

Associations between parental psychopathology and markers of severity in children with ADHD

Sharifah Shameem Syed Salim Agha

PhD 2017



Supervisors: Dr Kate Langley, Professor Anita Thapar, Professor Stanley Zammit

Acknowledgements

First and foremost I would to express my sincerest gratitude to my supervisors, Dr Kate Langley, Professor Anita Thapar and Professor Stanley Zammit for their invaluable advice, immense knowledge, extensive support and encouragement throughout. Thank you especially to Kate, for the constant guidance, patience and motivation during the course of my PhD. I am really grateful for this opportunity.

Special thanks to all my colleagues in the Child and Adolescent Psychiatry Section for providing such a stimulating and pleasant working environment, specifically Lucy Riglin, Naomi Warne, Miriam Cooper, Jo Doherty, Ruth Sellers, Caroline Warren, Valerie Russell, Katie Lewis and Gemma Lewis for their help, advice and moral support. I am also grateful to Olga Eyre and Rhys Bevan Jones for their helpful discussions, advice and continuous supply of hot chocolate and treats. Thank you also to all the families that have taken part in the research study, for without their contribution this research would not be possible. I would also like to express my gratitude to the Cwm Taf Health Board for their support.

Finally, I would like to thank my family and friends who have all been so supportive and understanding. I am especially grateful to my mother, father and sisters who have always inspired me and always gone out of their way to support me alongside endless prayers and words of encouragement. Last but not least, to my dear husband and children, Taufiq, Nabil and Hadiya, thank you for your love, patience, never-ending support and for always being there for me throughout this journey.

Thesis Summary

Associations between parental psychopathology and markers of severity in children with ADHD

Attention Deficit Hyperactivity Disorder (ADHD) is a disabling neurodevelopmental disorder that has major adverse consequences for individuals and their families. Although ADHD is recognized to be a familial and heritable disorder, little is understood about the relationship between parental psychopathology and variation in the clinical and cognitive presentations of children with ADHD.

The first aim of this thesis, which is based on a clinical sample of 570 children with ADHD, was to investigate the association between parental ADHD (based on diagnostic symptom criteria) and offspring clinical features. Results suggest parental ADHD indexes higher risk for a more severe clinical presentation of ADHD in children and higher levels of family conflict. The second aim was to investigate the influence of maternal ADHD and depression on children's clinical presentation outcome, on average two and half years after initial assessment. Maternal depression, but not maternal ADHD, was found to predict an increase in child conduct symptoms, but neither maternal depression nor maternal ADHD contributed to ADHD symptom levels, after adjusting for conduct symptom severity at baseline. Finally the third aim was to assess the role of parental psychopathology (ADHD or depression) in contributing to cognitive variation in children with ADHD. Parent ADHD but not parent depression was found to be associated with lower scores on tasks assessing working memory and set shifting abilities.

Overall, these findings extend the understanding of the association between parental psychopathology and phenotype variation in children with ADHD. It indicates that children with more severe clinical presentations and greater pre-frontal cognitive impairments are more likely to have a parent with mental health difficulties. This highlights the importance of considering parent mental health during clinical assessment which can have important implications when considering families' engagement with services, treatment and intervention strategies as well as planning the intensity of child follow-up.

Publications resulting from work in this thesis

Agha SS, Zammit S, Thapar A, Langley K. Are parental ADHD problems associated with a more severe clinical presentation and greater family adversity in children with ADHD? *European Child Adolescent Psychiatry*. 2013 Jun; 22(6):369-77.

Agha SS, Zammit S, Thapar A, Langley K. Maternal psychopathology and offspring clinical outcome: a four year follow-up of boys with ADHD. *European Child Adolescent Psychiatry*. 2016 July; 26(2):253-262.

Agha SS, Zammit S, Thapar A, Langley K. Parent psychopathology and neurocognitive functioning in children with ADHD. *Journal of Attention Disorders*. 2017 July; Epub ahead of print.

Roles and Responsibilities within the Study of ADHD Genes and Environment (SAGE)

The data presented in this thesis is from a clinical sample of children with ADHD recruited into the Study of ADHD Genes and Environment (SAGE) from 2007 until 2011.

I joined the study in 2008 and contributed substantially to the project. In this section some of my roles and responsibilities within the research project have been outlined.

I was considerably involved in the recruitment of research participants for the study which included organising and setting up of recruitment strategies / systems between research study and various clinics and CAMHS centres. I contributed to data collection for the sample which included administering questionnaires, cognitive tasks, conducting interviews and obtaining genetic samples from families. I interviewed parents, teachers and children of approximately 160 families. Additionally, I assisted in training research assistants and students working on the project.

Throughout the project, I organised and managed research recruitment records including updating recruitment figures with the UKCRN and central portfolio management system. I was also responsible for sending regular progress reports for Research & Development departments across the UK. I also assisted with writing ethics applications, amendments and extensions.

I contributed substantially to the coding of data as well as data entry and data cleaning. I also helped with the management and recording of blood and saliva samples obtained from families. I was involved in creating and checking algorithms (syntax) to derive main core variables for the study and participated in inter-rater reliability ratings of child ADHD and conduct disorder symptoms and diagnoses.

In 2013, a subset of participants that took part in the SAGE study was invited to take part in a follow-up study, where I was involved in recruitment and managing sample databases. I also contributed substantially to the cleaning of the data, deriving of main clinical variables and data analysis.

Overall, I have contributed to publications on the main project aims as well as additional publications related to supplementary questions. Additionally I was involved in the dissemination of project research findings to the Child and Adolescent Mental Health Services (CAMHS) network meetings and other various parent groups. I also contributed to the production of newsletters and co-organised a public engagement event for families who participated in the research study. Finally, I derived and cleaned the main variables (parental psychopathology, cognitive measure and family environment measures) that were used in this thesis.

Throughout my time on the project, I observed that most parents could identify with their children's symptoms. I also observed how chaotic their day to day life seems to be although this was not the case for all families. As a parent, I could relate to this and was interested in how having a parent with mental illness particularly, ADHD, might influence presentation or development of symptoms in their children. This formed the motivation for me to undertake a part time PhD program alongside my full time job. I allocated two days a week for each academic year. This experience has been really valuable and has certainly helped me to develop further as a researcher.

Data collection for the samples included in this thesis as well as deriving of some generic variables (e.g. ADHD diagnosis) was a team effort. All of the work relating to the research questions in this thesis including deriving variables, data analyses, interpretation and writing was undertaken by me.

Contents

Chapter 1	1
Introduction	1
Attention Deficit Hyperactivity Disorder (ADHD)	1
1.1 What is ADHD?.....	1
1.2 What indexes severity of ADHD?	15
1.3 Parental psychopathology	25
1.4 Family Environment	34
1.5 Summary	38
1.6 Study Aims.....	39
Chapter 2	40
Methods	40
Chapter description	40
2.1 Study of ADHD Genes and Environment (SAGE)	41
2.1.1 Recruitment procedure.....	41
2.1.2 Inclusion and exclusion criteria.....	42
2.1.3 Assessment and Measures.....	45
2.1.4 Sample characteristics and demographics.....	58
2.2 Follow up sub-sample	62
2.2.1 Recruitment procedure.....	62
2.2.2 Assessment and measures at Time 2	62
2.3 Summary	63
Chapter 3	64
Are parent ADHD problems associated with a more severe clinical presentation and greater family adversity in children with ADHD?	64
Chapter description	64
3.1 Introduction	65
3.2 Study Aims	68
3.3 Methods	69
3.3.1 Sample.....	69
3.3.2 Measures.....	69
3.3.3 Analysis	71
3.4 Results	73
3.4.1 Child Clinical Presentation	74
3.4.2 Family environment	77
3.4.3 Childhood-only parental ADHD vs adult parental ADHD	80
3.4.4 Further analysis with social class as a covariate	85
3.5 Discussion	87
3.5.1 Limitations.....	91
3.5.2 Clinical implications.....	94
3.6 Conclusion	94
Chapter 4	96
Maternal psychopathology and offspring clinical outcome: a follow-up of boys with ADHD	96
Chapter description	96

4.1 Introduction	97
4.2 Study Aims	99
4.3 Method	100
4.3.1 Sample.....	100
4.3.2 Measures.....	100
Analysis	102
4.4 Results	104
4.4.1 Mother ADHD and offspring outcomes	106
4.4.2 Mother depression.....	107
4.4.3 Further analysis with social class as covariate	110
4.5 Discussion	111
4.5.1 Limitations.....	116
4.5.2 Clinical Implications	119
4.6 Conclusion	120
Chapter 5	121
Parental psychopathology and neurocognitive functioning in children with ADHD	121
Chapter description:	121
5.1 Introduction	122
5.1.2 ADHD and neurocognitive deficits	122
5.1.3 Parental psychopathology and neurocognitive deficits in ADHD offspring: previous evidence	124
5.2 Study aims	127
5.3 Methods	128
5.3.1 Sample.....	128
5.3.2 Measures.....	128
5.3.3 Analysis	131
5.4 Results	132
5.4.1 Correlations between child clinical and neurocognitive measures	133
5.4.2 Parent ADHD and offspring neurocognitive outcomes.....	135
5.4.3 Parent Depression and offspring neurocognitive outcomes	140
5.4.4 Sensitivity analysis	140
5.4.5 Further analysis with complete families	144
5.5 Discussion	145
5.5.1 Limitations.....	149
5.5.2 Clinical implications.....	150
5.6 Conclusion	152
Chapter 6	153
Discussion	153
6.1 Summary of findings	153
6.2 Interpretation of findings	155
6.2.1 Parent ADHD	155
6.2.2 Mother depression.....	159
6.2.3 Neurocognitive factors – alternative index of severity.....	160
6.3 Implications	161
6.4 Strengths of studies within this thesis	162
6.5 Limitations	163
6.6 Future directions	169

6.7 Conclusions	172
References	173
Appendices.....	206
Appendix 3.1: Associations between mother ADHD (using DSM-5 criteria) and child clinical presentation.....	206
Appendix 3.2: Associations between father ADHD (using DSM-5 criteria) and child clinical presentation.....	206
Appendix 3.3: Associations between mother ADHD (using DSM-5 criteria) and family environment.....	207
Appendix 3.4: Associations between mother ADHD (using DSM-5 criteria) and family environment.....	207
Appendix 4.1 Baseline associations for chapter 4	208
Appendix A: Parent questionnaire on childhood ADHD symptoms	209
Appendix B: Parent questionnaire on childhood conduct symptoms	210
Appendix C: Parent questionnaire on current ADHD symptoms.....	211

