in areas of family functioning, but overall, most of the non-referred young children with clinical symptoms of ADHD were not severely impaired. The most significantly impaired subgroups were children with combined ADHD symptoms and those with co-occurring ODD symptoms, in which between 80-90% of children were rated as moderately or severely impaired. The findings indicate that assessing the impact of ADHD symptoms and co-existing difficulties in preschoolers may help verify the identification of children and families who are in the greatest need of early intervention efforts.

The third aim was to examine the relationships of perinatal maternal symptoms of anxiety or depression to the symptom dimensions of ADHD (i.e. inattentive compared to hyperactive-impulsive symptoms), ODD and CD, and to examine whether the effects varied with the type- or time of exposure. Information about maternal anxiety and depression (SCL-5) was obtained from the MoBa questionnaires completed at weeks 17 and 30 during gestation and at six months post-partum. Perinatal maternal symptoms of anxiety and depression represented relatively stable, but generally modest risk factors for preschoolers' symptoms of ADHD and ODD. There was no significant variation with time during early- and mid-to-late gestation, or postnatally. Covariate adjustments highly attenuated the effects indicating that risk relationships depend on a number of other risk factors and correlates.

All the way through this thesis, we intended to examine sex differences of ADHD, co-existing behaviour disorders and functional impairment of ADHD, and whether there were sex differences compared to the potential risk associations of perinatal maternal symptoms of anxiety or depression to child symptoms of ADHD, ODD or CD (Studies I, II, III). A male predominance was seen among children with ADHD alone and among those with the combined subtype (ADHD-C). However, there were no sex differences among the diagnostic groups of children with ADHD and a co-occurrence of ODD and/or CD. Minor sex differences were also shown compared to the impairment of ADHD, but boys with ADHD-C and those with ADHD and concurrent ODD were rated more impaired than girls.

Boys whose mothers had symptoms of anxiety during their peripartum period were also found more susceptible than girls for symptoms of ADHD. Conversely, the prediction of child ODD symptoms by perinatal maternal symptoms of anxiety tended to be more marked



for girls than boys. These findings contrast with previous results on this topic, and are discussed in terms of methodological differences in the assessment of child psychopathology and possible underlying mechanisms.

The implications of the main findings in this thesis are that preschool children with symptoms of ADHD and concurrent ODD and CD present with many of the same clinical features as their older counterparts, but with a few exceptions: inattentive symptoms were not easily identified, and ADHD is far less debilitating in most settings. Furthermore, the increased understanding of how environmental risk factors, and among these, perinatal maternal anxiety and depression, are related to these frequently occurring and often overlapping mental health conditions could help build a theoretical knowledge that has implications for both prevention efforts and future research.

## LIST OF PAPERS

- I. Bendiksen, B., Svensson, E., Aase, H., Reichborn-Kjennerud, T., Friis, F., Myhre, A.M., Zeiner, P. Co-occurrence of ODD and CD in Preschool Children with Symptoms of ADHD. *J Atten Disord* 2014;doi:10.1177/1087054714538655.
- II. Bendiksen, B., Aase, H., Svensson, E., Friis, F., Myhre, A.M., Reichborn-Kjennerud, T., Zeiner, P. Impairment in Young Preschool Children with Symptoms of Attention-Deficit/Hyperactivity Disorder and Co-occurring Oppositional Defiant Disorder and Conduct Disorder. *Scand J Child and Adolescent Psych and Psychol*; Vol. 2 (3):95-105 (2014).
- III. Bendiksen, B., Aase, H., Diep, L., Svensson, E., Friis, S., Myhre, A.M., Zeiner, P. Perinatal Maternal Anxiety and Depression and Preschool Children's symptoms of ADHD, Oppositional Defiant Disorder and Conduct Disorder. *J Atten Disord*; Submitted May 15, 2015.

## ABBREVIATIONS

ADHD: Attention Deficit Hyperactivity Disorder

CD: Conduct Disorder

CBCL: Child Behaviour Check List

DSM-IV: The Diagnostic and Statistical Manual of the American Psychiatric Association, Fourth edition

DSM-5: The Diagnostic and Statistical Manual of the American Psychiatric Association, Fifth edition

ICD-10: The International Classification of Disorders, 10<sup>th</sup> edition, WHO

ODD: Oppositional Defiant Disorder

PAPA: The Preschool Age Psychiatric Assessment

PNA: prenatal maternal anxiety

PND: prenatal maternal depression

PNS: prenatal maternal stress

PPD: post-partum depression

PPNA: perinatal/peripartum maternal anxiety

PPND: perinatal/peripartum maternal depression

# 1. INTRODUCTION

## 1.1 General introduction

### 1.1.1 Clinical background of the study

“The child is father of the man” said the poet William Wordsworth some 200 years ago. The scope of this phrase comprises parent’s concerns when seeking help for their child. They worry that negative childhood experiences might have a long-term psychosocial impact on their child. A child with an attention problem may struggle with coping in academic performance and social functioning with their peers, whereas hyperactivity, impulsivity or behavioural problems often cause turmoil in both home- and classroom situations, thus bringing about conflicts with peers, teachers, siblings and parents. The disapproval or rejection that these children face might have a long-term impact on their self-esteem and further coping strategies.

Norwegian parents have reported that they were worried because of their children’s hyperactivity, impulsivity and attention problems for approximately four years previous to their clinical referral, and that in most cases their child’s problems started during early preschool age (2004). At the time of a diagnosis, psychological, social, learning and behavioural problems have often exacerbated (Pliszka, 2003). Hence, to identify inappropriate levels of inattention, hyperactivity and impulsivity in children before their entry to school, and before the establishment of more extensive and complex patterns of psychopathology occur, is crucial for work on prevention. On the other hand, the diagnoses of young children could be controversial. Preschool years are a critical transition period, in which rapid changes in language ability, motor development and the development of cognitive abilities take place (Chacko, Wakschlag, Hill, Danis, & Espy, 2009). It is therefore important not to pathologize normative behaviours in young children, as the “disorder threshold” may diverge from that observed among school-aged children.

In young preschool children, symptom presentation may diverge from later presentations in terms of numbers, severity and the clustering of inattentive and hyperactive-impulsive symptoms, the patterns of symptom overlap, the degree of impairment and which functional areas that are affected. The intensity of irritable moods, anger and temper outbursts may also differ and be of less concern than during adolescence or adulthood. Aggression is unlearned and peaks during the toddler period, but shows a normative decline over time as self-control, language and cognitive skills develop (Tremblay & Szyf, 2010; Tremblay et al.,

2005). Clinical problems in this age group have been linked to difficulties related to the nature, frequency, intensity and destructiveness of aggression (Wakschlag et al., 2007). A rigid adherence to diagnostic criteria may therefore not be useful in young preschoolers (Sonuga-Barke, Koerting, Smith, McCann, & Thompson, 2011). However, even if symptom dimensions may be considered an appropriate approach in young children, there is also a need to examine whether the diagnostic criteria are applicable for preschool children with symptoms of ADHD, its subtypes, the co-occurrence patterns and how symptoms potentially impact functioning at this early age.

Over the last decade, major efforts have been made to establish developmentally appropriate diagnostic criteria for preschool children. In addition to a number of specific checklists shown to have the potential of identifying the predecessors of psychopathology in preschoolers (Achenbach & Ruffle, 2000; Conners, Sitarenios, Parker, & Epstein, 1998; Gadow, Sprafkin, & Nolan, 2001; Goodman, 1997; Sprafkin, Volpe, Gadow, Nolan, & Kelly, 2002), the structured interview, “Preschool Age Psychiatric Assessment” (PAPA) (Egger & Angold, 2004) is based on parents’ reports and has been shown to be a reliable assessment of symptoms and diagnostic criteria for preschool children. A growing amount of evidence supports that certain symptom patterns of ADHD and sets of behavioural problems may represent an early onset of these disorders, which could also be possible to identify by modified diagnostic criteria during the preschool period (i.e. between 1.5 and 6 years of age) (Egger et al., 2006; Egger & Angold, 2009; Egger, Kondo, & Angold, 2006; Keenan & Wakschlag, 2002; Keenan et al., 2007; Keenan et al., 2011; Keenan, 2012; Kim-Cohen et al., 2005; Kim-Cohen et al., 2009; Lahey et al., 1994; Lahey et al., 1998; Lahey et al., 2004; Lavigne, Gibbons, Christoffel, & Arend, 1996; Lavigne et al., 1998b; Lavigne et al., 1998a).

Developmental psychopathology involves causal processes, but also implies continuities and discontinuities between normality and pathology, in which predispositions and person-environment interplays tend to operate through complex chain effects (Rutter & Sroufe, 2000). Antecedents in an antenatal and early-life environment have long been known to affect neurodevelopment and behaviour in humans. Prospective birth cohorts are among the study designs that have been found to be suitable for the investigations of risk and protective factors associated with child development (Glover, 2014). The Norwegian Mother and Child Birth Cohort Study (MoBa) (Magnus et al., 2006) represents an opportunity to couple questionnaire data from pregnancy and infancy with clinical data from the preschool ADHD study. Common shared or unshared risk- or protective factors are important topics

that need to be more systematically investigated in order to understand vulnerability and to promote work on prevention.

Another issue that warrants attention is the potential moderating role of the child's sex in the development of the dimensions of externalizing disorders. The marked male predominance that has generally been reported is not fully understood (Biederman et al., 2005; Blatt-Eisengart, Drabick, Monahan, & Steinberg, 2009; Kim-Cohen, Moffitt, Caspi, & Taylor, 2004; Latimer et al., 2012; Sandman, Glynn, & Davis, 2013). Systematic investigations of underlying processes, but also thorough descriptions of clinical presentations and symptom patterns in young children, may thus inform our understanding of the role of sex compared to child externalizing symptom presentations.

### 1.1.2 Clinical classification and perspectives

#### 1.1.2.1 *Attention Deficit Hyperactivity Disorder (ADHD)*

ADHD is one of the most common mental disorders, affecting about 5% of children and adolescents worldwide (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). Like many childhood mental disorders thought to resolve themselves with age, ADHD has been shown to persist into adulthood in up to 60% of children (Biederman et al., 2006; Lara et al., 2009). Even if the diagnostic criteria are tailored to children from the age of six, preschool studies estimated from studies indicate prevalence rates between 2% to 6% (Egger & Angold, 2006; Ezpeleta, de la Osa, & Domenech, 2014; Wichstrom et al., 2011).

ADHD is classified as a neurodevelopmental disorder according to the DSM-IV/DSM-5 classification system (American Psychiatric Association, 2000; American Psychiatric Association, 2013), and typically manifests itself before school entry. The developmental deficits vary from specific language delay to learning or cognitive deficits. ADHD is characterized by developmentally inappropriate levels of hyperactivity, impulsivity and inattention across multiple settings (American Psychiatric Association, 2000; American Psychiatric Association, 2013). ADHD frequently co-occurs with other neurodevelopmental disorders (Gillberg et al., 2004; Gillberg, 2010), emotional disorders (Jensen et al., 2001) and behavioural disorders (Connor, Steeber, & McBurnett, 2010; Pliszka, 1998; Pliszka, 2000).

The nosology of the DSM implies a specific set of symptom criteria to be met (criterion A), but requirements also include that symptoms result in a distress or disability that makes symptoms clinically significant (criterion D) (American Psychiatric Association, 2000). The impact of symptoms may vary according to context, which has been reflected in

the ICD-10 classification, in which environmental constraints are taken into account (WHO (1993), 1993; WHO (2007).Geneva: Author, 2007)

The symptom presentation of ADHD has been shown to vary within different age groups. Among school-aged children and adolescents with ADHD, 30% present with the inattentive subtype (ADHD-IA) and 10% with the hyperactive-impulsive subtype (ADHD-HI), whereas 60% of children have combined inattentive and hyperactive-impulsive symptoms (ADHD-C) (Ford, Goodman, & Meltzer, 2003; Lahey, Pelham, Loney, Lee, & Willcutt, 2005; Lahey & Willcutt, 2010). In 4-year-olds, inattentive symptoms (ADHD-IA) are rare, and the most common presentation is ADHD-HI (60%) and ADHD-C (30%) (Byrne, Bawden, Beattie, & DeWolfe, 2000; Egger et al., 2006; Gimpel & Kuhn, 2000; Lahey et al., 1998).

The male-female ratio for ADHD in school-aged children is 3 to 1 in community-based samples, and ranges closer to 9 to 1 in clinical samples (Gaub & Carlson, 1997; Gershon, 2002), but generally, sex differences have been reported to be less pronounced in preschool samples (Egger et al., 2006; Healey, Miller, Castelli, Marks, & Halperin, 2008; Posner et al., 2007).

#### 1.1.2.2 *Oppositional Defiant Disorder (ODD)*

The prevalence rates of ODD range from 2.6% to 15.6% in community samples (Boylan, Vaillancourt, Boyle, & Szatmari, 2007) and from 28% to 65% in clinical samples (Rowe, Maughan, Costello, & Angold, 2005). The lifetime prevalence is estimated to be 10.2% for males and 9.2% for females (Nock, Kazdin, Hiripi, & Kessler, 2007), with rates found to be relatively stable from preschool age to adolescence (Maughan, Rowe, Messer, Goodman, & Meltzer, 2004). In the DSM classification system (American Psychiatric Association, 2000; American Psychiatric Association, 2013), ODD is classified among disruptive behavioural disorders. Symptoms reflect a pattern of negativistic, defiant, disobedient and hostile behaviour towards authority figures, which is severe enough to impair the child's functioning for at least six months, and does not occur solely during an episode of psychotic or mood disorder. Children with ODD often display substantially impaired social adjustments and interpersonal relationships (Greene et al., 2002), which are found to persist into adulthood (Burke, Rowe, & Boylan, 2014; Harpold et al., 2007). Core features of ODD are commonly measured as domains of temperament (Wakschlag et al., 2007), and negative emotionality may be a precursor to the development of the behaviours of ODD, or instead the temperamental and behavioural measures could be tapping into the same construct. Research

over the past decade has given rise to the idea of ODD as a more complex, multidimensional category that captures a wider range of psychopathology beyond the manifestations of disruptive behaviour. ODD has long been recognized as a significant predictor of later CD (Burke, Loeber, Lahey, & Rathouz, 2005; Loeber, Green, Keenan, & Lahey, 1995; Loeber, Green, Lahey, Frick, & McBurnett, 2000), although some research indicates that only roughly 10% of children with ODD go on to develop CD (Lahey et al., 2009; Lavigne et al., 2001). Children with ODD have an increased risk of developing later comorbid internalizing disorder compared to children without ODD or ADHD alone (August, Realmuto, Joyce, & Hektner, 1999; Boylan et al., 2007; Lahey et al., 2009).

### 1.1.2.3 *Conduct Disorder (CD)*

In community-based samples, the prevalence rates of Conduct Disorder (CD) range from 1.8 to 16% for school-aged boys and 0.8% to 9% for girls (Loeber, Burke, Lahey, Winters, & Zera, 2000; Maughan et al., 2004). The prevalence of CD seems to increase with age, and has been found to steeply rise from the early teens (Maughan et al., 2004).