Index of Tables

Table 2.1:	ADHD diagnostic criteria for DSM-IV and DSM-5 ADHD	49
Table 2.2:	Demographics and characteristics of families (n=570)	58
Table 2.3:	ADHD diagnosis and comorbidity in children	60
Table 2.4:	Rates of parent ADHD and depression in the SAGE sample (n=570)	60
Table 3.1:	ADHD problems in mothers and fathers	73
Table 3.2:	Mother ADHD and child clinical presentation	75
Table 3.3:	Father ADHD and child clinical presentation	76
Table 3.4:	Associations between mother ADHD and family environment	78
Table 3.5:	Associations between father ADHD and family environment	79
Table 3.6:	Means and comparison of parent ADHD group in those with complete information on both mothers and fathers n= 96	80
Table 3.7:	Mother and father childhood-only ADHD and child clinical presentation	81
Table 3.8:	Mother and father childhood-only ADHD and family environment	82
Table 3.9:	Comparisons between mother childhood-only vs. mother persistent ADHD	83
Table 3.10:	Comparisons between father childhood-only ADHD vs father adult ADHD	84
Table 3.11:	Comparison of estimates for associations unadjusted and adjusted for social class	86
Table 4.1:	Comparison of Time 1 measures between those who took part at both times vs those in Time 1 only	105
Table 4.2:	Associations between maternal psychopathology and (a) child ADHD symptoms at Time 2 and (b) child conduct symptoms at time 2	108
Table 4.3:	Mean scores for child ADHD symptom change scores and child conduct symptom change scores	109
Table 4.4:	Further adjustment for low social class: associations between mother psychopathology and child ADHD and CD symptoms at Time 2	110

Table 5.1:	Correlation matrix between child clinical symptoms and neurocognitive tasks	134
Table 5.2:	Associations between parent ADHD (mother/father) and child neurocognitive performance	136
Table 5.3:	Associations between parent ADHD (mother/father) and child neurocognitive performance adjusting for covariates (low parent education status, low social class, child age, child IQ, ADHD severity, and conduct symptom severity)	137
Table 5.4:	Associations between parent depression (mother/father) and child neurocognitive performance	138
Table 5.5:	Associations between parent depression (mother/father) and child neurocognitive performance adjusting for covariates (low parent education status, low social class, child age, child IQ, ADHD and conduct symptom severity)	139
Table 5.6:	Associations between mother ADHD and child neurocognitive performance	141
Table 5.7:	Associations between father ADHD and child neurocognitive performance	142
Table 5.8:	Associations between mother depression and child neurocognitive performance	143
Table 5.9:	Comparison of neurocognitive task performance between children from complete families (information from both parents) and families where information is available for one parent only.	144

Index of Figures

Figure 2.1:	Flowchart of recruitment into the SAGE and follow-up sub sample (Time 2)	44
Figure 2.2:	IED test screen example showing two simple colour-filled shapes (Taken from CANTABeclipse Test Administration Guide, manual version 3.0.0, 2006 Cambridge Cognition Limited)	54
Figure 2.3:	IED test screen example showing two overlapping dimensions (Taken from CANTABeclipse Test Administration Guide, manual version 3.0.0, 2006 Cambridge Cognition Limited)	55
Figure 2.4:	The CGT task screen for the decision stage (Taken from CANTABeclipse Test Administration Guide, manual version 3.0.0, 2006 Cambridge Cognition Limited)	57
Figure 2.5:	The CGT task screen for the gambling trial. (Taken from CANTABeclipse Test Administration Guide, manual version 3.0.0, 2006 Cambridge Cognition Limited)	57

Chapter 1

Introduction

Attention Deficit Hyperactivity Disorder (ADHD)

1.1 What is ADHD?

Attention deficit hyperactivity disorder (ADHD) is a common but complex neurodevelopmental disorder affecting 3.4% of children (Polanczyk *et al.*, 2015). It has a significant impact on the lives of children and their families, which has far reaching influences with a range of negative outcomes (Deault, 2010). ADHD has often been associated with difficulties in school and friendships, disturbances in family relationships and marital functioning, lower educational attainment and higher rates of unemployment (Harpin, 2005; Barkley *et al.*, 2006). ADHD is also considered a major public health problem (Lesesne *et al.*, 2000), as it is one of the most frequent reasons for referral and follow-up in child and adolescent mental health clinics (Salmon and Kemp, 2002) and is a financial burden to society and families (Polanczyk *et al.*, 2007; Holden *et al.*, 2013; Telford *et al.*, 2013). It has been reported that the economic burden of ADHD is not limited to health care services but also extends to education, social and youth justice services (Ford *et al.*, 2008). In the UK an annual total cost of £670 million is spent on treatment of ADHD (Telford *et al.*, 2013). Preschool children with high levels of hyperactivity in the general population have been found to have 17 times higher than average costs per annum compared to children without hyperactivity problems, specifically mental health, education, social services and

criminal justice costs. This difference in cost was found to be even greater for boys and those with conduct problems (Chorozoglou *et al.*, 2015).

1.1.1 Definition

According to the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) (American Psychiatric Association, 2000) or more recently the DSM-5 (American Psychiatric Association, 2013), ADHD is characterised by impairing levels of two core clinical features/dimensions, which are inattention and hyperactivity-impulsivity. ADHD symptoms usually begin in childhood, should be present for more than six months and cause impairment and difficulties in at least two settings (e.g. home, school or leisure activities). An individual may present with either patterns of both inattentive and hyperactive-impulsive symptoms (combined type) or one symptom pattern may predominate (inattentive-type or hyperactive/impulsive type). ADHD is also known as Hyperkinetic Disorder in the International Classification of Diseases 10th Edition (ICD-10) (WHO, 1993). These classification systems have slightly different ways of establishing diagnosis but the core clinical symptoms are similar in both. The ICD-10 criteria are more stringent; for example, children must show symptoms in all three clinical dimensions (Hyperactivity, Inattention and Impulsivity) whereas in DSM a diagnosis is possible if the child has enough symptoms in just one dimension. For ease of interpretation and comparison across studies, the DSM criteria are used throughout this thesis as it is more widely used in research. This thesis utilises both DSM-IV and 5 as work contributing to this thesis started in 2011 prior to the

publication of DSM-5 in 2013. Further details of the diagnostic criteria used in each chapter are explained in section 2.1.3 in chapter 2.

The DSM-IV and DSM-5 diagnostic criteria for ADHD are mostly similar, although there are three main differences. These changes reflect the fact that ADHD has increasing recognition as a disorder affecting individuals across the lifespan and evidence that ADHD can continue and persist into adulthood (Asherson *et al.*, 2016). The first change is the age of onset for presence of ADHD symptoms is now before age 12 years in DSM-5 instead of age 7 years as was previously set in DSM-IV. Whilst previously not specified, DSM-5 has included specific criteria for older adolescents (aged 17 years and older) and adults where a minimum of five symptoms (rather than six) are required for diagnosis (American Psychiatric Association, 2013). In addition there are also descriptions and examples of how symptoms may manifest in adults. Previously in DSM-IV, ADHD could be defined according to subtypes; combined, inattentive and hyperactive/impulsive subtype. Given the evidence that these ADHD subtype distinctions are not stable across time (Lahey *et al.*, 2005; Willcutt *et al.*, 2012), DSM-5 does not emphasise the distinction between ADHD subtypes but instead describes them as different presentation of the disorder reflecting change in how the disorder might present in individuals over time (Thapar and Cooper, 2015). These alterations aim to make it easier to identify individuals first presenting to ADHD services in adulthood and are generally acceptable and useful in clinical settings (Coghill and Seth, 2011; Epstein and Loren, 2013). Whilst the impact of these changes needs to be explored in more detail, there are suggestions that such changes may increase the reported prevalence of ADHD (Dalsgaard, 2013; Vande Voort *et al.*, 2014). Despite the slight increase in ADHD prevalence, these studies also found that clinical correlates and

risk factors did not significantly differ between children with symptoms before age 7 and 12 (Polanczyk *et al.*, 2010; Vande Voort *et al.*, 2014) except that children presenting with a later onset (by age 12 years) were more likely to be from an ethnic minority and lower income families. This indicates that the age of onset extension leads to recognition of more children with ADHD symptoms that are in need of care and this further supports the age of onset criterion in the DSM-5 (Polanczyk and Moffitt, 2014).

1.1.2 Causes of ADHD

Despite its clinical importance, the causes and pathophysiology of ADHD are not well understood. There is evidence to suggest that ADHD is a familial disorder and there is a strong inherited contribution to ADHD (Biederman *et al.*, 1992). Family studies of ADHD have found that first degree relatives of those with ADHD are 2 – 8 times more likely than relatives of unaffected individuals to have ADHD (Faraone *et al.*, 2005; Thapar *et al.*, 2012). However, the way in which ADHD is inherited is likely to be complex (Thapar *et al.*, 2013). Twin studies have shown that mean heritability estimates for ADHD are about 76% (Thapar *et al.*, 1999; Faraone *et al.*, 2005; Thapar and Cooper, 2015), which indicates that genetic and non-inherited / environmental factors and their interplay all play a role in the aetiology of the disorder (Thapar *et al.*, 2012).

Given the high heritability of ADHD, there has been much effort in the field to try and identify genes that are associated with the disorder (Thapar *et al.*, 2012). Evidence in terms of genetic risk suggests that there is no single gene that causes ADHD; instead it

is influenced by multiple genes (Thapar *et al.*, 2013). Multiple and different types of genetic variants have been identified to be associated with ADHD. One such type of genetic variation is known as a copy number variant (CNV); CNVs are defined as rare chromosomal deletions and duplications (Thapar and Cooper, 2015). A higher burden of large (>500kb) and rare (<1% frequency) CNVs have been found to be increased in ADHD cases compared to controls (Williams *et al.*, 2010, 2012). CNV's found with greater frequency in ADHD have been found in loci also implicated for schizophrenia and Autism Spectrum Disorder (ASD) (Williams *et al.*, 2010; Thapar *et al.*, 2012). This implies that ADHD may share some of the same biological basis as other neurodevelopmental disorders and this further strengthens the notion of ADHD being a neurodevelopmental disorder.

In addition to CNVs, common genetic variants have been found to play a role in the aetiology of ADHD (Thapar and Cooper, 2015). One approach to identifying common risk variants is to conduct a genome wide association study (GWAS). This is a 'hypothesis free' method which compares thousands of common genetic variants (single nucleotide polymorphism; SNPs) across the genome between cases and controls (Wray *et al.*, 2014). GWAS are advantageous as one is able to look at multiple variants simultaneously in an unbiased manner in contrast to candidate gene studies, where pre-specified genetic variants are investigated based on previous presumed knowledge of the trait aetiology of a particular disease. However, extremely large samples are needed to find evidence of association at genome wide levels of significance given that SNPs usually have very small effects on risk (Manolio *et al.*, 2009) and that GWAS associations are subject to rigorous corrections for multiple testing (Wray *et al.*, 2014). The initial findings from ADHD GWAS did not find any

genome wide significant findings for ADHD (Lesch *et al.*, 2008; Neale *et al.*, 2008; Neale, Medland, *et al.*, 2010; Neale, Medland, *et al.*, 2010; Hinney *et al.*, 2011; Stergiakouli *et al.*, 2012; Zayats *et al.*, 2015). The negative findings were likely to be due to small underpowered samples (Franke, Neale and Faraone, 2009). However recently, 12 genome wide significant associations were reported by the largest international collaborative study that brought together 18,000 ADHD cases and 35,000 controls (Psychiatric Genetics Consortium (PGC)-ADHD subgroup report, (International Society of Psychiatric Genetics (ISPG) meeting Toronto 2015). These results are still very recent, therefore it is too soon to understand what the implications of these findings are, but these results are promising and provide more clues into the underlying genetic aetiology of the disorder.

Another way of studying the role of common genetic variants is by generating composite measures of common genetic risk variants; polygenic risk score analysis. This involves summing an individual's load of multiple risk alleles from common variants across the genome (Wray *et al.*, 2014). Risk alleles are identified as alleles that show even modest evidence of association (association below a nominal significance level) with the disease in a discovery GWAS sample, weighted by the effect size of association in the discovery sample (Wray *et al.*, 2014). The presence of these risk alleles are then identified and summed in a separate (target) sample. The resultant polygenic risk score (PGRS) in the target sample can then be analysed, for example by comparing the PGRS between cases and controls. ADHD polygenic risk scores were found to be higher in subjects with ADHD compared to controls (Hamshere *et al.*, 2013). Another study which used polygenic risk scores derived from a general population sample for ADHD trait scores was found to predict ADHD diagnosis in a case

control sample (Stergiakouli *et al.*, 2015). These findings highlight that common genetic variants are involved in the genetic architecture of ADHD and that these effects are the same in cases and in the population which indicates that ADHD is a continuous trait. Whilst studies of rare and common variants like those described provide some information about the aetiology of ADHD, evidence from ADHD genetic studies suggest that there are many different ways in which genetic factors can contribute to risk of ADHD which demonstrates the complexity of the aetiology of ADHD. However, there is a lot more work needed to understand the specific genetic factors associated with ADHD and biological pathways that they affect (Langley and Thapar, in press)

Environmental factors also play a role in the aetiology of ADHD and there are several factors that have been found to be associated with ADHD. Identifying which environmental risk factors are causal is difficult as associations or correlations found do not necessarily imply causality (Thapar and Cooper, 2015). Observed associations can occur as a result of reverse causation (behaviour influencing the environment), selection bias, information bias or unmeasured confounding factors (Thapar *et al.*, 2013). One case in point is maternal smoking in pregnancy. Several pre- and perinatal factors such as maternal smoking, alcohol use and stress during pregnancy, have been found to be associated with ADHD (Mick *et al.*, 2002; Langley *et al.*, 2005; Glover, 2011) but one of the most frequently cited risk factors associated with ADHD is maternal smoking with an estimated odds ratio of 2.36 from a pooled analysis of evidence (Langley *et al.*, 2005). Although these are strong associations, there is some debate and uncertainty as to whether the association with ADHD is indeed causal. Natural experiments especially those with a genetically sensitive design suggest that associations between maternal smoking during pregnancy and ADHD in the offspring

may be due to confounding genetic factors (Thapar *et al.*, 2009). This indicates that some of these environmental exposures may have partly genetic origins but does not rule out the potential environmental risk. It is therefore important to note that evidence found for environmental risk factors should be interpreted with caution as there is still a lot to be understood about exactly how these different factors contribute to ADHD. Despite the uncertainty about their causal role in ADHD, factors such as smoking and alcohol use during pregnancy are still considered as generally harmful to other child health outcomes (Thapar *et al.*, 2012). As smoking in pregnancy is not causal, it is therefore not adjusted for in this thesis.

Studies of premature and low birth weight children have also found associations with ADHD symptoms, particularly with inattentive symptoms or ADHD inattentive subtype (Bhutta *et al.*, 2002; Groen-Blokhuis *et al.*, 2011). Once again, it is difficult to conclude if this is a causal risk factor for ADHD, though findings indicate that there is a need to be aware of increased ADHD risk in premature / low birth weight children (Thapar *et al.*, 2012).

Psychosocial adversities such as low income, low social class, adverse family environments, hostile parenting, marital discord or early neglect have been highlighted as important environmental risk factors for psychiatric disorders in children including ADHD (Scahill *et al.*, 1999; Thapar *et al.*, 2013). There is however no clear evidence that these psychosocial factors are causal. One main complexity arises from the direction of effects between psychosocial adversity and ADHD (Thapar *et al.*, 2013), for example family conflict may be a cause or consequence of ADHD symptoms. Longitudinal and twin studies have shown that child ADHD symptoms can impact on mother–son

hostility (Lifford, Harold and Thapar, 2008, 2009) and treatment of child ADHD symptoms improves mother-child relationships (Schachar *et al.*, 1987). However, one exception is exposure to severe early neglect, where evidence from a quasi-experimental study found that exposure to extreme social deprivation and neglect of children raised in Romanian orphanages was associated with inattention and overactive patterns of subsequent behaviour (Rutter *et al.*, 2007).

Other environmental factors like exposure to toxins (lead and polychlorinated biphenyl (PCBs)) (Nigg, 2008; Bouchard *et al.*, 2010; Eubig, Aguiar and Schantz, 2010) and nutritional deficiencies (magnesium, zinc and polyunsaturated fatty acids) or effects of sugar and artificial colourings have been implicated in ADHD (Kozielc and Starobrat-Hermelin, 1997; Arnold and DiSilvestro, 2005; Nigg *et al.*, 2012). However more evidence is needed to make firm conclusions about their role in causing ADHD (Thapar and Cooper, 2015).

On the whole, multiple genetic and environmental factors have been found to contribute to ADHD risk. However these factors are not independent of each other and the complex interplay between genes and environment are important in understanding ADHD. For example, gene-environment correlations are of relevance. Correlations between the parent genotype and environmental risk are known as passive gene-environment correlation. A parent with genetic predispositions will transmit risk genes to the child and also create the home environment that is influenced by their own heritable characteristics. On the other hand, genetically influenced attributes in children can also shape the environmental exposure by evoking responses. This is known as evocative gene-environment correlation. For example adoption and twin studies have found evidence of parent child hostility in adoptive parents of children who are genetically predisposed to ADHD symptoms (Lifford, Harold and Thapar,

2009; Harold *et al.*, 2013). The environmental risk (hostility) appears to be evoked by children's behaviour (State and Thapar, 2015). Therefore consideration of the role of gene-environment correlation is important when investigating genetic and environmental risk factors for disorders such as ADHD.

Overall, the evidence so far shows that there is no single risk factor that can cause or explain ADHD. Even though it is well established that ADHD is highly heritable, both inherited and non-inherited factors and their interplay contribute to the aetiology of ADHD. The complexity of ADHD aetiology is demonstrated by the multiple and different types of genetic and environmental risk factors that have been found to be associated with ADHD. There remains much to be understood about the aetiology of ADHD, necessitating research into this area. Furthermore, considering the complexity and heterogeneity associated with ADHD, we know that the majority of the risk factors identified have small effects sizes which make them hard to detect and requires investigation of a variety of different factors. Coupled with studies suggesting that many putative risk factors are not necessarily causal, there is still much work to be done.

1.1.3 Prevalence of ADHD

There have been many different prevalence estimates reported for ADHD ranging from 1% to 20% (Polanczyk *et al.*, 2007) and this is one factor that has led to debates about whether ADHD is a true disorder or a cultural construct or product of western culture (Moffitt and Melchior, 2007). A large meta-analysis across 102 studies reported a world-wide pooled prevalence of 5.3% for those under 18 years of age (Polanczyk *et al.*, 2007). A more recent meta-analysis specifically based on DSM-IV diagnostic criteria

gave an estimate of 5.9% to 7.1% (Willcutt, 2012). In the world-wide studies (Polanczyk *et al.*, 2007; Willcutt, 2012), variation in prevalence was not found to be associated with geographical location but instead was largely accounted for by methodological differences across studies (Polanczyk *et al.*, 2007). In these studies, ADHD was defined using different diagnostic criteria (ICD-10 vs DSM), and this could account for some of the variation in prevalence estimates. As mentioned previously, the ICD-10 has more stringent criteria than DSM-IV. It is reported that studies based on ICD-10 criteria tend to report lower prevalence than those using DSM-IV diagnostic criteria (Polanczyk *et al.*, 2007). In addition, studies without an impairment criterion had higher prevalence estimates compared to the studies with (Willcutt, 2012). Differences were also found depending on sources of information used (either from parents, teacher or self-reports) and other methodological factors contributed to this variation, such as sample size, method of ascertainment and age range (Polanczyk *et al.*, 2007).

According to a large population based sample of British children and adolescents, prevalence of DSM-IV ADHD in the UK is reported to be 2.23% (Ford, Goodman and Meltzer, 2003) which seems to be lower compared to the rates above. A possible explanation for lower prevalence is that diagnosis was assigned only if symptoms had caused significant impairment, and as previously discussed inclusion of impairment can decrease prevalence estimates. Furthermore the age range of children included was 5 to 15 years whilst the meta-analyses discussed above included a wider age range of children and adolescents. Even though the rates seem conservative, this study was conducted to inform service planning in the UK and therefore methods of obtaining information were comprehensive and similar to clinical practice. Thus the rates are

representative and a good estimate of ADHD prevalence in the UK (Ford, Goodman and Meltzer, 2003).