According to the DSM-IV/DSM-5 (American Psychiatric Association, 2000; American Psychiatric Association, 2013), CD symptoms reflect a repetitive and persistent pattern of behaviour, in which the basic rights of others or major age-appropriate societal norms or rules are violated. CD is defined on the basis of the presence of three of 15 diagnostic criteria, which must have been present for the past 12 months, and that significantly impact social, academic or occupational functioning. The DSM-5 has kept a distinction between the onset of adolescence and the childhood-onset subtype of CD, in which the childhood-onset subtype requires one symptom to be present before the age of 10, and has been found to have different clinical correlates from the adolescent-onset subtype (American Psychiatric Association, 2013; Moffitt & Caspi, 2001; Moffitt et al., 2008). The childhood-onset CD is also called lifetime persistent antisocial behaviour and is alone; in children with ADHD, this has been found to be associated with a more severe and persistent pattern into adulthood, including cognitive deficits, family dysfunction and a moderate degree of genetic vulnerability compared to the adolescent-onset subtype, which has been shown to be more closely linked to negative forms of social learning within one's peer group (Mannuzza, Klein, Abikoff, & Moulton, III, 2004; Moffitt et al., 2008).



## 1.2 Comorbidity

### 1.2.1 Concept and Models

In a patient with a specific index disease, the term “comorbidity” refers to any additional co-existing ailment, or the presence of two or more disorders in the same patient, and at the same time (FEINSTEIN, 1964). The underlying etiological mechanisms of psychiatric disorders are not fully understood, thus, as applied by the current diagnostic classification systems (American Psychiatric Association, 2000; American Psychiatric Association, 2013) and also in this thesis, the definition of psychiatric comorbidity is fairly broad and synonymous with the terms “additional disorders”, “coexisting disorders”, co-occurring disorders”, “concurrent disorders” and “overlapping disorders” (Angold, Costello, & Erkanli, 1999; Gillberg, 2010).

Epidemiological studies over the past three decades have shown that mental disorders co-occur more often than expected by chance (Kessler et al., 1994; Kessler, Chiu, Demler, Merikangas, & Walters, 2005), but it has been claimed that the concept of comorbidity conceals more than it clarifies. The fact that various mental disorders rarely occur in isolation could be viewed as evidence that co-morbidity is an artefact of current diagnostic systems derived from mistaken diagnostic concepts and boundaries, and which imposes categorical distinctions that do not exist in nature (Maj, 2005a; Maj, 2005b). Nevertheless, the scope of the comorbidity phenomenon challenges the thinking of mental disorders as discrete and separate entities.

The “KRNK models” of comorbidity developed by Klein and Riso and Neale and Kendler (Klein, Riso, & Anderson, 1993; Neale & Kendler, 1995) are primarily based on the hypotheses that underlying liability factors, whether correlated or independent, might give rise to different manifestations in individuals, but these models also include causation models in which one disorder directly, or reciprocally, may cause another disorder. Liability may represent types or categories of risk, or a continuum of risk to disorder (Klein et al., 1993; Krueger & Markon, 2006; Neale & Kendler, 1995). Externalizing disorders exhibit substantial familial transmission; however, they do not only run in families, but also tend to run together in the same individual (Hicks, Krueger, Iacono, McGue, & Patrick, 2004; Krueger, 1999). One theory is that rather than transmission of risk for a specific disorder from parents to offspring, a broad liability that increases risk for a spectrum of externalizing disorders is transmitted (Hicks et al., 2004). In a similar line of reasoning, the environmental risks accounting for some of the phenotypic variability of the externalizing disorders could be due to shared or unshared underlying liabilities (Hicks, Foster, Iacono, & McGue, 2013),

which emphasize the need of concurrently examining the putative risk factors for externalizing disorders instead of simply focusing on just one disorder.

### 1.2.2 Co-occurrence of ODD and CD in children with ADHD

The developmental course of ADHD is characterized by increasing rates of psychiatric comorbidity, mainly within the externalizing disorder spectrum. Even so, learning disorders and emotional disorders also co-occur in nearly 50% of children with ADHD (Gillberg et al., 2004). The assessment and identification of early co-occurrence patterns of Conduct Disorder (CD) and Oppositional Defiant Disorder (ODD) have implications for prevention and intervention in young children with symptoms of Attention Deficit Hyperactivity Disorder (ADHD). The comorbidity of behaviour disorders, such as ODD and CD in childhood, has been associated with an increased severity of ADHD (Connor & Ford, 2012) and the prediction of psychiatric admissions in adulthood, a risk that seems particularly high among girls with ADHD and co-occurring CD (Dalsgaard, Mortensen, Frydenberg, & Thomsen, 2002).

Comorbidity rates of ODD or CD in clinically referred preschool children with ADHD is 50-65% and 20%, respectively, which nearly correspond to rates in school-aged children (Kadesjo, Hagglof, Kadesjo, & Gillberg, 2003; Posner et al., 2007; Wilens et al., 2002b). Comorbidity rates in community-based preschool samples are lower, with concurrent ODD in 20% and CD in 14% of children with ADHD (Wichstrom et al., 2011).

ODD and CD have largely been merged into a single disruptive category in preschool studies examining comorbidity with ADHD (Bufferd, Dougherty, Carlson, & Klein, 2011; DuPaul, McGoey, Eckert, & VanBrakle, 2001; Kadesjo, Kadesjo, Hagglof, & Gillberg, 2001; Lavigne, Lebailly, Hopkins, Gouze, & Binns, 2009). Knowledge of younger preschoolers is still limited, as previous preschool samples often studied children from the age of 4.5-6 years old (Keenan, Shaw, Walsh, & Delliquadri, 1997; Wilens et al., 2002b). Furthermore, some preschool studies on this issue either have relatively small sample sizes (Keenan et al., 1997; Pierce, Ewing, & Campbell, 1999; Tandon, Si, & Luby, 2011) or have only used checklists for the assessments (Gadow & Nolan, 2002; Kadesjo & Gillberg, 2001; Lavigne et al., 1998b; Pierce et al., 1999), which emphasizes the need for further studies using validated instruments for the assessments.

Community-based studies of school-aged children have found that the co-occurrence patterns vary between the ADHD subtypes, in which ODD and CD have been found to be more strongly associated with ADHD-HI and ADHD-C than ADHD-IA (Eiraldi, Power, &

Nezu, 1997; Willcutt, Pennington, Chhabildas, Friedman, & Alexander, 1999). Some preschool studies have found ODD to be more strongly related to ADHD-C than the other ADHD subtypes (Kadesjo et al., 2003; Lavigne et al., 2009; Nolan, Gadow, & Sprafkin, 2001; Riley et al., 2008), but studies that address the relationship between co-occurring CD and ADHD subtypes in preschoolers are missing. The distinctions between ODD and CD have been supported by longitudinal studies, in which male gender and callous unemotional traits seem more strongly related to CD than ODD (Frick & Nigg, 2012; Frick, Ray, Thornton, & Kahn, 2013).

Sex differences in co-occurrence patterns of ADHD might vary with age (Monuteaux, Mick, Faraone, & Biederman, 2010), and across clinical- and population-based samples (Carlson, Tamm, & Gaub, 1997). In general, sex differences between ADHD and behaviour disorders have been found less marked among preschool children than among school-aged children (Bufferd et al., 2011; Gadow et al., 2001). The presentation of “pure” ADHD or ODD seem to be twice as common in preschool boys compared with girls (Egger & Angold, 2006; Egger et al., 2006; Kim-Cohen et al., 2005), while a similar sex distribution has been reported for the comorbidity of ADHD and ODD (Bufferd et al., 2011; Nolan et al., 2001; Tandon et al., 2011). Preschool studies addressing sex differences in co-occurrence patterns of ADHD and CD are also missing.

More knowledge of the similarities and distinctions in symptom patterns and symptom overlap between ODD and CD in young children with symptoms of ADHD is highly warranted. Studies have shown that clinical presentations, associated impairments, underlying risk factors and developmental trajectories (Frick & Nigg, 2012; Lahey et al., 2009; Mannuzza et al., 2004; Stringaris & Goodman, 2009), as well as intervention strategies, may diverge (Hawes, Price, & Dadds, 2014; Masi et al., 2013).

## **1.3 Impairment**

### **1.3.1 Concept and clinical implications**

Impairment generally refers to the ways that symptoms interfere with adequate performance in important aspects of a person’s life. The most common conceptualizations for children supported by empirical data indicate three main areas: within family, social and school functioning (Ezpeleta, Keeler, Erkanli, Costello, & Angold, 2001).

Impairment has been verified as being a more important determinant of referrals, service use and treatment than diagnosis alone (Angold, Costello, Farmer, Burns, & Erkanli,

1999; Pelham, Jr., Fabiano, & Massetti, 2005; Pickles et al., 2001), but is also an independent predictor from symptom counts of further difficulties and negative outcomes (Mordre, Groholt, Sandstad, & Myhre, 2012).

The relationship between the number of symptoms and the associated impairment is important because if the two facets were perfectly correlated, no additional information would be obtained by the measurement of impairment. Nonetheless, a range of studies have found that the relationship between symptoms and the impairment from ADHD is only moderate (Gathje, Lewandowski, & Gordon, 2008; Gordon et al., 2006; Pickles et al., 2001). Children may fulfil the diagnostic symptom threshold (criterion A) without being disabled, while on the other hand having sub-threshold level of symptoms, but still being impaired (criterion D) (Angold, Costello, Farmer, Burns, & Erkanli, 1999).

Whether a particular set of behaviours should be considered as “difficult” will depend on the child’s context, and within a certain family context a child’s negative behaviour or symptoms could be reinforced by family accommodation, thereby leading to an increased level of impairment. Children’s symptoms might also add a substantial burden and constraint upon the family depending on family resilience and the co-parental relationship.

Little evidence has thus far been provided on functional impairment in young preschool children, with preschool children generally facing substantially lower expectations and demands than school-aged children. The diagnostic threshold of disorders is most likely filtered through the expectations and demands put upon the child, as the syndrome boundary for young preschoolers could represent degree rather than kind (Sonuga-Barke et al., 2011).

### 1.3.2 Impairment related to ADHD and co-occurring ODD and/or CD

Symptoms of ADHD during primary school age and adolescence impact on several important daily life functional areas, including school functioning with classroom disruption and substandard academic achievements (Atkins, Pelham, & Licht, 1985; Loe & Feldman, 2007), and even at the subthreshold level, ADHD predicts poorer educational outcomes during adolescence (Bussing, Mason, Bell, Porter, & Garvan, 2010). Disturbed parent and sibling relationships (Johnston & Mash, 2001), social skills deficits and impaired peer relationships (Erdley, Nangle, Newman, & Carpenter, 2001; Nijmeijer et al., 2008) are commonly reported associated problems.

In preschool studies, a cross-situational impairment in 4-6-year-olds has been found to predict a diagnosis of ADHD three years later (Lahey et al., 2004). Preschool studies have

reported that a majority of children who fulfil the symptom criteria of ADHD also met the impairment criteria (Egger & Angold, 2006; Lahey et al., 2004; Wilens et al., 2002a). However, limited information has been provided about impairment in specific functional domains, and to what level symptoms of ADHD actually cause impairment in preschoolers. Moreover, one may well question the clinical significance of the assignment of impairment practiced by some preschool studies, where a cut-off level for a score of 1 on a scale from 0-30 has been set (Egger & Angold, 2006; Wichstrom et al., 2011).

The different subtypes of ADHD have been found in studies associated with different levels of impairment among school-aged children and adolescents. Academic performance is often the most severely affected area in children with inattentiveness, whereas those with ADHD-C are found to have significantly lower global-, social- and pro-social functioning than those with only ADHD-HI or ADHD-IA (Willcutt et al., 2012). In general, the comorbidity of behavioural disorders in children with ADHD has been found to be associated with added impairment (Connor et al., 2010; Connor & Ford, 2012; Pliszka, 1998; Pliszka, 2003), and also according to reports from preschool studies (Egger et al., 2006; Kadesjo et al., 2003). Still, there is a lack of information about the impact of ADHD-IA in preschoolers, as most studies have failed to identify “pure” inattentiveness (Egger et al., 2006; Lavigne et al., 2009; Posner et al., 2007; Wichstrom et al., 2011). Additionally, information about impairment specifically related to ODD compared to CD is sparse for this age group, as most studies did not differentiate between these two diagnoses in their reports of impairment.

Preschool studies show minor sex differences in impairment from ADHD (Ezpeleta et al., 2014; Posner et al., 2007), but little evidence has been provided for this age group since few studies have included such information. Yet, the way caregivers put an emphasis on consequences related to child symptoms in young girls compared to boys could help inform our understanding of the apparent age-dependent sex differences of ADHD. Representing a more silent minority, ADHD females could potentially be at an increased risk for being belatedly, or not at all, identified, which might imply long-term difficulties in terms of social, academic and emotional difficulties (Rucklidge, 2008; Rucklidge, 2010).

#### **1.4 Risk factors**

The heritability rates of ADHD from twin studies are reported to be approximately 70%-90% (Faraone et al., 2005; Thapar, Harrington, Ross, & McGuffin, 2000; Thapar, Langley, Owen, & O'Donovan, 2007), but environmental factors, as well as gene-

environmental interplay, also play a role in the development of the disorder (Banerjee, Middleton, & Faraone, 2007; Caspi & Moffitt, 2006; Freitag et al., 2012; Harold et al., 2011; Pemberton et al., 2010). Environmental risk factors, including both biological and psychosocial risks, have been shown to account for about 20-30% of the phenotypic variability of ADHD symptoms (Faraone et al., 2005). Common risks have a tendency to aggregate in certain parts of a population and psychopathology may result from the aggregate of adversity factors, rather than the presence of a single risk factor (Rutter, Yule, Morton, & Bagley, 1975; Rutter, Cox, Tupling, Berger, & Yule, 1975).

#### 1.4.1 Perinatal risk and protective factors

Prenatal exposure to toxins, including alcohol and nicotine (Alvik, Aalen, & Lindemann, 2013; Linnet et al., 2005), in addition to a number of obstetric risks (Pettersson et al., 2015; Sun & Buys, 2012), have been found to be associated with an increased risk of childhood ADHD and/or behavioural disorders. Postnatally, a shorter duration of breastfeeding has been found to be associated with an increased risk of ADHD (Mimouni-Bloch et al., 2013; Shamberger, 2012).

Depression, distress or anxiety is quite common conditions among women during childbearing and birth (Heron, O'Connor, Evans, Golding, & Glover, 2004). Perinatal maternal mood may therefore exert an influence on a number of obstetric risks, including prematurity and a low birth weight (Littleton, Breitkopf, & Berenson, 2007; Class, Lichtenstein, Langstrom, & D'Onofrio, 2011; Grote et al., 2010). Perinatal maternal anxiety, distress and depression have also been shown to be associated with a reduced breastfeeding initiation, cessation and duration (Seimyr, Edhborg, Lundh, & Sjogren, 2004).

#### 1.4.2 The Relationships of Perinatal Maternal Anxiety and Depression to children's symptoms of ADHD, ODD and CD

Depression or anxiety affect 15% to 25% of women during the peripartum period (Heron et al., 2004), and may exert long-term adverse effects on offspring's cognitive and behavioural development (O'Connor, Monk, & Fitelson, 2014).