ADHD is more frequently found in boys than girls, with a ratio of 4:1 in epidemiological samples and a ratio of 7-8:1 in clinical samples (Gaub and Carlson, 1997; Biederman *et al.*, 2002; Thapar and Cooper, 2015). In the UK, the population prevalence for boys and girls are 3.65% and 0.85% respectively (Ford, Goodman and Meltzer, 2003). The difference in childhood prevalence between girls and boys can partly be explained by differences in expression of symptoms of the disorder (Biederman *et al.*, 2002). In two separate reviews of gender differences in ADHD, it was found that girls with ADHD tend to manifest fewer hyperactive symptoms and less disruptive behaviour than boys (Gaub and Carlson, 1997; Gershon, 2002). In clinical samples, parents and teachers rate girls with ADHD as less hyperactive than boys (Gershon, 2002) and girls are observed to show less disruptive behaviour in classrooms (Abikoff *et al.*, 2002). Girls with ADHD in clinical samples are also found to have a higher rate of internalizing or emotional problems than boys (Gershon, 2002). Girls with ADHD are less likely to be identified for referral to clinic as they typically do not display disruptive behaviour especially in school compared to boys with ADHD. Perhaps part of the discrepancy between male and female prevalence of ADHD in clinical samples are due to referral bias (Gershon, 2002). Additionally it is argued that girls with ADHD may have distinct presentations of ADHD and in some an ADHD diagnosis may have been missed when other disorders like anxiety and depression present at the same time (Quinn and Madhoo, 2014). Another factor that may contribute to this gender difference includes perception and stigma associated with ADHD, that people believe girls are unlikely to have ADHD and therefore ADHD in girls is often overlooked (Quinn and Madhoo,

2014). These issues may explain why ADHD is more prevalent in boys than girls in both epidemiological and clinical samples. In adults, the distribution of ADHD in men and women is more balanced with a ratio of 1.6:1 (Kessler *et al.*, 2006). Several explanations have been proposed for why there is a more balanced gender ratio in adults, one of which is that women with ADHD are perhaps more likely to seek treatment as they tend to report higher levels of impairment than men (Fedele *et al.*, 2012; Quinn and Madhoo, 2014).

The gender difference in ADHD may also be explained by differences at a genetic level, via a polygenic multiple threshold model. This model proposes that girls are less frequently affected by ADHD because they need a higher threshold of genetic liability to manifest ADHD symptoms compared to boys (Cloninger *et al.*, 1978; Rhee and Waldman, 2004). There are some studies that have shown support for this model, whereby relatives of affected girls are found to have more ADHD symptoms than relatives of affected boys (Gaub and Carlson, 1997; Smalley *et al.*, 2000; Goos, Ezzatian and Schachar, 2007). However more evidence is needed to confirm the validity for this model. Overall it appears that in children at least, there seems to be a gender difference in prevalence and this may be due to either genetic factors, clinical presentation or just an artefact of underlying social and methodological issues (Williamson and Johnston, 2015). This highlights that it may be important for studies of children with ADHD to consider possible differences in gender.

There is a growing concern and common assumption that the prevalence of ADHD has increased recently (Polanczyk *et al.*, 2014). Certainly evidence from studies based on medical records and administrative data have reported increased rates of ADHD

diagnosis and prescription of medication for treatment over time (Toh, 2006; McCarthy *et al.*, 2012; Getahun *et al.*, 2013). However, it is argued that these studies do not reflect true prevalence as they are biased by just including children who are brought to medical attention (Moffitt and Melchior, 2007; Polanczyk *et al.*, 2014). Indeed, increased clinic rates are thought to reflect increased awareness of ADHD amongst parents and teachers and access to treatment (Thapar and Cooper, 2015). A recent systematic review and meta-analyses of ADHD prevalence in the last three decades, reported no evidence to suggest an increase in number of children in the general population who meet criteria for ADHD when using standardised diagnostic procedures (Polanczyk *et al.*, 2014). Time trend studies on population-based cohorts also found little evidence of increased rates of ADHD symptoms over time (Collishaw, 2015). One study examining change in population prevalence of common child mental health problems across 3 cohorts, found a decline in mean problem scores including hyperactivity from 1999 to 2008 (Sellers *et al.*, 2015). The study also found that in more recent cohorts, children were rated by parents and teachers as having greater impairment and difficulties in adaptation (Sellers *et al.*, 2015). This indicates that increased rates of ADHD diagnosis may reflect changing impact of symptoms. In summary, although there are definite increases in service use, diagnosis and treatment of ADHD, the evidence does not support common assumptions to indicate that there is an increase in prevalence of ADHD.

1.2 What indexes severity of ADHD?

1.2.1 Clinical variation in children with ADHD

Just like most other medical and psychiatric disorders, ADHD is a complex and heterogeneous disorder. The heterogeneity in ADHD is apparent at different levels from the aetiology of the disorder, to clinical presentation of behavioural symptoms, to responses to treatment. The clinical presentation of ADHD is extremely varied, where two individuals with an ADHD diagnosis may not necessarily have the same pattern of symptoms, impairment, age of onset, comorbidity, and persistence over time (Sonuga-Barke and Taylor, 2015). Children with ADHD who present with different comorbidities have been found to present with different baseline characteristics, outcome and responses to treatment (Jensen *et al.*, 2001). Therefore, one important factor in the study of ADHD is to understand more on how the clinical presentation in children with ADHD may differ and how this may relate to differential aetiology. Not only would this provide important information regarding the aetiology of the disorder, but it could also help in identifying more homogenous subgroups of children with ADHD. This would enable the identification of those who may be at more risk of developing more severe psychopathology and enable better prevention and possible intervention strategies.

1.2.2 Comorbidity

In both community and clinical samples, it has been shown that children with ADHD are frequently found to have at least one other co-occurring psychiatric disorder (Pliszka, 2000; Kadesjo and Gillberg, 2001; Larson *et al.*, 2011; Jensen and Steinhausen,

2015). A large nationwide Danish sample of children and adolescents diagnosed with ADHD in psychiatric hospitals has reported that approximately 50% of patients had one comorbid disorder and 26% had more than one comorbid disorder (Jensen and Steinhausen, 2015). The most common comorbidities in childhood are with behavioural disorders such as conduct disorder and oppositional defiant disorders (Jensen and Steinhausen, 2015).

Approximately 30-50% of children with ADHD are estimated to have a diagnosis of oppositional defiant disorder / conduct disorder (Spencer, 2006). Oppositional defiant disorder (ODD) can be described as patterns of angry / irritable moods and defiant behaviour that is persistent and more frequent than is appropriate at one's developmental age (American Psychiatric Association, 2000; Spencer, 2006). Conduct disorder (CD) is a more severe form of such behavioural problems, characterised by repetitive and persistent rule breaking which includes patterns of aggressive behaviour, destruction of property, stealing, lying and truancy (American Psychiatric Association, 2000). Conduct disorder in children with ADHD is relevant clinically because research suggests that children with CD as well as ADHD fare much worse than those with ADHD alone (Taylor *et al.*, 1996). Having ADHD with comorbid CD also indexes worse impairment and a poorer prognosis into adolescence and adulthood (Moffitt, 1990; Langley *et al.*, 2010). Evidence from family and twin studies also suggests that conduct disorder in children with ADHD indexes a higher familial and genetic loading, therefore indicating that ADHD comorbid with CD may be a more severe subtype of ADHD (Silberg *et al.*, 1996; Thapar, Harrington and McGuffin, 2001). In the ICD-10, there is a special classification for a combined diagnosis category of ADHD and CD called hyperkinetic conduct disorder (WHO, 1993; Swanson *et al.*, 1998),

recognising suggestions that the aetiology, presentation and prognosis of these individuals is distinct from those with ADHD alone. There is not, however, an equivalent classification within DSM diagnoses of ADHD.

ADHD also co-occurs with other neurodevelopmental disorders such as Autism Spectrum Disorders (ASD) (Jensen and Steinhausen, 2015). Evidence estimates that 20-50% of children with ADHD meet criteria for ASD (Rommelse *et al.*, 2010). There is also considerable overlap with neurodevelopmental disorders at a trait level; children with ADHD often have deficits in social interaction and communication difficulties, and children with ASD show high rates of inattention or hyperactivity (Goldstein and Schwebach, 2004). Even though ASD and ADHD co-occur, there has been limited research available on this co-occurrence, possibly as a consequence of the fact that a diagnosis of ASD was previously considered an exclusion criterion for ADHD in the DSM-IV (American Psychiatric Association, 2000). ADHD is also frequently comorbid with other neurodevelopmental disorders involving language, learning and motor development (Jensen and Steinhausen, 2015). It is estimated that about 30% of children with ADHD have a specific learning disability (DuPaul and Stoner, 2014). There is also an association between ADHD and intellectual disability (Simonoff *et al.*, 2007). On the whole, studies have consistently found that children with ADHD perform more poorly in school and on standard intelligence tests when compared to controls (August and Garfinkel, 1990; Spencer, 2006; Jensen and Steinhausen, 2015). Other commonly studied comorbidities with ADHD include anxiety and mood disorders. It is estimated that 13-51% of children and adolescents with ADHD have comorbid depression or anxiety disorder (Gillberg *et al.*, 2004; Spencer, 2006; Jarrett and Ollendick, 2008). The wide variability in estimates of comorbidity between studies can be attributed to

methodological issues such as choice of informants and diagnostic measures (questionnaire / interviews), ways of combining data from all informants and the age of participants (Jensen, Martin and Cantwell, 1997). It has been suggested that the increased overlap between ADHD and anxiety or depression may be just an artefact of psychiatric referrals; however evidence of comorbidity with anxiety or mood disorders has been found in epidemiological and non-psychiatric referred populations as well (Angold, Psych and Costello, 1993; Jensen, Martin and Cantwell, 1997).

Family studies have found higher rates of mood disorder amongst first degree relatives of children with ADHD compared to those without an affected relative (Biederman *et al.*, 1991, 1992) which indicates that ADHD and depression may share familial risk. Furthermore, large collaborative studies have suggested significant overlap between common genetic variants for ADHD and major depressive disorder (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). Adolescents with both ADHD and depression are more likely to have a worse outcome and are at higher risk of long term impairment than those with ADHD or depression alone (Blackman, Ostrander and Herman, 2005; Biederman, Ball, *et al.*, 2008). Similarly, children and adolescents with both ADHD and anxiety are more likely to have additional psychopathology, are more impaired in psychosocial functioning and have a stronger family history of anxiety disorders (Spencer, 2006). On the whole, these findings suggest that presence of a range of comorbid disorders can worsen the impairment and outcomes of ADHD.

1.2.3 Impairment in children

A clinical diagnosis of ADHD requires not only symptom presence, but also impairment in everyday functioning and presence of symptoms across different settings, for

example in the home and at school (American Psychiatric Association, 2013). Functional impairment can be described as difficulties that interfere with managing day to day activities (American Psychiatric Association, 2013; Adler, Spencer and Wilens, 2015). Impairment is important as an issue distinct from ADHD symptomatology, as one study has shown that symptom severity is only moderately correlated with impairment with 25% of variance in academic and social functioning was explained by ADHD symptoms (Gordon *et al.*, 2006). In a review of epidemiological studies of ADHD, Faraone and colleagues (2003) found a proportion of children with clinically elevated levels of ADHD symptoms did not report severe functional impairment (Faraone, Sergeant, *et al.*, 2003). On the other hand some children with sub-threshold ADHD were reported to have significant symptoms and functional impairment (Hong *et al.*, 2014). Therefore this indicates that symptoms and impairment are separate but overlapping domains that are both important in the assessment of ADHD.

ADHD in childhood has often been associated with a very broad range of functional impairment including poor school performance, negative social behaviour, impaired peer relationships, disrupted family life and strained parent child relationships, increased parental stress and parental psychopathology (Johnston and Mash, 2001; Deault, 2010). As ADHD changes with age and development, what constitutes functional impairment also changes across different developmental stages (Adler, Spencer and Wilens, 2015). Children with ADHD in preschool settings are found to exhibit more problem behaviours, non-compliance, temper outbursts and fewer social skills compared to controls (DuPaul *et al.*, 2001). At this stage impairment may be associated with hyperactive-impulsive features as evidence of inattention may not be

apparent in context of preschool (Lahey *et al.*, 2005). As they get older, children enter formal education and will face new challenges in the academic and social environment. The inability to adapt to the demands of the new environment results in the child falling behind which may be the start of difficulties at school and in the home (Taylor and Sonuga-Barke, 2008). This includes increasing demands for self-regulation and managing attention during lessons (Sonuga-Barke *et al.*, 2005). At this stage children with ADHD are also reported to experience more peer rejection and difficulties in social interaction (Mrug, Hoza and Gerdes, 2001; Mrug *et al.*, 2012). The transition into adolescence and adulthood will again bring about new challenges which can for some individuals, result in impaired functioning across a range of outcomes. As children get older, even though symptoms may decline, continuing symptoms can still cause functional impairment in some individuals (Langley *et al.*, 2010). Impairment experienced in adulthood may be relevant to other domains such as maintaining employment, driving problems and relationship or marital breakdowns (Harpin, 2005; Klein, Mannuzza, Ramos Olazagasti, *et al.*, 2012). Additionally the presence of comorbidity in ADHD have been found to be associated with more functional impairment than those with ADHD alone (Blackman, Ostrander and Herman, 2005; Larson *et al.*, 2011). Thus it seems that there are different areas of impairment and for each individual the pattern and magnitude at which these difficulties occur can be different. Impairment in ADHD is therefore an important indicator of clinical variation and severity, which is distinct from symptom severity and comorbidity.

1.2.4 Persistence and prognosis of ADHD

Whilst previously considered as restricted to childhood (Hill and Schoener, 1996), long term follow-up studies have shown that ADHD persists into adulthood in 20-50% of individuals (Kessler *et al.*, 2010; Klein, Mannuzza, Olazagasti, *et al.*, 2012). Rates of persistence reported in many studies vary and is dependent on the definition of persistence and other factors in each study; for example prevalence rates are much lower when ADHD persistence is defined as syndromatic persistence (meeting full diagnostic criteria) compared to symptomatic persistence (meeting sub threshold criteria) (Biederman *et al.*, 2011). Even though some core ADHD features such as hyperactivity may decline with age, some features, particularly inattentive symptoms, may persist and can still cause impairment in some individuals (Klein, Mannuzza, Olazagasti, *et al.*, 2012). ADHD persistence can be considered as a marker of severity of ADHD as it is associated with increased risk of additional problems including substance misuse, poor educational attainment, antisocial behaviour, unemployment, friendship difficulties and social problems (Wilens, Faraone and Biederman, 2004; Asherson *et al.*, 2007). Follow up studies of children with ADHD, have found that ADHD persistence is associated with a stronger family history of ADHD and mood disorder, the presence of comorbidities, especially conduct disorder, and impairment in educational and psychosocial functioning in young adulthood (Biederman *et al.*, 1996, 2010, 2011).

In addition to persistence, the long term outcomes of childhood ADHD are concerning as many studies have shown childhood ADHD to be related to a number of negative outcomes later in life compared to controls (Barkley *et al.*, 2006; Klein, Mannuzza, Olazagasti, *et al.*, 2012; Dalsgaard *et al.*, 2015). In a 33 year prospective longitudinal

study, individuals with ADHD compared to controls were found to have significantly worse education, occupational, economic and social outcomes, more divorces and high rates of ongoing ADHD, substance use disorder and antisocial personality disorder (Klein, Mannuzza, Olazagasti, *et al.*, 2012). A large Danish population study found an increased mortality rate amongst individuals with ADHD especially for those with comorbid disorders, with the most common cause of mortality being due to accidents (Dalsgaard *et al.*, 2015). Therefore given the increased recognition of ADHD persistence and long term impairment associated with ADHD, it is important to identify long term indicators of severity.

1.2.5 Neurocognitive functioning in ADHD

ADHD is also characterised by neurocognitive deficits as well as by its core clinical features (Willcutt *et al.*, 2005). Neurocognitive deficits are commonly found in children with ADHD and provide an alternative index of severity (Stefanatos and Baron, 2007). It is increasingly being recognised that neurocognitive processes underlying ADHD may have traction as endophenotypes (heritable traits or phenotypes that are thought to be closer to the biological aetiology of a clinical disorder than its symptoms) (Gottesman II and Gould, 2003; Doyle, Willcutt, *et al.*, 2005) and could help understand the mechanisms underlying ADHD. Some have argued that neurocognitive measures also provide a more 'objective' and non-behavioural measure of impairment in children with ADHD that is not based on parent reports of symptoms (Gualtieri and Johnson, 2005; Stefanatos and Baron, 2007).

Children with ADHD show deficits in various neurocognitive domains including executive function (Willcutt *et al.*, 2005; Seidman, 2006) and abnormal reward

sensitivity (Sonuga-Barke, 2002). Executive functioning (EF) is an umbrella term used to describe cognitive functions such as working memory, response inhibition, set shifting, planning and organisation that help the brain manage and act on information (Pennington and Ozonoff, 1996; Martinussen *et al.*, 2005). In a large meta-analysis of EF measures, children with ADHD exhibited significant impairment on 13 different EF tasks compared to those without ADHD in both clinic and community samples (Willcutt *et al.*, 2012). The effect sizes found were of medium effect, but the most consistent and strongest associations were observed for response inhibition, vigilance, working memory and planning (Willcutt *et al.*, 2005).

Another neurocognitive domain that has been identified to be associated with ADHD is motivational deficits or abnormal reward processing (Barkley, 1997; Sonuga-Barke, 2002). Children with ADHD have been shown to exhibit aversions to delay, show preferences for smaller and immediate rewards and impaired decision-making (Toplak, Jain and Tannock, 2005; Garon, Moore and Waschbusch, 2006; DeVito *et al.*, 2008; Groen *et al.*, 2013). Individuals with ADHD are often involved in more risky situations and behaviours. In some models of ADHD, risky behaviour is thought to be explained by inhibition deficits or perhaps greater preference for immediate over delayed rewards and poor decision making (Sonuga-Barke, 2002; Groen *et al.*, 2013).

Neurocognitive deficits are also common in families of children with ADHD. Though evidence is not consistent (Murphy and Barkley, 1996; Asarnow *et al.*, 2002), reports of neurocognitive deficits in both affected and unaffected relatives imply that the deficits are part of underlying mechanisms to ADHD liability (Nigg *et al.*, 2004; Doyle, Biederman, *et al.*, 2005). A few studies have found weaker executive and motor

function ability in parents of children with ADHD compared with parents of controls (Nigg, Swanson and Hinshaw, 1997; Curko Kera *et al.*, 2004). There have also been reports of moderate correlations between executive functioning in parents and probands (Nigg *et al.*, 2004). There are however, other studies which do not find significant differences in EF deficits (sustained attention, set shifting, and working memory) in parents of children with ADHD when compared to controls (Murphy and Barkley, 1996; Asarnow *et al.*, 2002). Therefore some initial findings suggest that these deficits are related to parental deficits, possibly indicating heritable effects but more work is needed to further understand these associations.

Just like the complex clinical nature of ADHD, there exists heterogeneity in EF performance amongst children with ADHD (Doyle, 2006). Not all children with ADHD exhibit significant deficits in EF; poor performance on neurocognitive tasks can be indicative of ADHD but normal scores do not rule out a diagnosis of ADHD (Nigg *et al.*, 2005; Doyle, 2006). The deficits are also diagnostically non-specific as executive function deficits are found in other neurodevelopmental disorders such as ASD (Robinson *et al.*, 2009). Neurocognitive performance has also been associated with factors such as age, comorbidity and family history that can affect the variability of performance in children with ADHD (Doyle, 2006). It has also been proposed that EF can change across the life span (Seidman, 2006; Diamond, 2013). This indicates that EF deficits may be present in only a subset of individuals (Willcutt *et al.*, 2005) and that their associations may change dependent on other factors. This varied presentation of neurocognitive deficits is seen in other multifactorial complex psychiatric disorders (Hill, 2004; Kar and Jain, 2016). Therefore neurocognitive deficits in children with

ADHD can be impairing and represent another, possibly, more objective index of severity of the disorder.

Thus from the discussions above, ADHD is a highly heterogeneous disorder which adds to the complexity of understanding its aetiology. Heterogeneity and severity can be captured by many constructs including comorbidity, persistence over time, functioning (impairment) and neurocognitive deficits. Exploring and understanding more about this heterogeneity is important to further our knowledge about ADHD and can help identify subgroups with poorer outcomes and prognosis.

1.3 Parental psychopathology

Parental psychopathology is one of the most common and consistent risk factors for offspring mental health problems including ADHD (Downey and Coyne, 1990; Clark *et al.*, 2004; Bornovalova *et al.*, 2010; McLaughlin *et al.*, 2012). Previous research has found that children who have a parent with mental illness have higher rates of psychiatric disorder, greater risk for psychosocial problems, poorer social functioning and lower academic performance (Sameroff and Seifer, 1983; Beardslee *et al.*, 1996; Weissman *et al.*, 1997). The genetic and environmental mechanisms that contribute to inter-generational links in psychopathology are complex (Stein and Harold, 2015). Factors such as genetic risks, exposure to parent negative emotions, cognition or behaviour and increased family stress are all different mechanisms through which parental psychopathology may influence offspring psychopathology (Johnston and Mash, 2001; Deault, 2010; Stein and Harold, 2015).