Preschool children exposed to prenatal maternal anxiety (PNA) (Loomans et al., 2011; Loomans et al., 2012; O'Connor, Heron, & Glover, 2002; O'Connor, Heron, Golding, & Glover, 2003) and/or prenatal maternal depression (PND) (Carter, Garrity-Rokous, Chazan-Cohen, Little, & Briggs-Gowan, 2001; O'Donnell, Glover, Barker, & O'Connor, 2014; Van Batenburg-Eddes et al., 2013) have been found to have an increased risk of Attention Deficit

Hyperactivity Disorder (ADHD) and Conduct Disorder (CD). Postnatal maternal depression has been shown to be associated with impaired maternal sensitivity, insecure infant attachment and less optimal mother-child interactions, which may negatively impact on children's cognitive and behavioural development (Carter et al., 2001; Shaw & Vondra, 1995). Maternal post-partum depression (PPD) has been found to predict ADHD and behavioural problems in young children (Carter et al., 2001; Kim-Cohen, Moffitt, Taylor, Pawlby, & Caspi, 2005; Sciberras, Ukoumunne, & Efron, 2011).

The risk phenotype of prenatal maternal emotional complaints or distress seem fairly broad, including adverse life events (Huizink et al., 2007), maternal state or trait anxiety (Pluess, Bolten, Pirke, & Hellhammer, 2010; Van den Bergh & Marcoen, 2004), as well as maternal depressive symptoms (Field, 2011). Distress, anxiety and depression may possibly be operating through the same mechanisms, although exactly how the maternal psychological state is communicated to the foetus is unknown. One hypothesized biological plausible mechanisms are that elevated levels of maternal stress hormones cross the placental barrier if the placental capacity to degrade it is exceeded, hence influencing the developing brain of the foetus (Seckl & Holmes, 2007). However, the relationship between biological measures and maternal perceived distress, anxiety or depression is also conflicting, where some have shown a positive relationship between biological stress measures (i.e. low baseline cortisol awakening levels in early pregnancy) and maternal trait anxiety (Pluess et al., 2010), whereas others have found that the flattened cortisol daytime profile was related to prenatal maternal depression rather than anxiety, because of the introduced confounding by these two frequently co-occurring dimensions (Van den Bergh, Van, Smits, Van, & Lagae, 2008).

Both naturalistic and human studies show contradictory results compared to specifically vulnerable periods during gestation (Baier, Katunar, Adrover, Pallares, & Antonelli, 2012; Beydoun & Saftlas, 2008; Charil, Laplante, Vaillancourt, & King, 2010; Weinstock, 2008), which may reflect confounding since women exposed to stressors early in their pregnancy could be affected by this for a longer period than those exposed at a later time point (O'Connor et al., 2014). In some studies, the increased risk for child symptom development has been found to be equally related to pre- and postnatal exposure (Carter et al., 2001; Giallo, Woolhouse, Gartland, Hiscock, & Brown, 2015; O'Donnell et al., 2014).

Biological and psychosocial environmental risk and protective factors could potentially influence males and females differently during gestation and infancy. Antenatal maternal anxiety has been found to predict ADHD more strongly in preschool boys than girls, while findings of sex differences linked to child behavioural problems seem to be

inconsistent (Loomans et al., 2011; O'Connor et al., 2002). Moreover, some studies have provided support for an overall pattern of a greater risk of behavioural problems in boys than girls from both pre- and postnatal maternal depression (Carter et al., 2001; Shaw & Vondra, 1995).

Traditionally, studies have dealt with postnatal maternal anxiety and depression by treating these as possible confounders rather than making direct comparisons, which may represent a potential bias. Limitations in previous preschool studies also include an insufficient assessment of ADHD, ODD and CD, in which symptom checklists comprise the basis for phenotype definition, and where symptoms of ODD and CD have been merged into one behavioural disorder construct (Carter et al., 2001; Loomans et al., 2011; O'Connor et al., 2002). Furthermore, because the ADHD subtypes are found to be associated with different comorbidities and neurocognitive correlates (Willcutt et al., 2012), perinatal risk relationships could differ for these phenotypes. There seems to be an increasing understanding that there is a sharing of risk factors between ADHD, ODD and CD, but research suffers from a disproportionate focus on ADHD compared with ODD and CD. The diversity in methodological approaches might partially explain the lack of consensus regarding specific sources of exposure (i.e. anxiety or depression), timing effects (i.e. early-, mid- or late-gestation, or post-partum), as well as the different characteristics of psychopathology in offspring.



## **2. AIMS OF THE STUDY**

The overall aim of this thesis was to provide more knowledge of early characteristics and risk factors for ADHD, ODD and CD in young preschool children in order to promote work on early identification and prevention of ADHD.

The first aim was to investigate the patterns of co-occurrence of ODD and CD in 3-year-old non-referred children with clinical symptoms of ADHD by utilizing both categorical diagnoses and dimensional symptom measures, while also examining how comorbidity patterns of ODD or CD were related to specific subtypes of ADHD, whether the severity of ADHD-IA or ADHD-HI symptoms were related to certain co-occurring patterns of ODD or CD. The objective was also to examine sex differences in the prevalence of ADHD, its subtypes and the co-occurring patterns of ODD and/or CD (Paper I).

The second aim was to investigate the level of impairment in preschool children with symptoms of ADHD, both with and without the co-occurrence of ODD and CD. Our objective was to examine to what extent symptoms of ADHD, below and above the diagnostic threshold, impacted on daily life functioning in various functional domains for young children. In addition to examining whether ADHD subtype or co-occurrence of ODD and/or CD symptoms affected the level of impairment. We also wanted to examine how the dimensional symptom measures of ADHD-IA, ADHD-HI, ODD and CD predicted the level of impairment, and whether there was sex differences related to the impairment of ADHD (Paper II).

The third objective in this thesis was to examine how prenatal and/or postnatal maternal symptoms of anxiety or depression were associated with the symptoms of ADHD-HI, ADHD-IA, ODD and CD in preschool children, whether the potential effect varied with the time of exposure, was influenced by preconception maternal symptoms, obstetric risk factors or breastfeeding duration, and whether the potential impact varied between boys and girls (Paper III).

### **3. MATERIAL AND METHOD**

#### **3.1 Study Design**

The present study used data from The Norwegian Mother and Child Cohort Study (MoBa) and The Preschool ADHD Study. The MoBa is a population-based prospective birth cohort study of approximately 107,000 children run by the Norwegian Institute of Public Health, with the primary goal of identifying environmental and genetic factors for diseases in pregnancy and childhood (Magnus et al., 2006; Magnus, Haug, Nystad, & Skjaerven, 2006). Questionnaires at several time points were coupled with a case-control design and the clinical assessment of 1,208 participants from “The Preschool ADHD Study” when the children were 3.5 years old.

#### **3.2 Participants**

All participants were recruited from the Norwegian Mother and Child Cohort Study (MoBa), a population-based prospective birth cohort study of roughly 107,000 children run by the Norwegian Institute of Public Health (Magnus et al., 2006). Seventy percent of pregnant women in Norway were invited to participate in the MoBa study. The recruitments were made through a postal invitation in connection with a routine ultrasound examination at 17 to 18 weeks of gestation, and took place from 1999 to 2009. The participation rate of the MoBa study was 38.7%.

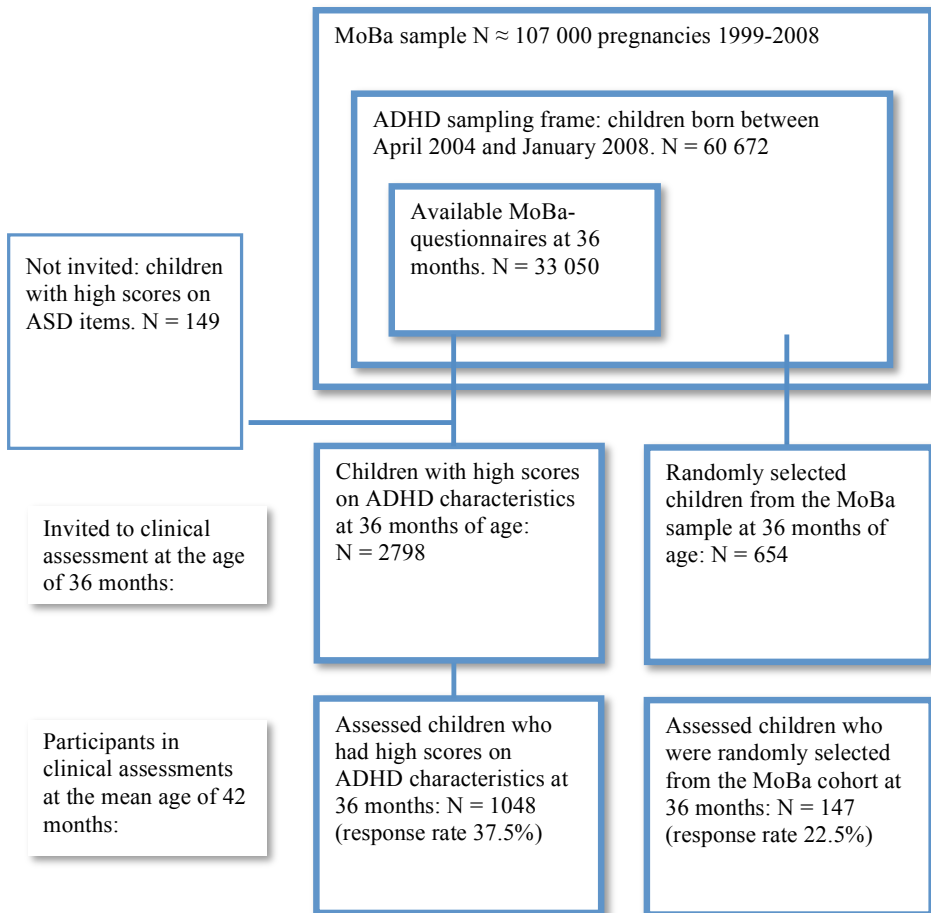
To help identify a large number of preschoolers who might be at risk of developing ADHD, 3-year-old children with a sum score above the 90th percentile on 11 questions regarding hyperactivity, impulsivity and inattention in the 36-month MoBa questionnaire were invited to a clinical assessment. Six of these 11 questions were selected from the Child Behaviour Checklist (Achenbach & Ruffle, 2000), and five questions were from the symptom criteria for AD/HD in DSM-IV-TR (American Psychiatric Association, 2000). A total of 3,452 children were invited from August 2007 to June 2011, of whom 2,798 had high scores on the screening questions. Of these, 1,048 (37.5%) children completed the clinical assessments, including the diagnostic evaluation, which constitutes the participants in Papers I and III. Participants in the second paper were children who had available data on the

ADHD impairment score ( $n = 853$ ), and in addition, one or more ADHD symptom(s), with a total of 807 children.

After parental consent, the children participated in a one-day clinical assessment at Oslo University Hospital when aged 36-44 months, together with at least one parent.

The exclusion criteria were severe medical conditions or high scores on autistic symptoms, and one of the parents had to speak the Norwegian language.

Figure 1. Enrolments into the MoBa and the Preschool ADHD-study.



Note: MoBa: The Norwegian Mother and Child Cohort; ASD: Autism Spectrum Disorder.

### 3.3 Methodological Assessments

#### 3.3.1 The Preschool Age Psychiatric Assessment (PAPA)

One of the parents, most often the mother, was interviewed with “The Preschool Age Psychiatric Assessment” (PAPA) (Egger & Angold, 2004). This semi-structured interview provides information about psychiatric symptoms, including frequency, intensity, age of onset and presence in different settings relevant for preschool children. The task of the interviewer is to ensure that the interviewee understands the questions and that he or she provides clear information concerning the symptom at hand. Interviewers continue to probe until there is enough information to decide whether the symptom is present at pre-specified levels of severity. If so, its onset date is recorded along with its frequency of occurrence and its presence at home and at day care. A three-month primary period is used as the behaviour of preschool children changes rapidly during this period (Egger & Angold, 2004).

#### 3.3.2 Diagnostic classification and measures

The clinical assessment included questionnaire data from parents and preschool teacher on development, language, temperament and behaviours, neuropsychological testing performed by a trained psychologist and neuromotor evaluations performed by a child psychiatrist. A structured, clinical interview to assess psychiatric symptoms, “The Preschool Age Psychiatric Assessment” (PAPA) (Egger & Angold, 2004), was performed by trained psychology students and supervised by a clinically trained psychologist or child psychiatrist.

In combination, the information collected formed a basis for the diagnostic evaluation and classification. Diagnoses were generated using algorithms implementing criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (American Psychiatric Association, 2000).

#### *Attention Deficit Hyperactivity Disorder (ADHD)*

According to DSM-IV-TR diagnostic criteria, a diagnosis of ADHD requires (criterion A) at least six (of nine) inattentive (ADHD-IA subtype), or six (of nine) hyperactive-impulsive symptoms (ADHD-HI subtype). If both subtypes are present, criteria for the combined subtype (ADHD-C) are met. In addition, symptoms must be maladaptive and inconsistent with developmental level and cause impairment. The severity of ADHD was assessed by total symptom counts of HI, IA and total ADHD symptoms (Connor & Ford,

2012). Each symptom was scored 0 (no), 2 (yes, moderate) or 3 (yes, severe). Correlations between the number of symptoms and severity scores were .97 for IA symptoms, .97 for HI symptoms and .98 for total ADHD symptoms. Hence, measures of total symptom counts were used, as they equated measures of symptom severity.

In the second paper, we used the ADHD symptom threshold groups and its subtypes, which were generated with the use of algorithms that implemented symptom criteria (criterion A) of the DSM-IV-TR (1). The low ADHD symptom group consisted of children with one or more ADHD symptoms, but who were below the diagnostic threshold of each subtype. An inter-rater reliability check was carried out by a second rater, blind to any knowledge about the child and family, and rescored from audiotapes of 79 randomly selected interviews. The average intraclass correlations (*ICC*) were .98 for total number of ADHD symptoms and .94 for a total impairment score of ADHD.

#### *Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD).*

The DSM-IV-TR diagnostic criteria of ODD and CD include eight and 15 diagnostic symptoms, respectively. In PAPA, the symptoms of ODD are modified by cut-points based on the top 10% of frequency for preschoolers (Egger et al., 2006). Five diagnostic symptoms for CD were excluded because they are not applicable to preschoolers (“stealing with confrontation”, “forced sexual activity”, “breaking into a house or car”, “running away from home” and “truancy”). The modified and more age-appropriate criteria include eight symptoms, and have exhibited a moderate validity (Egger et al., 2006; Keenan et al., 2007). A DSM-IV-TR diagnosis of ODD requires four or more oppositional symptoms and a diagnosis of CD three or more conduct symptoms. According to PAPA, symptoms must be present for at least three months and cause functional impairment.

On the basis of the DSM-IV-TR symptoms criteria (criterion A), we created diagnostic threshold groups of ODD, CD or both. The average intraclass correlations (*ICC*) was .98 for total number of ODD symptoms, .85 for impairment score of ODD, .91 for total number of CD symptoms and .99 for impairment score of CD.

#### *Continuous symptom measures, categorical diagnoses and symptom groups*

Inattentive (ADHD-IA), hyperactive-impulsive (ADHD-HI), oppositional defiant (ODD) and conduct (CD) symptoms were assessed according to the diagnostic interview (PAPA) and the DSM-IV-TR. The continuous outcome measures were used in Papers I, II and III. In addition to the continuous outcome measures, the categorical DSM-IV-TR

diagnoses of ADHD, its subtypes, ODD, CD and the co-occurring groups of ADHD, ODD and/or CD were used as outcome measures in Paper I. In Paper II, outcome measures were most typically the continuous and categorized measurement of impairment of ADHD, while the symptom threshold groups according to the DSM-IV-TR (criterion A) of ADHD, its subtypes and the co-occurring symptom clusters of ODD and CD were the predictors.

### 3.3.3 Functional Impairment

Papers I and II used an evaluation of impairment, which was concluded for each section of the PAPA interview. Whenever a parent reported his or her child exhibiting at least one diagnostic symptom discussed in the PAPA, impairment was scored for six functional domains: 1) family (relationships with parents and siblings); 2) friends (the ability to make them and keep them); 3) learning (the child's learning capacity in structured activities such as drawing, doing puzzles, and so on); 4) play and leisure activities (participation in play and showing the normal range of variation); 5) quality of life (the interference of symptoms with the child's quality of life); and 6) burden to family (the interference of symptoms with family routines and daily life). Each subscale of impairment was given a score of between 0 and 3, with 0 meaning "no", 1 meaning "yes, minor difficulties", 2 meaning "yes, definite difficulties" and 3 meaning "yes, severe difficulties". The summed score of all six coded functional domains formed a total impairment score with a range of 0 to 18. The scale was found to have sufficient psychometric properties with a Cronbach's alpha of 0.83 and the corrected item total correlations between the different subscales and the total impairment score, 0.55-0.65.

#### *Measures of impact and functional impairment*

In the first paper, the impact and functional impairment was scored as present when symptoms caused reduced function in two or more functional areas for all the diagnostic groups.

In the second paper, continuous measures for the impairment score of ADHD was used, though the different severity levels of impairment of ADHD in this sample were also examined. A sum score of 3 on the total impairment scale was in the 75<sup>th</sup> percentile for the entire sample and was considered to indicate a moderate level, whereas a score of 5 was in the 90<sup>th</sup> percentile and indicated a more severe level of impairment.

### 3.3.4 Perinatal maternal symptoms of anxiety and depression

The participants in MoBa completed questionnaires at weeks 17 and 30 during pregnancy and when children were six, 18 and 36 months. The questionnaires during pregnancy cover maternal physical and mental health, diet, work situation, exposure to toxins and social support, while the questionnaires at six, 18 and 36 months cover children's diet, development, physical and mental health (Magnus, Haug, Nystad, & Skjaerven, 2006).

A short version of a widely used self-administered instrument of psychological distress, the Symptom Check List (SCL), which was originally derived from the SCL-25 (Hesbacher, Rickels, Morris, Newman, & Rosenfeld, 1980), was included in the MoBa questionnaires at three time points: week 17 of gestation ( $T_1$ ), week 30 of gestation ( $T_2$ ) and at six months post-partum ( $T_3$ ). The SCL-25 is a valid measure of psychological distress (Sandanger et al., 1998), and has demonstrated high correlations ( $r = 0.91$ ) with the SCL-5, with a reported Chronbach's alpha of 0.88 (Strand, Dalgard, Tambs, & Rognerud, 2003). The SCL-5 includes two symptoms on aspects of depression ("feeling hopeless about the future", "feeling depressed/sad/blue"), and three questions on aspects of anxiety ("constantly frightened/anxious/ fearful", "nervous, inner turmoil", "frequently worried or uneasy"). The scale for each question includes four categories of response ("not at all", "a little", "quite a bit" and "extremely", rated 1-4, respectively). The scale score is calculated as the mean of the item scores. In the general population, cut-off scores at- or above 2 for psychological distress has been recommended (Strand et al., 2003), but SCL-5 has not been validated in a perinatal context. The SCL-5-item scales revealed a good reliability and internal consistency in this sample, whereas the Cronbach's alpha was 0.81 and 0.79 at  $T_1$  and  $T_2$ , and 0.84 at  $T_3$ . In Paper III, we chose to differentiate between maternal anxiety and depression during pregnancy and postnatally because it is unclear as to whether maternal pre- or postnatal anxiety or depression constitutes the higher risk for the adverse outcome in offspring.

Measures of perinatal maternal symptoms of anxiety and depression were included in Paper III. The Chronbach's alpha showed a moderate reliability for the subscales of SCL-5: 0.77 ( $T_1$ ), 0.76 ( $T_2$ ), and 0.80 ( $T_3$ ) for the 3-item anxiety scales and 0.72 ( $T_1$ ), 0.62 ( $T_2$ ) and 0.70 ( $T_3$ ) for the 2-item depression scales. We validated the 2-item depression scale against a widely used instrument, the "Edinburgh Postnatal Depression Scale" (EPDS) (Cox, Holden, & Sagovsky, 1987) included in the MoBa questionnaire at six months postnatal. The Chronbach's alpha was 0.84 for the six-item version of EPDS in this sample. The Pearson Product Moment Correlation between the EPDS scale and the SCL-2 depression score postnatally was satisfactory,  $r = 0.65$ .

### 3.3.5 Covariates

#### *Background characteristics*

All three papers included information about maternal and paternal educational level, which was obtained from the MoBa questionnaire at the 17-week gestation. We lacked information about the paternal educational level for 59 children and about the maternal educational level for 26 children, although the missing cases were equally distributed among the different symptom groups. Information about maternal age at delivery and marital status was obtained from the Norwegian Medical Birth Registry (Magnus et al., 2006). The educational levels of the parents were moderately correlated ( $r = 0.57$ ;  $P < .001$ ), and we chose to use the maternal educational level as a covariate and measure of socioeconomic status for our analysis in all three papers.

#### *General intellectual ability*

A measure of the child's general intellectual functioning was obtained as a part of the neuropsychological assessment with the use of a short form of the Stanford–Binet Intelligence Scale, Fifth Edition (Roid, 2003), which was administered by a trained psychologist.

#### *Pregnancy, labour/delivery, neonatal and postnatal covariates*

From the MoBa questionnaires at the 17<sup>th</sup> and 30<sup>th</sup> gestational week, we included information about maternal smoking status during pregnancy (coded as the number of cigarettes/day). Information of birth weight, APGAR score, gestational length and the delivery by caesarean section were obtained from “The Norwegian Medical Birth Registry” (Magnus et al., 2006). Caesarean section was planned/elective for 63 mothers and acute, or unspecified, for 140 women. There was no significant statistical difference between elective and acute caesarean section with respect to the number of symptoms of ADHD-HI, ADHD-IA, ODD or CD, or compared to the SCL-5 scores at gestational weeks 17 and 30 or at six months postnatally. We therefore used a binary covariate in the analyses (caesarean section: no = 0, yes = 1), while an APGAR score is determined by an evaluation of the newborns on five criteria: Appearance, Pulse, Grimace, Activity and Respiration, with a score ranging from zero to 10 (APGAR, 1953). The duration of breastfeeding was assessed from the MoBa questionnaires when children were six and 18 months old. We chose to dichotomize this variable into less than or more than nine to 11 months, based on explorative analyses and



current clinical recommendations, in which fully breastfeeding is recommended for at least six months, and when the supplementation of baby food is introduced, a continuation of breastfeeding until children are 10-12 months old.

### **3.4 Data Analyses**

The statistical analyses in Papers I-III were performed using SPSS, version 21. In Paper III, STATA/IC 13 for Windows, version 13.1 was used in addition to SPSS, version 21. All tests were two-tailed.

In Paper I, binary logistic regression analyses were conducted to examine the odds ratios of having co-occurring ODD and/or CD in children with ADHD, and adjusted for possible confounding and/or interactions of background factors and comorbidity.

The associations between the numbers of ODD and/or CD symptoms to the numbers of ADHD symptoms were examined by Pearson Product Moment Correlations and by hierarchical multiple linear regression analyses. Comorbidity patterns of ODD and/or CD across different subtypes of ADHD were compared by crosstabs, and the Mantel Haenzel's odds ratios were reported. A one-way analysis of variance with a Bonferroni correction for post-hoc comparisons was carried out to examine the relationship between the co-occurring groups with ADHD, ODD and/or CD and the severity of symptoms of ADHD-IA and ADHD-HI. We examined sex differences in ADHD, its subtypes and in co-occurring symptom clusters by independent sample t-tests for continuous measures and Pearson chi-square tests or Fisher's exact tests for the categorical measures.

In Paper II, frequencies and proportions of the covariates among children with ADHD symptoms below and above the diagnostic level were assessed for the symptom groups with ADHD alone and/or co-occurring symptoms of ODD and/or CD. One-way between-group analysis of variance with Bonferroni correction for post-hoc comparisons was conducted to investigate the impact of subtype and the co-occurrence of ODD and/or CD on the level of impairment related to ADHD. The relationship between the number of symptoms and the impairment score of ADHD was examined by Pearson Product Moment Correlation. We used multiple linear regression analyses to test the ability of ADHD-IA, ADHD-HI, ODD and CD symptoms to predict the impairment score, and possible confounding and interactions of background variables and comorbidity were also tested. In order to avoid collinearity and to help facilitate interpretation, continuous variables were centred into z-scores before interaction terms were created (Cohen, 2003). Sex differences of impairment were examined

according to subtypes and the co-occurring symptoms of ODD and/or CD by crosstabs, chi-squared tests and independent-sample t-tests. In Paper III, means with standard deviations, median with interquartiles and minimum and maximum values were presented for maternal symptoms of anxiety and depression and continuous variables, while numbers and percentages were given for categorical variables.

We conducted mixed effect Poisson regression analyses to examine the relationships, and whether there were variations of these relationships over time, between the number of ADHD-HI, ADHD-IA, ODD and CD symptoms and maternal symptoms of anxiety and depression measured at weeks 17 ( $T_1$ ) and 30 ( $T_2$ ) of gestation, and at six months post-partum ( $T_3$ ), both with and without adjusting for covariates of interest. Likelihood ratio tests were used to investigate whether the relationship between maternal symptoms of anxiety or depression and the number of symptoms in children differed between the three time points. Mixed effect Poisson regression models were also fitted separately for boys and girls due to significant interactions between child sex and the covariates of interest (i.e. parity, mother's age and education, caesarean and marital status).

For covariates measured at one time point, Poisson regression models were used to assess the relationships between the four symptom groups and each covariate. A crude and adjusted relative risk (*RR*) with a 95% *CI* was given using a robust sandwich estimator of variance, though the two-sided p-values were not corrected for multiple testing.

### **3.5 Ethical Considerations**

The Regional Ethics Committee and the Norwegian data inspectorate approved the study in 2007. Assessments were carried out according to the ethical standards, and the principles of the Helsinki Declaration were followed. Parents returned a written consent prior to the clinical assessment.

## 4. SUMMARY OF RESULTS

### 4.1 Paper I

We examined comorbidity patterns of Oppositional Defiant Disorder and Conduct Disorder in preschool children with ADHD. Of the 1,048 children included, 163 children (16%) fulfilled the diagnostic criteria for ADHD, with 72% with the ADHD-HI subtype, 6% with ADHD-IA and 23% with the ADHD-C subtype.

Among children fulfilling the diagnostic criteria for ADHD, the proportion of children with co-occurring ODD (31%) were greater than co-occurring CD (10%). However, the odds of having ADHD were higher among children with CD than among those with ODD: ODD (OR 6.7, 95% CI: 4.2- 10.8) vs. CD (OR 17.6, 95% CI: 5.9- 52.9). A hierarchical linear regression analysis showed that ODD and CD had about the same power to predict the number of ADHD symptoms: ODD, ( $\beta = 0.25, p < .001$ ) and CD, ( $\beta = 0.23, p < .001$ ).

A co-occurrence of ODD and CD was differently related to the ADHD subtypes, as co-occurring ODD and/or CD was uncommon among children with ADHD-IA (i.e. only one child). Thirty-three percent of children with ADHD-HI had co-occurring ODD:  $OR = 5.8$ , 95%  $CI (3.7, 9.2)$ ,  $p < .0001$ , while 8% had co-occurring CD:  $OR = 3.6$ , 95%  $CI (1.6, 8.1)$ ,  $p = .002$ . Among children with the ADHD-C subtype, the proportion of children with a co-occurrence of ODD (30%) was also greater than CD (19%), but the odds for CD were greater than for ODD:  $OR = 10$ , 95%  $CI (4.0, 25.2)$ ,  $p < .0001$  vs.  $OR = 3.9$ , 95%  $CI (1.9, 8.2)$ ,  $p < .001$ , respectively. Children with a co-occurring CD also had more severe inattentiveness compared with those with concurrent ODD or ADHD only (i.e. a higher number of inattentive symptoms): ADHD and CD ( $M = 5.0, SD = 2.9$ ) vs. ADHD and ODD ( $M = 3.5, SD = 2.4$ ) vs. ADHD only ( $M = 3.7, SD = 2.3$ ). There were no differences in the severity of inattentiveness among groups with ADHD alone, a co-occurrence of ODD or children with a co-occurrence of all three disorders, or when compared to the severity of hyperactive-impulsive symptoms.

Sex differences were only observed among children within the diagnostic groups of ADHD, but not compared to the numbers of ADHD-IA- or ADHD-HI symptoms, or among children with co-occurring ODD or CD. The male female-ratio for ADHD was 1.3 to 1, and most prominent among those with the ADHD-C subtype: a male-female ratio of 2.3 to 1.

## 4.2 Paper II

Symptom groups were based upon the DSM-IV-TR symptom criteria (criterion A) only, thereby ignoring the impairment criterion (criterion D). Of the 807 children included in this study, 73% had ADHD symptom counts below threshold (between one and six for ADHD-IA and ADHD-HI or between one and 10 for the ADHD-C subtype), whereas 27% had ADHD symptom counts above the diagnostic threshold.

The strongest impact of ADHD symptoms in these young preschoolers was in the areas of family functioning, creating discord within family relationships and putting an added burden upon families, where 24% and 32%, respectively, of children with threshold ADHD symptoms were moderately or severely impaired (i.e. score above the 75<sup>th</sup> percentile) compared to 5% and 9% of those below the diagnostic level. Minor impairment was reported in areas such as play, friends and learning. Overall, 33% of preschoolers with clinical ADHD symptoms were rated as impaired at a conservative cut-off and 57% when a more liberal cut-off was used. Children who fulfilled the diagnostic symptom criteria of ADHD were rated almost three times as impaired as children with symptom counts below the diagnostic level. A positive linear relationship between impairment score and the number of ADHD symptoms was demonstrated, but with no distinct breaking point at any level of impairment indicating a diagnostic threshold. A multivariate analysis showed that background characteristics explained 2% of the variance and the numbers of ODD and CD symptoms an additional 13%, while ADHD symptoms explained an additional 19% of the variance of the impairment score of ADHD. An interaction between the symptoms of ADHD-IA and ADHD-HI indicated a multiplicative effect of combined ADHD symptoms.