Looking more specifically at ADHD, case-control studies have shown higher rates of psychopathology including ADHD and depression amongst parents of children with ADHD compared with parents of unaffected children (Faraone and Biederman, 1997; Sprich *et al.*, 2000; Chronis *et al.*, 2003; Margari *et al.*, 2013). Some studies have also shown evidence of even higher rates of parental psychopathology in children with comorbid ADHD and oppositional defiant disorder or conduct disorder compared to children with ADHD alone (Schachar and Wachsmuth, 1990; Barkley *et al.*, 1991; Faraone, Biederman and Monuteaux, 2000a; Sprich *et al.*, 2000; Johnston and Mash, 2001).

Evidence suggests that ongoing psychopathology in parents can influence the course and outcome of a range of psychopathology in children which makes understanding the role of parental mental health problems on children an important endeavour (Bornovalova *et al.*, 2010; Melchior and van der Waerden, 2016; Middeldorp *et al.*, 2016a). Many studies investigating the impact of parent mental illness on offspring in general have focused on depression, particularly maternal depression, and been based on population samples or samples of offspring of depressed mothers (Downey and Coyne, 1990; Weissman *et al.*, 1997; Goodman *et al.*, 2011). There is limited evidence however regarding how parental psychopathology, particularly parent ADHD, can influence the presentation of ADHD in children. A few studies have found that a family history of psychopathology in first degree relatives is a predictor of ADHD persistence (Biederman *et al.*, 2010, 2011). However it is unclear if associations are specific to a particular disorder or parent (i.e. mother or father). One study examining comorbidities in a cross-sectional community sample of children diagnosed with ADHD found parent mental health to be independently associated with offspring comorbid

disorders (Silva *et al.*, 2015). More work in this area, especially looking at specific conditions in parents, is therefore needed.

On the other hand, these effects may be bidirectional as there is also evidence of child effects on parents of children with ADHD. Difficulties associated with ADHD symptoms in children (such as child temperament and unregulated behaviour) can evoke hostility and negative reactions from parents (Johnston *et al.*, 2002; Harold *et al.*, 2013; Lee *et al.*, 2013). Parents with mental health difficulties may be more vulnerable and sensitive to such challenges and stress which can affect their well-being (Anastopoulos *et al.*, 1992). Thus, the relationship between parental psychopathology (e.g. parent ADHD or parent depression) and presentation in children with ADHD is complex as both parent and child characteristics can interact to influence or change the development of the ADHD in children (Margari *et al.*, 2013). Considering the evidence suggesting the negative associations between parental psychopathology and offspring wellbeing, it is clear that further work is needed, for example investigating the associations between specific psychopathological disorders in parents and their relationship with the clinical and neurocognitive presentation of children with ADHD.

1.3.1 Parent ADHD

As described in section 1.2, there has recently been increasing interest in and awareness of adult ADHD as there is now more evidence which shows that ADHD can persist into adulthood (Barkley *et al.*, 2002; Kessler *et al.*, 2005; Biederman *et al.*, 2010). The prevalence rates for adult ADHD range from 1 – 7.3% (Kessler *et al.*, 2006; Fayyad *et al.*, 2007; Simon *et al.*, 2009). The differences in prevalence rates across studies are due to variability in methodology and uncertainties regarding the definition

of ADHD in adults. One meta-analysis of adult ADHD using strict DSM-IV diagnostic criteria reported a pooled population prevalence of 2.5% in the general population (Simon *et al.*, 2009). As discussed later in chapter 2, there are no universally accepted diagnostic criteria for ADHD in adults (McGough and Barkley, 2004). Prior to the DSM-5, the definition of ADHD was mostly focused on children with limited guidance for adults. As a result, the definitions used in different studies have influenced reported prevalence rates. Some studies have strictly followed the DSM-IV criteria whereas other researchers, who have questioned the validity of the DSM-IV criteria in adults, have used modified diagnostic criteria (DuPaul, Schaughency, *et al.*, 2001; Faraone and Biederman, 2005; Almeida Montes, Hernandez Garcia and Ricardo-Garcell, 2007). Another reason for differences in estimated prevalence rates especially of follow up studies from adolescence to adulthood could be due to the change of rater / informant from parent-report to self-report. The prevalence rate of ADHD is said to be higher when based on parent reports compared to self-reports (Barkley *et al.*, 2002; Simon *et al.*, 2009). Other reasons to account for this variability include differences in methodology such as sample age and ascertainment (eg. clinical sample vs population based samples) (Simon *et al.*, 2009).

Whilst clinicians are advised to be flexible in the application of ADHD diagnostic criteria to adults, the diagnosis of ADHD in adults typically requires symptoms to begin in childhood (McGough and Barkley, 2004; Kessler *et al.*, 2006), even if an ADHD diagnosis is not recognised until adulthood. Existing definitions of adult ADHD require a combination of history of symptoms present in childhood and symptoms present currently (Weiss and Murray, 2003). In establishing that adult ADHD is a valid disorder, researchers have shown that neurocognitive and biological findings (brain

abnormalities and genetic transmission) in adults are similar to those in children with ADHD (McGough and Barkley, 2004). ADHD in adults is associated with a number of functional impairments and poor outcomes as well as with a wide range of comorbidities such as mood, anxiety and substance misuse disorders compared to adults without ADHD (Murphy and Barkley, 1996; Kessler *et al.*, 2006; Fayyad *et al.*, 2007; Hechtman *et al.*, 2016). Despite differences regarding definition and prevalence, evidence on the whole demonstrates that adult ADHD is a relatively common and impairing disorder.

Very recently, several longitudinal population studies have suggested that adult ADHD may not necessarily be a continuation of childhood ADHD (Moffitt *et al.*, 2015; Agnew-Blais *et al.*, 2016; Caye *et al.*, 2016). These recent studies found evidence of a proportion of individuals meeting diagnostic criteria for ADHD only during young adulthood, suggesting that the onset of ADHD can occur in adulthood. It has been proposed that childhood and adult onset ADHD may be distinct syndromes (Agnew-Blais *et al.*, 2016; Caye *et al.*, 2016). These findings are both interesting and provocative as they challenge the existing model of ADHD being a neurodevelopmental disorder (Faraone *et al.*, 2016). However research on this is still in its early stages. There are many questions about the nature of this new adult-onset ADHD that need to be answered for example whether it is secondary to other disorders such as substance misuse or how it differs from neurodevelopmental disorders with an early age of onset (Agnew-Blais *et al.*, 2016; Caye *et al.*, 2016; Faraone *et al.*, 2016). The adult ADHD definition in this thesis used the 'childhood-onset' criterion set out in the DSM-IV and DSM-5 as this remains at present the recognised definition of adult ADHD (Kessler *et al.*, 2006; American Psychiatric Association, 2013; Faraone *et al.*, 2016) and because

work on this thesis began before the concept of an 'adult-onset' ADHD was introduced.

Given that adult ADHD is impairing and that ADHD is familial, it is essential to understand how parent ADHD is associated with the family environment and development or expression of ADHD in children. It is estimated that about 25 - 50% of children with ADHD have a parent with ADHD (Johnston and Mash, 2001; Chronis *et al.*, 2003; Minde *et al.*, 2003; Johnston *et al.*, 2012) and well over half of adults with ADHD have at least one child with ADHD (Biederman, Faraone, *et al.*, 1995; Minde *et al.*, 2003; Kessler *et al.*, 2006; Johnston *et al.*, 2012) Within ADHD samples, high levels of ADHD symptoms have been found amongst biological parents which shows the strength of a familial contribution in ADHD (Epstein *et al.*, 2000; Smalley *et al.*, 2000). ADHD in parents may impact on children both through genetic mechanisms and environmental mechanisms such as parenting (Johnston *et al.*, 2012). It is argued that parents with ADHD can either impede or help facilitate the development of their child with ADHD (Johnston *et al.*, 2012). Some studies have found that high levels of mother ADHD and child ADHD were associated with more positive parenting (Psychogiou *et al.*, 2007, 2008). This has been described as a 'similarity-fit' hypothesis, which predicts that parent and child similarity means a parent can synchronise parenting and empathise with their child's ADHD symptoms. For example, both parent and child may enjoy fast paced activities together or share a similar 'cognitive tempo' (Weiss, Hechtman and Weiss, 2000; Johnston *et al.*, 2012).

On the other hand, there is evidence to suggest that parent ADHD can impede child development. Parents with ADHD may be unusually sensitive or reactive to their

child's ADHD symptoms as a result of their own symptoms (e.g. distractibility) (Johnston *et al.*, 2012). A parent with ADHD may also experience difficulty with self-regulation skills which make it difficult for them to implement such skills in their own children (Weiss, Hechtman and Weiss, 2000). In both community and clinical samples, parent ADHD is often found to be associated with family disorganisation and chaos, less effective child rearing techniques like problem solving and inconsistent or over-reactive discipline (Banks *et al.*, 2008; Johnston *et al.*, 2012).

Treatment trials report that ADHD in parents is a significant barrier to successful ADHD treatment in the child (Jans *et al.*, 2015). Offspring of parents with ADHD in both clinical and community samples have also been found to have poorer treatment outcomes after implementation of parental training or pharmacological interventions (Sonuga-Barke, Daley and Thompson, 2002; Mikami *et al.*, 2010; Chazan *et al.*, 2011; Chronis-Tuscano *et al.*, 2011). Therefore parental psychopathology and specifically parent ADHD, is an important consideration when treating children with ADHD.

Despite indications of the importance of ADHD in parents, little is known about whether parent ADHD can influence the clinical presentation and course of the disorder in children. There has been limited research in this area and results are somewhat mixed with differences in the way parent ADHD typically in clinical samples of children with ADHD has been defined and the timing of when parent ADHD is measured (Biederman, S. V Faraone and Monuteaux, 2002; Goos, Ezzatian and Schachar, 2007; Takeda *et al.*, 2010; Segenreich *et al.*, 2014). There are also mixed findings with differences between paternal and maternal influences on child ADHD (Biederman, S. V Faraone and Monuteaux, 2002; Goos, Ezzatian and Schachar, 2007;

Takeda *et al.*, 2010). These are discussed further in Chapter 3 of this thesis. It is therefore necessary to undertake work in this area and this need has informed the aims of this thesis.