Ninety percent of children children with ADHD-C had moderate or severe levels of impairment, and they turned out to have significantly higher scores and being almost twice as impaired as children with ADHD-HI or ADHD-IA: ADHD-C (M, 6.4; SD, 3.8), vs. ADHD-HI (M, 3.5; SD, 3.4) vs. ADHD-IA (M, 2.9; SD, 2.7); Welch statistics (3, 41.7), 37.8;  $P < .001$ ).

Eighty-one percent of children with co-occurring ODD were found to have moderate or severe levels of impairment compared to 53% of those with co-occurring CD and 58% of children with a co-occurrence of both ODD and CD. Children with ADHD and concurrent ODD had significantly higher impairment scores than children with subthreshold ADHD symptoms and children with ADHD only: ADHD and ODD (M, 6.1; SD, 4.3) vs. subthreshold ADHD symptoms (M, 1.4; SD, 1.9) vs. ADHD only (M, 3.2; SD, 2.9); Welch

statistics ( $4, 54.8$ ) = 25.9;  $P < .001$ ). Impairment scores were not significantly different among groups of children with ADHD only, co-occurring CD or a co-occurrence of all three disorders, but all of these groups were significantly more impaired than children with subthreshold ADHD symptoms.

More boys than girls had impairment scores above the 90<sup>th</sup> percentile, which indicated a severe level of impairment: 69% of boys compared to 31% of girls. Among those with ADHD and co-occurring ODD, boys had higher impairment scores than girls: ( $M = 7.5, SD = 5.0$ ) vs. ( $M = 4.4, SD = 2.3$ ),  $t(32.2) = 2.7, P = .01$ , but largely there were only minor sex differences in the impairment of ADHD.

### 4.3 Paper III

The individual scores for maternal anxiety and depression were only moderately correlated over time. The Spearman's correlation coefficient between maternal anxiety score at week 17 of gestation ( $T_1$ ) and week 30 of gestation ( $T_2$ ),  $r = .57$ , between  $T_1$  and postnatal ( $T_3$ ),  $r = .45$ , and between  $T_2$  and  $T_3$ ,  $r = .49$ , while the respective figures for maternal depressive scores were .51, .41 and .42.

The average scores of perinatal maternal symptoms of anxiety (PPNA) and depression (PPND) were fairly stable over time compared to the effects on all symptom groups ( $P > .9$  for the interactions between PPNA x time and PPND x time).

In the adjusted multivariate model, one additional unit increase of the maternal anxiety/depression score increased the mean number of symptoms of ADHD-IA by a cofactor of 1.4%, ADHD-HI by 1.1%, ODD by 2.1%/2.6% and CD by .2%/.8%. The effect of pre- and postnatal maternal depression scores on CD symptoms turned out to be non-significant after the adjustments, and was the most strongly attenuated by maternal anxiety (maternal anxiety model) or depression (maternal depression model) previous to conception. A positively directed interaction between maternal depression during pregnancy and maternal smoking was shown for the effect on ODD symptoms,  $P = .025$ , but not observed for ADHD symptoms. Moreover, there were no interactions between PPNA/PPND and obstetric risks such as gestational age, birth weight, APGAR score or caesarean section, nor between PPNA/PPND and breastfeeding duration on any of the outcomes. However, breastfeeding, maternal age, education and social support did attenuate the effects of PPNA/PPND on the likelihood of ADHD and CD symptoms.

We found no interactions between a child's sex and PPNA/PPND, but stratified analyses were performed because of significant interactions between a child's sex and a number of covariates (i.e. parity, mother's age and education, caesarean and marital status). Although the effects generally were small, there was a tendency towards boys, who had been exposed to maternal anxiety, being more likely than girls to display symptoms of ADHD: ADHD-IA ( $RR = 1.017$ , 95%  $CI = 1.01, 1.03$ ,  $P = .003$ ) vs. ( $RR = 1.005$ , 95%  $CI = .99, 1.02$ ,  $P = .52$ ), respectively, and for ADHD-HI: boys ( $RR = 1.012$ , 95%  $CI = 1.00, 1.02$ ,  $P = .02$ ) vs. girls ( $RR = 1.008$ , 95%  $CI = .99, 1.02$ ,  $P = .13$ ). On the other hand, girls were found more likely than boys to display ODD symptoms from the exposure of PPNA: ( $RR = 1.022$ , 95%  $CI = 1.00, 1.04$ ,  $P = .04$ ) vs. ( $RR = 1.001$ , 95%  $CI = .99, 1.03$ ,  $P = .22$ ), respectively. Sex differences related to timing were minor, but boys were found more susceptible than girls during from the exposure of PPND during mid-to late-gestation,  $P = 0.048$  vs.  $P = 0.43$ .

## 5. DISCUSSION

### 5.1 Discussion of the Main Findings

#### 5.1.1 The presentation of ADHD in young preschool children

The distribution of clinical subtypes of ADHD was in line with most previous large community- and clinically-based preschool studies, in which the ADHD-HI was the most prevalent and the ADHD-IA subtype the least common (Byrne et al., 2000; Lahey et al., 1998b; Ramelli, Zanda, Bianchetti, & Leoni, 2010; Wichstrom et al., 2011), and which differ from those observed in older children, adolescents and adults, where ADHD-HI is the least common subtype (Willcutt et al., 2012). Inattentive symptoms were uncommon unless combined with hyperactive-impulsive symptoms, but the ADHD-C subtype was also less commonly observed among these young preschoolers than among older children. Only 6% of children in this study were categorized by the ADHD-IA subtype. However, several large preschool studies have failed to identify the inattentive subtype among young preschoolers (Byrne et al., 2000; Egger et al., 2006; Lavigne et al., 2009; Posner et al., 2007; Wichstrom et al., 2011). Hyperactivity and impulsivity have been reported to decline over time during the preschool period (Lahey et al., 2005; Lahey et al., 2006). By contrast, inattentive symptoms have been found to increase with age (Galera et al., 2011; Lahey & Willcutt, 2010), and to predict a more persistent pattern of ADHD in younger children (Lahey, Pelham, Loney, Lee, & Willcutt, 2005). Because of ADHD-IA have been found to be less transient and more stable than ADHD-HI, more work is needed in order to identify inattentiveness at this young age. Both inattentiveness and impulsivity have been found to be linked to deficient social competence (Pelham, Jr. & Fabiano, 2008) and low self-esteem (Glass, Flory, Martin, & Hankin, 2011) in children with ADHD; thus, this late recognition during the development could represent a major concern for early prevention and intervention programmes. The capacity for focused attention may gradually develop during the preschool period; consequently, attention problems might not be apparent until later during development. On the other hand, the assessments of inattentive symptoms primarily focus on school-based tasks in current nosology, which might not be particularly appropriate for these young children. Given the less demanding surroundings and the modest requests for attention capacity in this age group compared to older children, attention problems could just be harder to spot at this early age.

### 5.1.2 Co-occurrence of ADHD, ODD and CD in preschool children

Longitudinal studies have shown that ODD/CD are the most prevalent co-occurring disorders among children with ADHD, and associated with an increased severity and adverse outcomes (Dalsgaard, Mortensen, Frydenberg, & Thomsen, 2013; Biederman et al., 2008a; Biederman et al., 2008b; Connor et al., 2010). For this reason, co-occurring behavioural problems are important targets for early prevention and intervention efforts. Children with ADHD and concurrent CD have been found to have an earlier onset, as well as a more stable course of antisocial behaviours (Pardini, Obradovic, & Loeber, 2006; Loeber et al., 1995; Moffitt, Caspi, Harrington, & Milne, 2002). We found that children with ADHD had almost seven times higher odds of ODD and 17 times higher odds of CD than those without ADHD. Symptoms of CD are often more low incidence behaviours, yet 14% of non-referred preschoolers have been found to sometimes “use an object to harm somebody” and 20% do occasionally tell “lies” (Keenan et al., 2007). However, clinical CD symptoms are quite rare among preschool children without problems, and have been demonstrated to discriminate between 3-year-old children with and without externalizing disorders (Rolon-Arroyo, Arnold, & Harvey, 2014).

The temporal order of the occurrence and patterns of co-existing psychopathology related to ADHD may provide important clues in an understanding of the early development of clinical features. Based on several longitudinal studies, ODD was long recognized as a precursor and significant predictor for later CD in children (Burke et al., 2005; Loeber et al., 2000), thereby supporting a direct causation model of comorbidity (Krueger & Markon, 2006; Neale & Kendler, 1995). However, only about 10% of children with ODD have been shown to develop CD later during its course (Lavigne et al., 2001), and more recent evidence indicates that ODD may be distinguished from CD in terms of symptomatology, patterns of comorbidity and developmental trajectories (Lahey et al., 2009; Nock et al., 2007; Stringaris & Goodman, 2009). The acknowledgement of these distinctions was basically our reason for not combining these two disorders into one disruptive behaviours category. Co-occurring behavioural disorders are highly prevalent among school-aged children and adolescents with ADHD (Pliszka, 1998; Pliszka, 2000). The comorbidity rates in this study were approximately 20% lower for both ODD and CD compared with the corresponding rates reported from samples of school-aged children (Pliszka, 1998). Nevertheless, co-occurring ODD was found at three times the rate of CD, which corresponds to patterns of co-occurrence observed in older children (Biederman & Faraone, 2005). In children without ADHD (i.e. below the DSM-IV diagnostic threshold), ODD was present 10 times more often than CD,



which probably reflects that defiance and non-compliance are more common than CD symptoms in 3-year-olds, independent of ADHD, but in addition that ADHD and CD are closely related disorders already at this early age.

The close interrelationships between ADHD, ODD and CD in this study point towards an early emergence of these comorbidity patterns. Multivariate comorbidity models for externalizing disorders provide support for shared or unshared continuous liability factors (Kendler, Prescott, Myers, & Neale, 2003; Krueger, 1999; Krueger & Markon, 2006). These models have found support for a genetic basis for the coherence of both internalizing and externalizing spectra of disorders. Interestingly, an underlying liability and temperament are both latent entities that could help explain the coherence or differences of specific individual domains (Krueger & Markon, 2006). While externalizing disorders have been linked to underlying traits of disinhibition, the comorbidity between externalizing disorders have been found to be linked to traits of negative affect, disinhibition and novelty seeking (Clark, 2005). Results from genetic studies have shown inconsistent results regarding the cause of comorbidity between ADHD and CD, in which some findings are compatible with the comorbid variant of ADHD and CD being either a genetically distinct or a more severe subtype of ADHD (Christiansen et al., 2008; Thapar, Harrington, & McGuffin, 2001). However, Rhee and colleagues (Rhee, Willcutt, Hartman, Pennington, & DeFries, 2008) examined the causes of comorbidity between ADHD and CD in a twin sample, and found that the hypothesis that there are shared genetic and environmental influences on ADHD and CD better fit the data than comorbidity due to the presence of an ADHD+CD subtype.

We found a higher proportion of children with CD than ODD having the ADHD-C subtype, and more severe inattentiveness among children with CD. Inattentive symptoms have been found to predict a more persistent pattern of ADHD in younger children (Lahey et al., 2005; Lahey & Willcutt, 2010), whereas findings from Mannuzza and colleagues (Mannuzza, Klein, Abikoff, & Moulton, III, 2004) indicate that early-onset CD among young children with ADHD may predict a persistent pattern of later CD. Following this, our data could imply that early co-occurring CD represents a more severe subtype of ADHD in these young preschoolers, and hence be in accordance with reports of an increased symptom severity of ADHD in co-occurring CD compared to co-occurring ODD or ADHD alone in school-aged children (Connor & Doerfler, 2008; Connor & Ford, 2012). The distinction between ODD and CD in children with ADHD may also have implications for prevention and intervention strategies. An intervention review by Furlong and colleagues (Furlong et al., 2013) found that behavioural and cognitive-behavioural group-based parenting programmes

for early-onset conduct problems in children aged 3 to 12 years were effective and cost-effective for improving child conduct problems, parental mental health and parenting skills in the short term, but very small and non-significant effect sizes were found for child cognitive and educational abilities as well as those with severe conduct problems pre-treatment. Parent behaviour training (PBT) has largely been found effective for preschoolers at high risk for ADHD (Charach et al., 2013), but data concerning ADHD-specific behaviours in 5-18 year old children are ambiguous (Zwi, Jones, Thorgaard, York, & Dennis, 2011). Maladaptive aggressive behaviours seem to be core features of CD (Frick, Ray, Thornton, & Kahn, 2014; Monuteaux, Fitzmaurice, Blacker, Buka, & Biederman, 2004; Monuteaux, Biederman, Doyle, Mick, & Faraone, 2009). However, predatory aggressions rather than reactive aggression have been found to characterize non-responders to treatment (Masi et al., 2011). Existing evidence has suggested that about 20 to 50% of youths with CD exhibit callous-unemotional (CU) traits (i.e. lack of empathy and guilt and shallow emotions) (Kahn, Frick, Youngstrom, Findling, & Youngstrom, 2012). The hurtful dimension of ODD (i.e. spiteful and vindictive) (Stringaris & Goodman, 2009b) may also be a marker of proactive aggression and callousness. These children and youths are found to have deficits in emotional reactivity and fear, show low sensitivity to punishment and are not only at risk for antisocial behaviour, but also show less sensitivity to treatment (Kahn, Frick, Youngstrom, Findling, & Youngstrom, 2012). Studies of multimodal, non-pharmacological treatment of children and youths with disruptive behaviour disorders (DBD) have found that non-responders were more severe at baseline, more frequently had a diagnosis of CD than ODD, and exhibited higher scores on narcissistic-, impulsive- and CU-traits than those who responded to treatment (Masi et al., 2013). Children's feelings of guilt and emotional arousal, as well as the capacity of voluntary inhibition of behaviour, are crucial inner psychological forces that promote conscience and inhibit disruptive or antisocial conduct (Kochanska, Barry, Jimenez, Hollatz, & Woodard, 2009). Those children who fail develop the normal capacity for moral reasoning and inhibition of aggressive behaviours throughout their socialization processes may benefit more from the addition of an emotion recognition empathy training component to standard parent training than those without these traits (Dadds, Cauchi, Wimalaweera, Hawes, & Brennan, 2012).

In conclusion, our findings suggest that there are differences in co-occurrence patterns of ODD and CD in children with ADHD, which may be identified early during the preschool years. Taken together with the existing knowledge, which indicate that the response to treatment may differ among children with ODD and CD, the distinctions between concurrent

ODD and CD in young children with ADHD should be further examined. Such knowledge should be implemented in the future planning of prevention and intervention strategies for young children with symptoms of ADHD and concurrent behaviour problems.