1.3.2 Parent Depression

It is well established that in both community and clinical samples parent depression particularly maternal depression is an important risk factor for adverse child development (Downey and Coyne, 1990; Tully, Iacono and McGue, 2008; Goodman *et al.*, 2011). Maternal depression is one of the most widely studied types of parental psychopathology and studies have consistently found that children of mothers with depression have higher risk of developing a range of psychiatric problems compared to those without (Downey and Coyne, 1990; Goodman and Gotlib, 1999). It is reported that 40 to 45% of children with a depressed mother in a community and clinical sample have a diagnosable psychiatric disorder (Beardslee *et al.*, 1993; Chronis *et al.*, 2007).

In families of children with ADHD, parents are reported to have a higher rate of depression and frequency of depressive symptoms when compared to parents of controls (Biederman *et al.*, 1987; Brown and Pacini, 1989). This elevated rate of depression found amongst parents is even greater in those who have a child with ADHD and comorbid ODD and / or CD (Johnston and Mash, 2001; Chronis *et al.*, 2003). Family studies of ADHD and depression show support for a familial link between ADHD and depression (Faraone and Biederman, 1997). This link appears to be stronger in families of children with comorbid ADHD and conduct disorder but the association is also present for families of children with ADHD alone (Faraone *et al.*, 1997).

Difficulties in parenting are believed to be one environmental mechanism that can explain part of the link between parent depression and child mental health problems. Maternal depression has been found to have negative effects on parenting behaviours and increase parent child conflict (Lovejoy *et al.*, 2000; Johnston *et al.*, 2002). Parenting difficulties in parents with depression include negative affect which results in less interaction and flat verbal tones, being excessively critical, ruminations which result in negative thinking and deficits in problem solving (Lovejoy *et al.*, 2000; Stein *et al.*, 2012; Psychogiou and Parry, 2014).

Most of the literature on parent depression and child outcome has been focused on general population or twin samples and studies that ascertain depressed mothers. Depression is also one of the most common mental health problems affecting adults of a child bearing age (Marcus and Heringhausen, 2009). Few studies have, however, investigated the effects of maternal depression on children with ADHD, although this is an important area of study, not least because ADHD and depression are familially linked. In a clinical sample of children with ADHD, Cartwright and colleagues found that maternal depression was associated with expressed emotion (high levels of negative expressed emotion towards their children) and with lower levels of warmth (Cartwright *et al.*, 2011). In a clinical study of families of children with ADHD and a study of mothers with depression and anxiety, maternal parenting stress and maternal depressive cognitions (rumination) were found to mediate the relationship between maternal depression symptoms and parenting behaviour (Gerdes *et al.*, 2007; Stein *et al.*, 2012). Depressive symptoms in the primary caregiver have been shown to interfere with the ability of children to benefit from pharmacological treatment interventions. For example, in a multimodal treatment study of children with ADHD, parent

depressive symptoms and severity of child ADHD were found to be associated with lower response rates to treatment (Owens *et al.*, 2003). Thus far, the influence of maternal depression on clinical and cognitive outcomes of children with ADHD has not been studied widely. Chapters 4 and 5 in this thesis will examine the existing literature from the evidence available so far and subsequently examine the effects of parental depression in a sample of children with ADHD.

Given the high rate of parents with mental health difficulties, especially ADHD and depression, in families of children with ADHD, parental psychopathology is clearly an important area to address in understanding ADHD. Although there are some indications that parental psychopathology may be related to ADHD severity, findings are mixed and not conclusive. Therefore it is important to investigate associations between parental psychopathology and child presentation of the disorder to gain insight into how parental psychopathology may contribute to development of ADHD in the child. Considering the previous studies indicating the detrimental effects of parental psychopathology on treatment of childhood disorders, this is especially important to help inform treatment and intervention strategies.

1.4 Family Environment

ADHD has previously been found to be associated with psychosocial adversity (Biederman, Faraone and Monuteaux, 2002). Though it is difficult to determine if these associations are causal, family factors are still an important consideration in the development and outcomes of ADHD (Thapar and Cooper, 2015). The way in which ADHD develops has often been described using a developmental psychopathology

framework (Johnston and Mash, 2001). This model proposes that multiple risk and protective factors, including biology and family environment interact over time to influence the development of ADHD and other disorders (Rutter and Sroufe, 2000). It emphasises individual differences in the development of the disorder through the unique combination of various influences which carry different weight across individuals and their families (Johnston and Mash, 2001; Deault, 2010). Family factors may play a role in influencing the presentation and development of ADHD symptoms and comorbidity over time.

A review of studies of families of children with ADHD has found that across clinical and community samples, ADHD is associated with multiple difficulties within the family such as high levels of family conflict, conflicted parent–child relationships and increased parenting stress which can have a significant impact on child and family life (Johnston and Mash, 2001; Johnston *et al.*, 2012). These difficulties also appear to be more strongly associated in families of children with ADHD and comorbid ODD or CD (Biederman, Milberger, *et al.*, 1995; Scahill *et al.*, 1999; Burt *et al.*, 2003; Murray and Johnston, 2006).

Negative family environment can contribute to, or be caused by, ADHD symptoms. For example, a child with low genetic susceptibility to the disorder may develop clinically significant symptoms upon exposure to a chaotic and unresponsive environment. On the other hand the stressful and demanding nature of ADHD symptoms can play a role as well to provoke negative reactions from parents or siblings which can lead to disruptive family situations. The negative reactions received may then in turn exacerbate symptoms of the disorder (Johnston and Mash, 2001; Deault, 2010).

High levels of negative parent-child interactions are also common in families of children with ADHD in both clinical and community samples especially in younger children with conduct problems (Mash and Johnston, 1982; Lahey *et al.*, 1988; Danforth *et al.*, 1991; Chronis *et al.*, 2007). Observational studies report that mothers of children with ADHD are more direct, negative and less interactive (Barkley and Murphy, 1998; DuPaul, McGoey, *et al.*, 2001). In a longitudinal twin study, it was found that the nature of parent child relationships differed for mothers and fathers; child ADHD symptoms influenced mother-child relationships, whereas father-child relationships influenced ADHD symptoms in children (Lifford, Harold and Thapar, 2008). One other study on a community sample also found that attentional problems had a significant impact on mother child rejection (Gadeyne, Ghesquière and Onghena, 2004). The pattern of parent-child interactions and parenting amongst ADHD families can be explained using the theory of '*coercive family processes*' proposed by Gerald Patterson (1982), where unsuccessful interactions with a child with challenging behaviour can result in a parent responding negatively, which then further escalates the child's behaviour. Both parent and child are therefore caught in a coercive cycle where dysfunctional behaviours from both parent and child are reinforced (Patterson, 1982; Chronis *et al.*, 2007).

In a sample of children recruited from clinics and community, parents of children with ADHD are also reported to experience more stress than parents of children without ADHD (Theule *et al.*, 2011). Parenting stress in ADHD families has been found to be related to severity of ADHD symptoms, co-occurrence of conduct disorder and parent depression symptoms (Anastopoulos *et al.*, 1992; Theule *et al.*, 2011). The existing evidence shows that families of children with ADHD face many difficulties and it has

been implied that this may partly reflect the presence of ADHD in parents (Johnston *et al.*, 2012). Given the role of parents in providing care to their offspring, it is essential to understand how a parent with psychopathology can influence the care giving environment which can in turn influence the developmental course of ADHD. There is some evidence to demonstrate that adult ADHD is associated with greater child rearing impairments (Barkley, 2012). Parenting studies in community samples also have linked parent ADHD to less effective parenting (Murray and Johnston, 2006; Banks *et al.*, 2008), although as described above, this might not always be the case (Weiss, Hechtman and Weiss, 2000; Johnston *et al.*, 2012). Difficulties or impairment faced by a parent with mental health problems may interfere with their parenting skills. Mothers with ADHD compared to those without ADHD have been found to be poorer at monitoring child behaviour, were not consistent with discipline and have less effective problem solving behaviours (Murray and Johnston, 2006). Sonuga-Barke and colleagues found that high levels of ADHD symptoms interfered with parenting effectiveness and ability to benefit from parenting programs (Sonuga-Barke, Daley and Thompson, 2002). This highlights that it is important to understand how a parent with ADHD can influence the family environment; which can either attenuate or facilitate a child's development.

1.5 Summary

To summarise, ADHD is a neurodevelopmental disorder that can have a significant impact on the lives of children and their families and often extends into adult life. Evidence to date suggests that ADHD is a complex multi-factorial disorder where a combination of many genes and non-inherited factors and their interplay all contribute (Thapar and Cooper, 2015). ADHD is a highly heritable condition and ADHD presentation is characterised not only by its core symptoms and impairment but also by patterns of comorbidity and neurocognitive deficits. Due to the heritable and familial nature of ADHD as well as high occurrence of psychopathology in parents of children with ADHD, parental psychopathology is an important issue to address in understanding ADHD as it can index both genetic and environmental risks that may contribute to offspring presentation. This evidence has informed the aims of this thesis.

1.6 Study Aims

The main aim of this thesis is to explore associations between parental psychopathology and severity of child phenotype in a sample of children with ADHD.

This thesis is divided into three studies written up as chapters 3, 4 and 5.

- a. The first study (chapter 3) aims to investigate the association between parent ADHD and the clinical presentation and family environment of children with ADHD. This study utilised a cross-sectional design and asks the question: are parent ADHD problems associated with a more severe clinical presentation and greater family adversity in children with ADHD?
- b. Following on from the first aim, the next study (chapter 4) investigates the influences of mother ADHD / depression on the longer term outcome of psychopathology in a longitudinal sub-sample of children with ADHD. It asks the question: how does parental psychopathology influence the course and persistence of ADHD and comorbidity in children across time?
- c. Finally, chapter 5 will cross-sectionally examine association between parental psychopathology and neurocognitive functioning in children with ADHD, asking the question: does parental psychopathology contribute to neurocognitive variation in children with ADHD?

The next chapter (chapter 2) will describe the samples and measures used in this thesis. Chapter 6 will bring together results from the 3 studies mentioned above in a discussion, considering these findings as a whole, clinical implications, overall strengths and limitations and finally future directions.