### 5.1.3 Impairment of ADHD

According to parents' reports, symptoms of ADHD did create discord within the family relationships and put an added burden upon the family, but these young preschool children were not significantly debilitated in areas of friendship, learning and play compared to corresponding reports of older children (Coghill et al., 2006; Wille, Bettge, Wittchen, & Ravens-Sieberer, 2008). This may reflect less requirements for social interactions and learning for young children compared to the more demanding contextual environments school-aged children face, in which cognitive- and learning disabilities, grade failure and poorer educational outcomes during adolescence have been found to be associated with ADHD, even at a subthreshold level of the disorder (Bussing, Mason, Bell, Porter, & Garvan, 2010). Although only about 10% were moderately or severely impaired in these areas, children with ADHD symptoms above the diagnostic level were rated 5-8 times more likely to be impaired in learning, play and friendship than those with subthreshold symptoms in this study. Findings of perceived burden upon the family and disturbed parent and sibling relationships in families with ADHD are in line with studies from older children and adolescents (Deault, 2010; Johnston & Mash, 2001), and should therefore raise concern about early emerging coercive family patterns.

Previous studies of school-aged children have found that ADHD symptoms explain approximately 25-30% of the variance in impairment scores (Gathje, Lewandowski, & Gordon, 2008; Gordon et al., 2006), which is similar to the findings in our study. We found that the explained variance of impairment by ADHD symptoms was twice that explained by co-occurring ODD and/or CD, while parental education and marital status, the child's sex or IQ level did not add more than 2%. However, few studies have specifically addressed the question of which factors other than symptoms are the determinants of impairment in young children with symptoms of ADHD. The diversity of functional domains being scrutinized may partly explain some of the variance (Gordon et al., 2006), whereas learning and social interactions with peers turned out to be less relevant for this age group according to parental reports. Moreover, teachers' evaluations would possibly differ from those of parents' concerning their children's capacity for learning in structured settings, play and social interactions with peers. However, we must also assume that the impairment score covers

several aspects of daily living that go beyond separate symptom descriptions, and that psychiatric symptoms will only explain a smaller proportion of the variance in impairment. The score will probably also reflect factors such as attitudes toward parents and siblings, self-esteem and emotional problems. Our findings indicated that children's symptoms added a substantial burden upon the family, and the parent's ability to deal with this may also depend on family factors such as resilience and co-parental relationship.

In line with previous community- and clinically-based preschool studies (Egger & Angold, 2006; Egger, Kondo, & Angold, 2006; Nolan, Gadow, & Sprafkin, 2001), a considerably greater proportion of children with ADHD-C were reported to be significantly impaired, and exhibited twice the impairment level of children with either ADHD-IA or ADHD-HI. Children with symptoms of ADHD-IA were found to be even less impaired than children with ADHD-HI, although no firm conclusions can be drawn because of the small number of participants. In any case, the clinical significance of inattentiveness seems to be difficult for parents to evaluate in these young preschool children.

Corresponding to findings from some previous preschool studies (Gadow & Nolan, 2002; Kadesjo, Hagglof, Kadesjo, & Gillberg, 2003), we found that children with symptoms of ADHD and co-occurring ODD were more impaired than children with ADHD alone, though neither group significantly differed from children with co-occurring CD. To the best of our knowledge, no previous preschool studies have differentiated between the impact of ODD compared to CD in their reports on the impairment of ADHD, as the two diagnostic categories were mostly merged (Ezpeleta, de la Osa, & Domenech, 2014; Gadow, Sprafkin, & Nolan, 2001; Kadesjo, Hagglof, Kadesjo, & Gillberg, 2003; Lavigne, LeBailly, Hopkins, Gouze, & Binns, 2009; Nolan, Gadow, & Sprafkin, 2001; Wichstrom et al., 2011). Intriguingly, a recent study by Bunte and colleagues (Bunte, Schoemaker, Hessen, van der Heijden, & Matthys, 2014) examined the continuity and discontinuity of ADHD, ODD and CD in 3-year olds over a period of 9-18 months, and found that only the number of diagnostic symptoms identified the chronic CD group at reassessment, whereas the chronic ODD and ADHD-HI groups were identified by both impairment and the number of symptoms. In our study, roughly 80% of children with co-occurring ODD had moderate or severe levels of impairment compared to only 50% of those with co-occurring CD. These findings were unexpected, given that temper outbursts and defiance may be considered as normative and age appropriate in 3-4-year-old children, though of course these misbehaviours are annoying to others. The defiance, irritability and temper outbursts comprised in ODD might be highly context-specific and only manifest themselves in home settings, where parents shoulder most

of the burden. For an external observer, the clinical implications of the lower base-rate, and a more discrete and covert pattern of CD could thus be much more difficult to recognize and evaluate. In very young children, CD symptoms could be attributed to immaturity and transient behaviours, and consequently perceived as less impairing by the parents. However, the results cannot be generalized and need replication because of sample sizes in co-occurring groups with ADHD and CD. Since environmental expectations are probably increasing over the preschool period, there may be a need for a reassessment of preschoolers who display symptoms of externalizing disorder (Bunte et al., 2014).

#### 5.1.4 The risk related to perinatal maternal anxiety and depression

Perinatal maternal symptoms of anxiety and depression were found to be relatively stable, although modest predictors of child symptoms in our study. In accordance with previous research, maternal symptoms of anxiety and depression both predicted an increased risk for ADHD (Van Batenburg-Eddes et al., 2013) and behavioural problems (O'Donnell, Glover, Barker, & O'Connor, 2014). Our results support a rather broad phenotype, because even if maternal symptoms of anxiety on ADHD generally had a more marked effect than depression due to a less significant attenuation by covariate adjustments, the magnitude of the effect of PPNA did not substantially differ from the effect of PPND on most outcomes.

In contrast to previous studies (O'Connor, Heron, & Glover, 2002; O'Connor, Heron, Golding, & Glover, 2003; O'Donnell et al., 2014), PPNA/PPND did not predict child CD symptoms after the adjustments. On the other hand, preschoolers' symptoms of ODD were significantly predicted by both PPNA and PPND. Methodological differences could explain, at least in part, some of the observed discrepancies because of the assessment of CD/behavioural problems by "The Strength and Difficulties Questionnaire" (SDQ) (Goodman, 1997), which is used in some of these studies (O'Connor et al., 2002; O'Connor et al., 2003; O'Donnell et al., 2014), and includes diagnostic symptoms of both ODD and CD. Furthermore, the inclusion of covariates may also play a role. In our study, the prediction of ODD was only negligibly attenuated after the adjustments, whereas the effects of PPNA/PPND on CD symptoms were strongly attenuated by maternal depression or anxiety previous to conception, which might represent common genetic effects.

#### *Timing-effects*

Results from the ALSPAC study indicated that maternal anxiety during mid-gestation was a particularly sensitive period for the prediction of inattentiveness, hyperactive-impulsive symptoms and behaviour problems in preschoolers, which contrast our findings, in which the

effects of PPNA/PPND did not significantly differ for exposure in early or mid-to-late gestation, or for gestational constraint compared to the exposure during the first six-months postnatally.

Exactly how prenatal maternal stress, anxiety or depression is communicated to the foetus is unknown, but suggested mechanisms include foetal programming through elevated circulating maternal stress hormones and/or epigenetic mechanisms (Glover, 2011; Sandman, Davis, & Glynn, 2012). However, both animal and human studies show discrepancies regarding specifically vulnerable periods during gestation (Beydoun & Saftlas, 2008; Glover, 2011). Some studies that included the assessments of both pre-and postnatal exposure for their investigations, have found that both periods predicted offspring psychopathology (Carter, Garrity-Rokous, Chazan-Cohen, Little, & Briggs-Gowan, 2001; O'Donnell et al., 2014). O'Connor and colleagues (O'Connor et al., 2002), reported that postnatal anxiety was also a significant predictor for child behaviour problems, but the postnatal exposure did not impact the magnitude of the antenatal prediction. Conversely, other studies have found no effects of prenatal maternal emotional complaints once postnatal effects were taken into account (Bekkhuis, Rutter, Barker, & Borge, 2011; Kim-Cohen, Moffitt, Taylor, Pawlby, & Caspi, 2005). Methodological differences may account for some of these discrepancies when postnatal experiences are treated as a possible confounder, rather than making direct comparisons between antenatal and postnatal maternal mood. Moreover, developmental or adaptive programming models imply that the in utero exposure instigates an adaptive response, which may be carried forward in the development of persistent effects on offspring behaviour. O'Donnell and colleagues (O'Donnell et al., 2014) examined the relationship between prenatal maternal anxiety and child's later emotional and behavioural problems, and found that total problems assessed at five time points (i.e. at the ages of 4, 7, 9 and 13) remained high in the high prenatal maternal anxiety group across development. The effect of the exposure at week 18 did not significantly differ from that at week 32 during gestation (O'Donnell et al., 2014), which is in line with our results. Discrepancies in the findings of specific vulnerable periods during gestation or postnatally may be confounded, as mothers exposed to stressors early in pregnancy could be affected for a longer period than those exposed at a later time point (O'Connor, Monk, & Fitelson, 2014). The congruence between prenatal- and postnatal levels of maternal anxiety, depression or distress (Sandman, Davis, Buss, & Glynn, 2011) could well indicate a cumulative effect through the perinatal period (Clavarino et al., 2010; Korhonen, Luoma, Salmelin, & Tamminen, 2012; Van Batenburg-Eddes et al., 2013). Pre- and postnatal maternal anxiety and depression have been shown to

have moderate to high stability and bidirectional prospective relationships (Heron, O'Connor, Evans, Golding, & Glover, 2004; Skouteris, Wertheim, Rallis, Milgrom, & Paxton, 2009), while prenatal maternal anxiety and depression is found to be among the most important predictors of post-partum depression (Heron et al., 2004; Martini, Knappe, Beesdo-Baum, Lieb, & Wittchen, 2010). The case could also be that rather than specific timing effects, maternal symptoms of anxiety and/or depression over time, even at subclinical levels, may constitute an enduring risk for the development of emotional- and behavioural problems in children (Giallo, Woolhouse, Gartland, Hiscock, & Brown, 2015). Clavarino and colleagues (Clavarino et al., 2010) reported that antenatal maternal anxiety was associated with persistent attention problems in both 5- and 14-year-old children, but chronic maternal anxiety during the peripartum period and five years later was the strongest predictor of persistent attention problems in children, which pointed towards an accumulative effect of maternal anxiety. Some studies have found independent effects of antenatal- and postnatal maternal depression on toddler neurodevelopment (Koutra et al., 2013) and preschooler's behavioural problems (Carter et al., 2001). Maternal depression and anxiety post-partum are suggested to interfere with maternal sensitivity and responsiveness to their infants, thus increasing the risk of disturbed mother-child interactions (Stein et al., 2012). Even so, a number of studies focusing on postnatal maternal depression did not simultaneously investigate the impact of prenatal maternal mood or postnatal anxiety, which makes comparisons between studies that much more difficult.

The effect of timing could alternatively be linked to various defined outcomes, as shown by a large population-based study by Class and colleagues, who found that different patterns of psychopathology emerged following prenatal- compared to postnatal maternal distress, in which the exposure during the third trimester increased the risk of autism spectrum disorders (ASD) and ADHD, whereas an increased risk of suicide was observed in offspring whose mothers were stressed during the first postnatal year (Class et al., 2013). However, our results did not indicate any significant differences in timing effects of PPNA/PPND on the symptom dimensions within the externalizing disorders that were investigated.

#### *The effects related to obstetric risk factors and breastfeeding duration*

Attenuation of risk relationships between PPNA/PPND and outcomes by maternal factors such as age, educational level, parity, social support and obstetric factors were minor by each covariate, but in total the effects of PPNA/PPND on most outcomes were significantly reduced by the covariate adjustments. A number of obstetric risk factors have

been found to be associated with ADHD (Pettersson et al., 2015), but obstetric risks could also be related to pre- and postnatal factors such as maternal mood and breastfeeding (Henderson, Evans, Straton, Priest, & Hagan, 2003; Seimyr, Edhborg, Lundh, & Sjogren, 2004; Shamberger, 2012).

In line with Rodriguez and colleagues (Rodriguez & Bohlin, 2005), we found no interactions of maternal smoking and PNA/PND and independent effects of prenatal maternal emotional complaints and maternal smoking on ADHD-HI, while conversely, we found no effect of maternal smoking during gestation on ADHD-IA symptoms. However, maternal smoking during pregnancy significantly moderated the effect of prenatal maternal depression on the likelihood of ODD symptoms according to our results.

In contrast to previous results (Mick, Biederman, Prince, Fischer, & Faraone, 2002; Littleton, Breitkopf, & Berenson, 2007), we found a minor impact of gestational length or a child's birth weight on the likelihood of child ADHD symptoms, whereas a small effect for birth weight was shown for the associations with symptoms of ODD. Additionally, gestational length or birth weight did not modify the effect of PPNA and PPND, and only minor attenuation by these covariates was shown. One possible explanation for these minor effects could be a small variability, as most children in this sample were born at term and had a standard birth weight.

We found a marked protective effect of breastfeeding duration above nine months related to symptoms of ADHD, in particular with inattentive symptoms, which was similar for boys and girls, though there were no associations with symptoms of ODD or CD. Breastfeeding has been found to be protective against neurodevelopmental deficits, including cognition and ADHD traits (Groen-Blokhuis et al., 2013; Mimouni-Bloch et al., 2013; Shamberger, 2012). One of the hypothesized mechanisms involve long-chain polyunsaturated fatty acids (LC-PUFAs) in human breast milk (Groen-Blokhuis et al., 2013; McCann & Ames, 2005), in addition to gene-environment interactive effects (Caspi et al., 2007). Neuroendocrine factors such as oxytocin act as a hormone and as a neurotransmitter in the human brain, and also have a role in uterine contraction, milk letdown, social behaviour and emotional reactivity. Oxytocin might play a role in determining which mothers are more likely to experience depression, both during pregnancy and postnatally (Skrundz, Bolten, Nast, Hellhammer, & Meinschmidt, 2011; Zolkowitz et al., 2014). The marked protective effect of breastfeeding for ADHD is in line with previous studies (Shamberger, 2012). Yet, the effect did not moderate the impact of maternal anxiety or depression, which might support mechanisms independent of maternal emotional state.



In conclusion, our findings indicated quite similar effects of perinatal maternal anxiety and depression were found on ADHD-IA and ADHD-HI symptoms, whereas the effects on ODD tended to be a little more marked, and the effects on CD turned out to be non-significant after the adjustments. These findings support a broad phenotype for perinatal maternal emotional complaints, in which the exposure of maternal anxiety and depression may represent a risk for symptom development of ADHD and ODD in children. There was a tendency towards a more marked effect of anxiety on ADHD during mid-gestation, but adjusted analyses revealed no significant timing effects during childbearing or post-partum, which could imply mechanisms that involve both foetal programming effects, and that the consequences of an impaired mother-child interaction may be involved mechanisms.

#### 5.1.5 Sex differences

In the first study, we found the sex distribution of ADHD even less skewed than previously reports from preschool samples, with a male–female ratio of 1.3:1 compared with the 2:1 reported in earlier studies (Egger & Angold, 2006; Egger, Kondo, & Angold, 2006; Gadow & Nolan, 2002; Gimpel & Kuhn, 2000). In accordance with other studies (Decker, McIntosh, Kelly, Nicholls, & Dean, 2001; Gershon, 2002), we found a predominance of boys with ADHD-C. The bulk of evidence suggests a male predominance in ADHD and all its subtypes (Gaub & Carlson, 1997); this has been most pronounced in clinical samples from studies of both primary school children and preschoolers (Galera et al., 2011; Lavigne et al., 2009; Nolan et al., 2001; Willcutt et al., 2012), while findings from population-based preschool samples vary (Bufferd, Dougherty, Carlson, & Klein, 2011; Carlson et al., 1997; Gadow et al., 2001; Galera et al., 2011; Wichstrom et al., 2011). Male youngsters with overt and severe behaviour symptoms are more likely to be referred to psychiatric treatment settings, hence perpetuating the view that ADHD is more common in boys than girls (Biederman et al., 2005). As a result, the observed sex distribution of ADHD may be due to selection and referral bias (Coles, Slavec, Bernstein, & Baroni, 2012; Novik et al., 2006). Furthermore, the diagnostic criteria have been derived from predominantly male cohorts, thus skewing the inclusion/exclusion criteria in favour of more severe and overt behavioural symptoms, instead of a lower intensity of the ADHD symptom patterns (Biederman et al., 2002).

We found no sex differences within the diagnostic groups of children with ODD or CD, nor among those with ADHD and co-occurring ODD and/or CD, which is in line with findings from some previous community-based samples of preschool children (Nolan et al.,

2001; Tandon, Si, & Luby, 2011) and school-aged children and adolescents (Biederman et al., 2005). However, a male predominance in the co-occurrence patterns of ODD/CD in children with ADHD have previously been reported from both community- and clinically-based preschool samples (Bufferd et al., 2011; Kadesjo et al., 2003; Posner et al., 2007). The male-to-female-ratio among 3- to 7-year old children with ADHD in a clinic-based sample was found to be 7:1 when a comorbid diagnosis of ODD or CD was present, while a 3:1 ratio was shown among those with ADHD without ODD or CD, but there were few sex differences in associated impairment (Hartung et al., 2002). Differential comorbidity have been suggested to play a role in the higher prevalence of ADHD among boys in clinical samples by contributing to a referral bias.

The literature on potential sex differences in impairment of ADHD is limited by the fact that few studies included such measures for these investigations. In the second study, we found minor sex differences in impairment of ADHD, but more boys had impairment scores above the 90<sup>th</sup> percentile and boys with ADHD and concurrent ODD were found to be slightly more impaired than girls. Girls with ODD are found more cooperative conciliatory than boys, whereas boys are from as early as pre-school age, found to show more direct physical and competitive aggression and more readily become involved in conflicts than girls (Trepát & Ezpeleta, 2011). The absence of sex-differences in impairment of ADHD has previously been reported in both non-referred preschoolers (Ezpeleta et al., 2014) and school-aged children (Efron et al., 2014), but there are discrepancies in findings across all age groups from both community-based and clinical-based samples (Gaub & Carlson, 1997; Gershon, 2002; Hartung et al., 2002; Healey, Miller, Castelli, Marks, & Halperin, 2008; Lahey et al., 2007; Posner et al., 2007). Haley and colleagues (Healey et al., 2008) found no sex differences in impairment among preschool children with clinical symptoms of ADHD according to parental ratings, but teachers rated boys more impaired than girls. Sex differences in ADHD and concurrent behaviour disorders may not only be subjected to referral bias as discussed earlier, but also rater bias, which refers to the hypothesis that hyperactive boys will be rated as more hyperactive than equally disruptive girls, and negative halo effects, in which the assumption that the presence of a behaviour in one situation automatically means that the same behaviour will be present in other situations or domains (Hartung et al., 2002; Hartung, Van Pelt, Armendariz, & Knight, 2006). Lahey and colleagues (Lahey et al., 2007) examined sex differences in the predictive validity of ADHD among clinically referred 4 to 6-year old children over 8 years. The study included multiple forms of related functional impairments, which showed no significant sex

differences in the measures of global functioning, classroom academic problems, special education placements, unintentional injuries or negative social preference. Both boys and girls with ADHD exhibited higher levels of CD problems than comparison children, but girls with ADHD had a steeper increase in depression and anxiety during adolescence than boys. In girls, ODD is found associated with depressive and anxiety disorders (Trepát & Ezpeleta, 2011). Moreover, the stability of comorbid psychopathology among females with ADHD across development has been found greater than in males (Monuteaux, Mick, Faraone, & Biederman, 2010). Girls with ADHD are not only less likely to be referred to treatment unless they exhibit comorbid disruptive behaviour problems (Ohan & Visser, 2009), but they also are less likely to receive adequate treatment than boys (Dalsgaard et al., 2002; Posserud & Lundervold, 2013). In addition, ADHD has been found to be a significant predictor of CD in girls (Monuteaux, Faraone, Michelle, & Biederman, 2007). Inattentiveness (Elkins, Malone, Keyes, Iacono, & McGue, 2011), but also concurrent CD in girls with ADHD is associated with social dysfunctioning (Mikami & Lorenzi, 2011), and girls exhibit an higher risk for psychiatric admission and mortality in adulthood than males with ADHD (Dalsgaard et al., 2002; Dalsgaard, Ostergaard, Leckman, Mortensen, & Pedersen, 2015).

If sex differences in the fundamental nature of ADHD exist, then the prevalence, developmental course and associated impairments may differ for boys and girls. However, the latent structure of ADHD (Bauermeister, Alegria, Bird, Rubio-Stipeć, & Canino, 1992; Rhee, Waldman, Hay, & Levy, 1999) and the and the magnitude of the genetic influence of ADHD (Faraone et al., 2000; Faraone et al., 2001; Rhee & Waldman, 2004; Thapar, Hervas, & McGuffin, 1995) are found to be similar in males and females. However, this would not necessarily conflict with a conclusion that there is a sex difference in the degree of liability required to manifest ADHD. In order to examine the aetiology of sex differences in the prevalence of ADHD, Rhee and colleagues (Rhee & Waldman, 2004) investigated the inattentive and the hyperactive dimensions of ADHD separately in a twin-study of 886 twin pairs, and found support for a model which argue that girls are less frequently affected by ADHD because they have a higher threshold for the level of liability needed to manifest ADHD than boys. The authors suggested that further studies should examine why the two sexes differ in the degree of liability required to manifest ADHD.

In the third study we examined sex differences related to the perinatal risk of maternal anxiety and depression and child symptoms of ADHD-IA, ADHD-HI, ODD and CD. In accordance with findings by O'Donnell and colleagues (O'Donnell et al., 2014), we found no significant interaction between child sex and PPNA/PPND. However, separate analyses

showed that preschool boys tended to be more susceptible to symptoms of ADHD than girls following PPNA, which is in accordance with previous reports from preschool samples (Loomans et al., 2011; O'Connor et al., 2002). O'Connor and colleagues (O'Connor et al., 2002), found no sex-related difference in the prediction of behavioural problems, but some studies have found preschool boys are more susceptible than girls to behaviour problems from the exposure of prenatal maternal anxiety (Loomans et al., 2011; O'Donnell et al., 2014). Conversely, we found that girls exposed to both PPNA and PPND tended to be more likely to have symptoms of ODD than boys. These findings are intriguing considering that ODD, in addition to defiance and rule-breaking behaviours, also comprises an irritable dimension that is shown to be associated with later emotional disturbances (Rowe, Costello, Angold, Copeland, & Maughan, 2010; Stringaris & Goodman, 2009a). A greater susceptibility in girls compared to boys would therefore make sense. These findings seem to support the distinction between ODD and CD when examining risk factors and correlates; hence, one should try to avoid merging the two groups into one behaviour disorder construct. Sandman and colleagues (Sandman, Glynn, & Davis, 2013) have suggested that the adaptive flexibility of the female foetus in gestation might render them susceptible to more subtle but persistent consequences, and to be more vulnerable to emotional or affective problems later in life. For this reason, the observed sex-differences may reflect a different susceptibility for psychopathology in girls compared to boys. Circulating maternal stress hormones in utero are strongly correlated with testosterone in the amniotic fluid, where the responsiveness for the male and female foetus is shown to diverge during gestation (Gitau, Adams, Fisk, & Glover, 2005; Seckl & Holmes, 2007), which has been suggested to be responsible for the different timing effects of prenatal maternal distress in boys compared to girls (Sarkar, Bergman, Fisk, O'Connor, & Glover, 2007). The response to prenatal maternal depression during mid-gestation has been shown to entail more fearful temperament in 1-year-olds, as well as higher levels of anxiety in primary school girls compared with boys (Sandman et al., 2013). Regarding timing effects and child sex, previous studies have shown inconsistent results, even when the same types of exposure and outcome are scrutinized. O'Connor and colleagues (O'Connor et al., 2003) re-examined the children from the ALSPAC study when aged 7, and found PNA at 18 weeks of gestation to be the most significant predictor of conduct problems in girls, while the prediction at 32 weeks of gestation remained the most important for boys. By contrast, a study by De Bruijn and colleagues (de Bruijn, van Bakel, & van Baar, 2009) found early gestational maternal anxiety to predict more externalizing problems among boys than girls, while the third trimester constituted those same risks for girls. According to our

results, there was a tendency towards a more marked prediction of ADHD-HI symptoms by PPND during mid-to-late gestation for boys compared to girls, but we largely see that the effects of PPNA/PPND on the various symptom loads did not vary with time for either boys or girls.

In conclusion, sex differences were shown for both the inattentive and hyperactive-impulsive symptom dimension of ADHD related to the risks of perinatal maternal anxiety and depression, in which boys were found more susceptible than girls. Among preschoolers, more boys were found to have ADHD-C, ADHD only and to be severely impaired by ADHD. Co-occurring ODD was also more impairing in boys than girls with ADHD. On the other hand, perinatal maternal anxiety and depression predicted ODD symptoms more strongly in girls than boys, while no sex-differences were shown for the prediction of CD. In 3-year old children, there was an equal sex distribution among children with ADHD and co-occurring ODD and/or CD. Although these findings could make sense and be intriguing, they should be viewed in a context of a host of other potentially involved environmental risk factors or gene-environment interactions.

## **5.2 Methodological Discussion**

### **5.2.1 Study population**

Selection can bias measures of the associations if the probabilities of being selected are related to outcomes of interest. In the present study, bias could be a problem because the selection was a two-step process, first to the MoBa and then to the Preschool ADHD study. Although the original MoBa cohort is large and recruited broadly from the general population, the response rate was low at 39%, and the cohort has been shown to have an overrepresentation of mothers with a high income and high educational level, but an underrepresentation of young mothers, mothers living alone, mothers with more than two children and mothers smoking during pregnancy (Nilsen et al., 2009). The response rate in the Preschool ADHD study was also low, 37% in the sampled group and 23% in the control group, in which participating mothers had an even higher education compared to the MoBa. Participation rates might impact the representativity of a sample as compared to the general population, and hence reduce the generalizability of the results. Nilsen and colleagues have explored the impact of biased sampling in the MoBa study. They investigated seven exposure-outcome associations (e.g. prematurity, low birth weight, smoking during pregnancy, caesarean section, sex, parity, taking folic acids) in the MoBa and the “Autism

Birth Cohort” (“ABC study”). They found less than a 16% deviation in exposure-outcome associations compared to the nationwide population (Nilsen et al., 2013). They concluded that bias in an estimated risk for initial participation in the MoBa was minimal, but this might not be valid for later dropouts and for other exposure-outcome associations.

ADHD is highly hereditary (Faraone et al., 2005), and associated with mood disorders, learning disorders, personality disturbances and substance abuse into adulthood (Biederman et al., 2006; Biederman et al., 2012), which could potentially represent a barrier for taking part and filling in all these questionnaires. Furthermore, the selection of participants into the preschool ADHD study was unlike a randomly selected sample based on high ADHD traits, thus implying that findings cannot be generalized to the general population, but only to an “ADHD-high-risk-population”.

In study one, we examined the co-occurrence of ADHD, ODD and CD. Comorbidity might occur in a study population because of selection, “sampling bias model”, or “Berkson bias” (Krueger & Markon, 2006). It may also be caused by an external variable, or set of variables, that create spurious associations between disorders, “the spurious association model”. According to “the population stratification model”, co-morbid cases occur because distinct liabilities for two disorders segregate non-randomly in the population, and because there are a combination of risk factors more commonly observed in certain groups than others (e.g. socioeconomic status) (Krueger & Markon, 2006; Westreich, 2012). Due to a predominance of boys and greater symptom severities, Berkson’s bias could represent a problem in this present “high-risk sample”. We therefore assume that the odds of a co-occurrence of ODD and CD in this sample may have turned out higher than in an epidemiological sample, though lower than for clinically referred children.

The exclusion criteria do not include major mental health conditions other than high scores on autistic traits, so we have not excluded children with anxiety, depression or pediatric bipolar disorder. However, the sampling procedure was based on ADHD traits and the proportion of children with other psychiatric conditions may not be representative for the general population, including ODD and CD. ODD has been found to represent a complex, multidimensional category capturing a wide range of psychopathology, which implies negative emotionality and dysregulation (Stringaris & Goodman, 2009a), while children with ODD are found to be at risk for later development into emotional disorders (August, Realmuto, Joyce, & Hektner, 1999; Boylan et al., 2007; Lahey et al., 2009). Although the sampling procedures included a number of children with symptoms of ODD and CD, they did not include comparison groups of children with ODD and CD symptoms without high ADHD

traits, which possibly could have attenuated our estimated comorbidity rates. Nonetheless, the selection procedure made it possible to study a large number of children with an increased risk for ADHD within the available practical and financial resources. For this reason, the oversampling gave the studies enough power to investigate subtypes of ADHD, the co-occurrence of ODD and CD separately, sex-differences and impairment related to various functional areas.

In Study II, the selection of participants with a higher SES could also influence the parents' ratings of functional level associated with symptoms of ADHD. The underrepresentation of young mothers, mothers living alone and those with more than two children could potentially make us underestimate the perceived experience of burden associated with a child's ADHD and/or behaviour problems.

In Study III, the estimated risk associations were subjected to a higher SES and subsequently lower risks for several exposures among participants than the general population (Nilsen et al., 2009; Nilsen et al., 2013). Hence, non-random attribution may have influenced our results, as participating mothers were better educated, co-habiting and older than those lost to follow-up in both the MoBa sample and the preschool ADHD study. Because attrition has been found to be predicted by more social disadvantages, which are shown to be associated with behavioural problems, children with severe difficulties are probably underrepresented in our sample. In a similar line of reasoning, the reported risks associations in this study were most likely attenuated.

It may be that the well educated and well-organized participating sample had a healthier lifestyle throughout pregnancy, with fewer women who smoked or consumed alcohol, and who were less susceptible to experience anxiety, depression or obstetric complications. Our data also showed that higher maternal age, higher maternal educational level and breastfeeding duration were strongly positively correlated, but negatively related to both predictors and outcome measures.

### 5.2.2 Clinical assessments

There are primarily two issues that may introduce information bias in these studies, namely biased diagnostic criteria and rater bias.

Diagnoses were based on a structured interview, the "Preschool Age Psychiatric Assessment" (PAPA), which assesses symptoms and psychiatric disorders based on parents' reports, and has been found reliable for preschool children (Egger et al., 2006; Egger & Angold, 2004). A growing amount of evidence supports that symptom clusters and behavioural problems might

represent an early onset of disorders, which are also possible to identify by age-modified diagnostic criteria and categorical diagnostic constructs during the preschool period (i.e. between 1.5 to 6 years of age) (Egger et al., 2006; Keenan et al., 2007; Keenan et al., 2011; Lahey et al., 1998; Lahey et al., 2004; Lahey et al., 2006). The predictive validity of ADHD, ODD and CD symptoms has been found moderate for 4-year-old preschool children (Keenan et al., 2011; Lahey et al., 2006). A most recent study on the predictive validity of CD in 3-year-old children showed that initiating fighting, stealing and breaking/destroying things predicted CD symptoms at the age of 6 above and beyond for ODD and ADHD. In addition, baseline CD symptoms also predicted subsequent ADHD and ODD (Rolon-Arroyo et al., 2014).

Even though the PAPA has been deemed reliable for preschool children, it has been found to be difficult to establish a diagnosis of ADHD in children younger than the age of 4 or 5 years. Therefore, the children in this study may be too young to receive a formal diagnosis. Using the existing nosology could lead to both an over- and under-identification of disorders in preschool children (Wakschlag et al., 2007; Wakschlag, Tolan, & Leventhal, 2010; Wakschlag et al., 2012). This is especially problematic for the ADHD inattentive subtype, in which the low rates of inattentiveness (Bendiksen et al., 2014b; Bendiksen et al., 2014a) are in accordance with most findings from both community-based and clinically-based large preschool samples (Egger & Angold, 2006; Egger et al., 2006; Posner et al., 2007; Wichstrom et al., 2011), which may point towards an under-identification of inattentiveness in younger children. Inattentiveness has been found to predict persistence and further difficulties among young children with symptoms of ADHD (Lahey et al., 2004; Lahey et al., 2005; Lahey et al., 2006). We also found that children with inattentive symptoms were significantly less impaired by symptoms than those with combined symptoms, but they were also rated as less impaired than those with ADHD-HI. Findings could indicate that parents place less emphasis on inattentiveness, which represents a major challenge for work on the early identification of ADHD. Diagnostic criteria might not be developmentally sensitive enough to effectively capture early significant inattentive symptoms as they present in preschool children (Chacko et al., 2009). The capacity for focused attention probably gradually develops during the preschool period. Moreover, requirements for the attention capacity may be more modest for preschool children compared to older children. Thus, a reconsideration of the existing diagnostic criteria for ADHD in young preschool children may be required in order to capture these features at an earlier stage of development. Such a modification could be done by lowering the symptom threshold for



inattentive symptoms or by modifying the existing criteria into more developmentally relevant and appropriate tasks for this age group. Some preschool studies have based their reports on symptoms and ignored the impairment criterion when a diagnostic decision was made, while still others have considered the presence of impairment at a cut-off level below the 50<sup>th</sup> percentile, or not reported the actual level of functional impairment at all (Egger & Angold, 2006; Lavigne et al., 1998b; Lavigne et al., 1998a; Wichstrom et al., 2011). In an attempt to overcome these problems, we used dimensional measures of both symptom counts and impairment scores, in addition to categorical diagnostic symptom groups and different cut-off levels for impairment. Impairment related to functional areas such as learning, play and peer relationships was generally low among these young children with clinical levels of ADHD symptoms compared to previous reports from school-aged children (Coghill et al., 2006; Wille, Bettge, Wittchen, & Ravens-Sieberer, 2008). Our findings may therefore indicate that some of these functional areas are developmentally inappropriate for the assignments in younger preschoolers, at least as rated by parents. On the other hand, children with ADHD symptoms at clinical levels were considerably more debilitated in these domains than those with subclinical ADHD symptoms. The second possible problem of information bias concerns rating bias, as both symptoms and impairment scores were based solely on parents' ratings. Several problems may be associated with solely relying on one source for information: First, clinical diagnostic decisions are based on the assumptions that symptoms and impairment are related but separate constructs, in which impairment is meant to be an external validation of a disorder in order to avoid tautology (Pickles et al., 2001), but this does not necessarily hold true when the same rater evaluates both facets as in the second paper. Second, parental rater bias might contribute to increased rates of co-occurrence between ADHD, ODD and CD (Abikoff, Courtney, Pelham, Jr., & Koplewicz, 1993; Angold, Costello, & Erkanli, 1999). There is a general agreement among researchers and clinicians that information should be gathered from multiple informants, but the associations between teachers and parents ratings have been found to be weak to moderate in samples of both school-aged children (Wolraich et al., 2004; Achenbach, Edelbrock, & Howell, 1987) and preschoolers (Berg-Nielsen, Solheim, Belsky, & Wichstrom, 2012; O'Neill, Schneiderman, Rajendran, Marks, & Halperin, 2013). Disagreement between raters may reflect genuine differences in the behaviours observed across settings (Achenbach & Ruffle, 2000) or biases, thereby inflating parents- or teachers ratings in different ways (Hartung et al., 2006; Sayal & Taylor, 2005). Information from teachers would probably better reflect the true variance of children's behaviours in structured learning and play settings in the kindergarten, as well as

the evaluation of impact on areas other than those emphasized by parents. In the ADHD study, questionnaires were available from both parents and teachers, but two different checklists were used in this study and differences in coding did not allow for direct comparisons of the dimensional measures. Because parent's ratings from the structured interview gave the best dimensional and complete information, this was chosen, which corresponds to several other large preschool studies (Egger & Angold, 2006; Lavigne et al., 2009; Wichstrom et al., 2011). Parents' ratings have largely been found to be valid independent predictors of severity and a diagnosis of ADHD in preschoolers at follow up (Berg-Nielsen et al., 2012; O'Neill et al., 2013). However, it is important to bear in mind that the ratings, such as the impairment measures for younger children, are likely to be affected by parents' own tolerance or mental state, as well as reflecting the impact children's symptoms have on others (Jucksch et al., 2011).

For the third paper, perinatal maternal anxiety and depression was measured by SCL-5, a short version of the Hopkins symptom checklist assessing symptoms of anxiety and depression (Hesbacher et al., 1980). The psychometric properties of this short form have been validated in the general population (Strand, Dalgard, Tambs, & Rognerud, 2003), but not for pregnant women. However, we found an acceptable internal consistency for the SCL-5 scale in this sample, as well as for the 3-item subscale of maternal symptoms of anxiety and the 2-item subscale of maternal symptoms of depression. We also validated the post-natal depression scores against the "Edinburgh Postnatal Depression Scale" (EPDS) (Cox et al., 1987), which is a widely used instrument for these assessments.

The assessment of maternal perinatal symptoms of anxiety or depression did not include the last 10 weeks of gestation, which could potentially represent a bias for our estimation of timing effects.

It is always a possibility in a non-experimental/observational study that the observed associations could arise as a consequence of confounders and unmeasured risk factors or correlates. We did not examine parental psychopathology other than maternal symptoms of anxiety and depression, and we did not include the assessments of the parent-child relationship, early childhood separation from parents, nutrition, toxins (e.g. lead, pesticides, polychlorinated biphenyls) or medications (prescribed or non-prescribed) during pregnancy. Nevertheless, a variety of covariates were adjusted for, and the associations of still more potential risk correlates or risk factors were initially explored but not included because no significant associations were established with the main predictors (i.e. SCL-5 scores), or with any of the outcome measures.

Examinations of the relative contribution of genetic versus environmental influence and the potential influence by gene-environment interaction were not possible in this third study. It is hence unclear whether the possible programming effects of prenatal maternal anxiety or depression are moderated by genetic disposition, as most studies have focused on a limited set of polymorphisms (Braithwaite et al., 2013). The rather profound attenuation of the effects of PPNA/PPND by the maternal emotional state preconception on CD symptoms may suggest a genetic predisposition. ADHD and CD are both found to have high heritability rates, which imply both genetic risk and the effects of gene-environment interplay (Rhee & Waldman, 2002; Thapar, Cooper, Eyre, & Langley, 2013). Biological or psychosocial environmental risk factors could interact with underlying genetic influences and lead to an increased cumulative risk for offspring psychopathology (Pemberton et al., 2010).

## **5.3 Implications**

### **5.3.1 Clinical implications**

At the clinical level of disorders, a co-occurrence of ODD and CD was present in approximately 40% of children with ADHD, which is somewhat lower than corresponding rates in school-aged children. However, co-occurring patterns were similar to those observed in older children. A number of longitudinal studies have shown that these comorbidity patterns worsen the prognosis of ADHD (Connor, Steeber, & McBurnett, 2010; Biederman et al., 2008a; Biederman et al., 2008b); thus, diagnosing the co-occurrence of behaviour disorders in children with ADHD adds information that is relevant for treatment planning and early intervention efforts because they represent a long-term major mental health concern. Early identification and intervention could therefore potentially lessen the burden and alter the course of these disorders (Sonuga-Barke et al., 2011).

By using structured clinical assessments, it is possible to identify some significant symptom patterns, whether alone or in combination, in 3-year-old children. However, the identification may be challenged by the immense normal variations in behaviours. In line with most previous preschool studies, inattentiveness was difficult to identify unless hyperactive-impulsive symptoms were present at the same time. Among children with co-occurring CD, findings indicated more severe inattentiveness and a higher proportion of children presenting with ADHD-C than among those with co-occurring ODD. Consequently, ADHD-C and concurrent early CD might represent a particularly high risk for the development of chronic difficulties in these young children.

A systematic assessment of impairment of ADHD is also necessary in preschool children, and we found that parental ratings of functional impairment provided useful information about early problems within families. However, young preschoolers were mostly not severely debilitated by their symptoms, and impairment did not occur in areas of learning, play or friendship, which are commonly observed in older children. Rather than being linked to specific settings, parental ratings of functional impairment probably reflected a more global impact of symptoms on daily functioning across several settings in these young children. Parents' perception of relational difficulties within the family, and that their young children's behaviour was a burden for the families, may well indicate emerging coercive cycles, and hence be important targets for early prevention and intervention strategies. The assessment of impairment potentially identified the young children who were at the greatest risk for further difficulties, although symptoms of inattentiveness and CD were not recognized as being impairing by parental ratings.

The reports on sex differences from clinical samples of ADHD may represent an artefact of referral bias, rater bias or halo effects, and more work has to be done in order to reduce this gap in paediatric populations. The identification of girls with ADHD needs to be improved since they most likely receive inadequate treatment.

Maternal anxiety and depression are quite common mental health problems during the peripartum period, and we found moderate but quite similar effects of maternal anxiety and depression, which support a broad phenotype in which the exposure of maternal anxiety as well as depression may represent a risk for symptom development of ADHD and ODD in young children. There were no significant timing effects during the peripartum period, which could imply that the involved mechanisms may include both foetal programming effects and the consequences of postnatal depression, and which might also impair maternal sensitivity and result in disturbed mother-child interactions. Improving women's mental health during childbearing and birth could represent one of the most feasible strategies for modifying these potential risks for mental health problems in children.

### 5.3.2 Implications for future research

Further research on underlying mechanisms and genetics may benefit from the description of an early presentation and coherence of ADHD, ODD and CD before social and academic problems interfere with these characteristics.

The identification of inattentiveness when hyperactive-impulsive symptoms are not present at the same time seems particularly challenging in young preschool children and

should be recognized in the research on preschool children. Requirements for the attention capacity may be more modest for preschool children compared to older children, but the capacity for focused attention may probably also gradually develop during the preschool period. Thus, a reconsideration of the existing diagnostic criteria for ADHD in young preschool children seems to be required. A modification could be done by lowering the symptom threshold for inattentive symptoms, or by modifying the existing criteria into more developmental appropriate tasks for this age group. Clinicians administered cognitive tests could potentially also contribute to a better understanding of how to assess attention problems in younger children and the way the existing diagnostic criteria could be modified for this age group.

The distinction between ODD and CD in preschoolers with ADHD should receive more attention, and research on underlying cognitive and neurobiological mechanisms is needed in order to understand the potential distinctions or similarities. ODD and CD are assumed to have different developmental courses, also when concurrent with ADHD, and may well require different approaches compared to intervention strategies.

The study design used for the investigation of perinatal risk factors represents some challenges posed by disentangling the complex patterns of highly intercorrelated genetic predispositions, prenatal, obstetric and postnatal environmental putative risks and their relationships to psychopathology in children. Large prospective birth cohorts might be suitable, especially where information of the numerous possible confounding factors is included, but might be subjected to an inadequate and less reliable assessment of psychopathology in children if evaluated by the use of checklists only. Preconceptions of a maternal emotional state, which could represent common genetic effects, significantly confounded the effects of perinatal maternal anxiety and depression on symptom loads. A genetic sensitive study design of twins or siblings may therefore be needed to address the contribution of genetics or gene-environment interplay.

As previously discussed, sex does not appear to alter the risk associated with the familial transmission of ADHD or its comorbid conditions, which implicates that acquired factors associated with the development of ADHD may account for the apparently higher overall prevalence rates in boys compared with girls. In our study, boys were found more susceptible to ADHD following perinatal maternal symptoms of anxiety, while the likelihood of ODD symptoms was most pronounced for girls. For this reason, when investigating risk factors and their associations with ADHD and its frequent comorbid conditions, the examination of sex-

differences could provide important clues in understanding the differences in symptom presentations of these disorders in boys compared with girls.

## **5.4 Conclusions**

Some important differences in co-occurring patterns of ODD and CD in children with ADHD were identified, as the presence of ADHD predicted CD more strongly than ODD even if concurrent ODD occurred more frequently. Furthermore, children with co-occurring CD had a significantly greater severity of inattentiveness and a higher proportion with combined ADHD symptoms than those with co-occurring ODD. The impact of clinical symptoms of ADHD was primarily in areas of family functioning. Although children with ADHD-C and those with ADHD and co-occurring ODD were rated as significantly more impaired than other subgroups, the majority of children with symptoms of ADHD were only mildly- to moderately impaired.

The implications of the main findings in this thesis are that preschool children with symptoms of ADHD and concurrent ODD and CD present with many of the same clinical features as their older counterparts, though with a few exceptions; inattentive symptoms were not easily identified, and they are far less debilitated in most settings.

We found an increased risk of offspring ADHD and ODD symptoms posed by perinatal maternal symptoms of anxiety and depression, which exerted quite similar effects and represented relatively stable predictors across gestation and until six months postnatally. The impact of maternal symptoms of anxiety and depression was attenuated from the covariate adjustments, thereby suggesting that these relationships depend on a number of other risk factors.

Perinatal maternal anxiety was related to an increased symptom level of ADHD in boys only, while girls whose mothers had symptoms of anxiety or depression during the perinatal period were more susceptible to symptoms of ODD. Sex-differences related to ADHD and/ or co-occurring behaviour disorders in preschool children were generally minor, but boys presented more often with the combined subtype of ADHD, and boys with co-occurring ODD were significantly more impaired than girls.

The increased understanding of how environmental risk factors, and among these, perinatal maternal anxiety and depression, are related to frequently occurring and comorbid mental health conditions could also help build theoretical knowledge that has implications for both prevention efforts and future research.

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