Chapter 2

Methods

Chapter description

This chapter describes in detail the samples, recruitment processes and assessments that were used for investigations within this thesis. The main sample in this thesis is a clinical sample of children with ADHD recruited into the Study of ADHD Genes and Environment (SAGE) from 2007 until 2011. Chapters 3 and 5 utilise the SAGE sample whereas analyses in chapter 4 were based on a subset of the SAGE sample who were invited to take part in a follow up in 2013. Sample characteristics and demographics are also presented in this chapter.

2.1 Study of ADHD Genes and Environment (SAGE)

2.1.1 Recruitment procedure

A sample of children with ADHD and their parents was recruited into the Study of ADHD Genes and Environment (SAGE) from Child and Adolescent Psychiatry and Community Paediatric services in the UK between 2007 and 2011. Recruitment was undertaken with the help of local clinicians, who asked families with a child (aged 6-18 years) with a suspected or confirmed diagnosis of ADHD if they would be willing to take part in the research study. Upon agreement, the clinician obtained assent to forward the family's contact information to the research team. There was no information available on the number of patients approached by clinicians initially.

A member of the research team subsequently contacted the family, conducted a brief telephone screen for the presence of ADHD symptoms, determined exclusion criteria and briefly explained the study. If the child met the study criteria (see inclusion and exclusion criteria outlined below) and the family agreed, an appointment was made to visit the family at their home. An appointment letter was then sent together with information about the study, consent forms and questionnaires for parents to complete before the research visit. Research visits were conducted by trained psychologists who worked in pairs. One researcher interviewed the parent about the affected child whilst the other researcher administered the cognitive assessments and interviewed the child. A venous blood or saliva sample was obtained from the child and both biological parents where possible for the genetic aims of this study, but this information was not utilised as part of this thesis.

Before taking part in the study, parents and children aged 16 years and over gave informed written consent, and assent was obtained from children aged 15 years and under. Ethical approval for the study was obtained from the Wales Multicentre Research Ethics Committee (reference number: 06/MRE08/75). Data collection was funded by the Wellcome Trust (Grant No: 079711).

Following the assessment, a research report was sent to the referring clinician, which summarised the clinical diagnoses and information for each child, as well as the cognitive assessments conducted. As a thank you for taking part in the study, families were provided with £15 in the form of high street vouchers. Families were updated about the study and any related findings through regular newsletters.

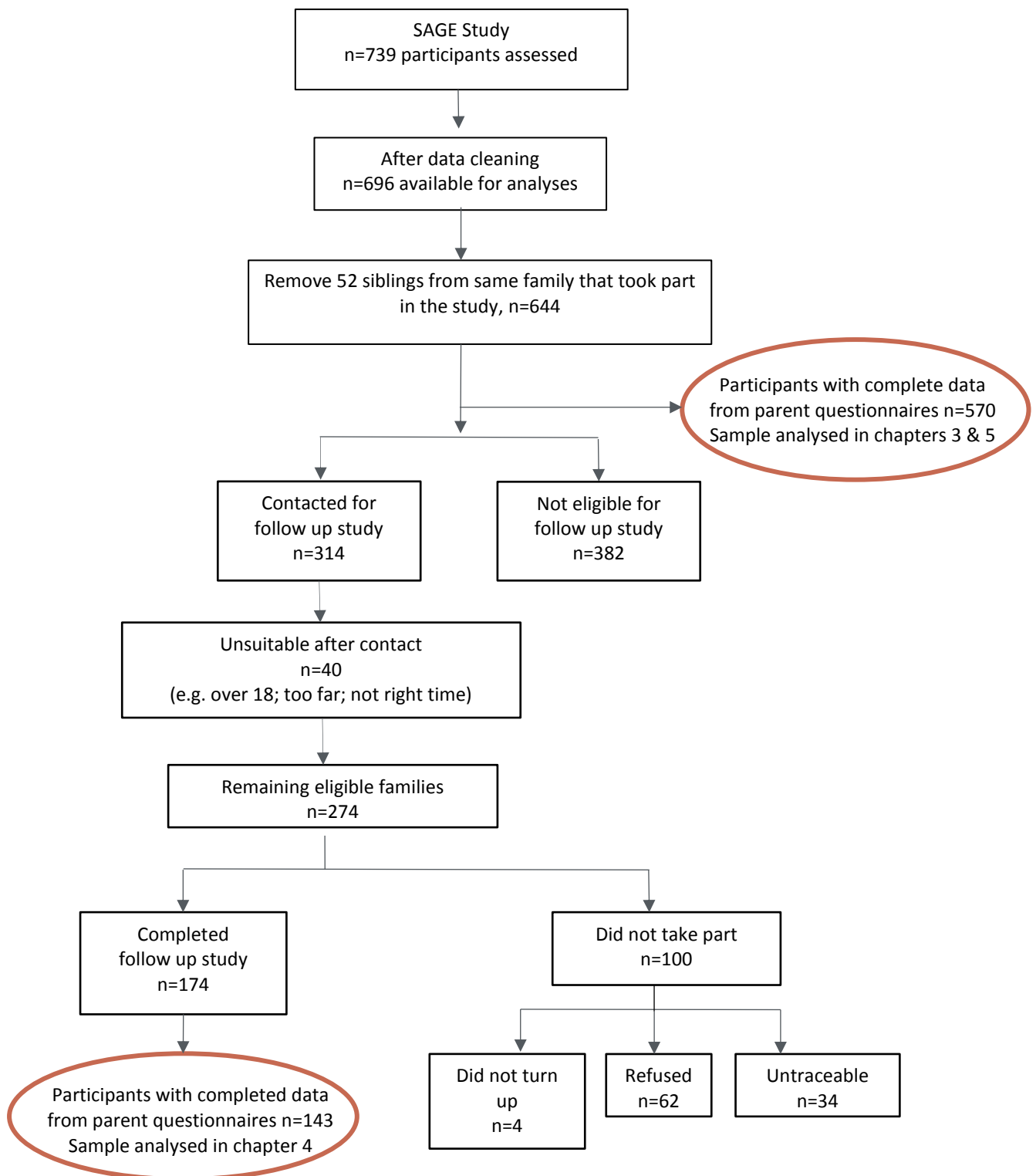
2.1.2 Inclusion and exclusion criteria

All children referred had to have a clinical diagnosis of ADHD or were being assessed at the time for such a diagnosis. Diagnosis of ADHD was confirmed by research diagnostic interviews (see details below) conducted as part of the study. All children were of British Caucasian origin (a criterion relevant to the genetic analysis) and each child had to be living with at least one biological parent. The children were included in the study regardless of IQ (assessed as part of the study protocol).

Children with any known major neurological or neurodevelopmental condition/genetic syndrome including fragile X syndrome, tuberous sclerosis, epilepsy, psychosis, Tourette's syndrome, any known diagnosis of autism or other pervasive developmental disorder were excluded from the study (in keeping with the DSM-IV and ICD-10 guidelines).

Data collection for the study ended in March 2011 with a total of 739 participants seen. After data cleaning and exclusions, a total clinical sample of 696 was available for analysis, 113 (16%) females and 583 (84%) males. There were 46 participants that had a sibling who had also participated in the study, i.e. where two children from the same family (siblings) participated in the study. For all analyses across chapters 3, 4 and 5, where more than one child from the same family participated in the study, only one child (oldest) was included in analyses. Therefore 52 participants were excluded and of the remaining 644, there were 570 participants with parent questionnaire data that was completed. Participants without parent questionnaire data (n= 74) consisted of more girls, were slightly older and were more likely to have a parent with lower educational status. Participants with or without parent questionnaire data however did not differ in terms of lower social class, lower income, IQ, ADHD and conduct symptoms. As parental psychopathology is the main predictor in this thesis, the sample utilised in this thesis is based on 570 children and families with questionnaire data available from parents. A flowchart of recruitment into the SAGE study and follow-up study (discussed in section 2.2) are shown in Figure 2.1. The next section will describe the assessments and measures used in the SAGE study. Details of the follow up study are discussed later in section 2.2.

Figure 2.1 Flowchart of recruitment into the SAGE and follow-up sub sample.



2.1.3 Assessment and Measures

Measures for this thesis were chosen from the battery of assessments undertaken with the SAGE sample.

2.1.3.1 *Diagnostic criteria: DSM-IV & DSM-5*

The investigations within this thesis utilise symptoms and diagnoses according to DSM criteria. The data used in this thesis were collected and analysed prior to DSM-5 being published; therefore initial diagnoses were based on criteria set out in the DSM-IV. All child diagnoses and adult ADHD had been initially assessed using DSM-IV criteria but were reviewed and updated according to DSM-5 criteria after its publication by two child and adolescent psychiatrists. All children who met diagnostic criteria for DSM-IV ADHD also met criteria for DSM-5 ADHD (Eyre *et al.*, 2017).

2.1.3.2 *Child psychopathology*

Child psychopathology was assessed using the Child and Adolescent Psychiatric Assessment (CAPA) (Angold and Costello, 2000), a semi-structured research diagnostic interview. The parent-report version of the CAPA was used to assess the child's clinical symptoms of ADHD, oppositional defiant disorder (ODD), conduct disorder (CD), tic disorder, anxiety disorders (separation anxiety, social anxiety and generalised anxiety disorder) and depression. An impairment section in relation to each disorder was included for each section of the CAPA. Children aged 12 years and above completed the child-report version of the CAPA (which does not include an ADHD section, but included all other diagnoses described above) (Angold and Costello, 1995). All interviews were audiotaped and administered by trained psychologists supervised

weekly by a child and adolescent psychiatrist. Typed clinical summaries were completed on each child and ICD-10 and DSM-IV diagnoses were generated. Total symptom scores and diagnosis were generated from the CAPA according to DSM-IV criteria. Oppositional, conduct, anxiety and depression symptoms were counted as present when endorsed by either the parent or child. Evidence has shown that in making a final diagnosis, information from both parent and child is desirable for adolescents (Angold *et al.*, 1995), although self-report in younger children is not considered sufficiently reliable (Edelbrock *et al.*, 1985). Tic disorders were also assessed and counted as present if there were reports of motor or vocal tics (but not both).

Inter-rater reliability for a diagnosis of ADHD was high with a kappa coefficient of 1.0 for any diagnosis of ADHD and inter-rater reliability for parent rated conduct disorder symptoms was excellent, with an intraclass correlation of 0.98. To assess pervasiveness of ADHD symptoms across settings, reports from schools were obtained first using the Child ADHD Teacher Telephone Interview (CHATTI) (Holmes *et al.*, 2004), as this was similar to the parent measure of a semi-structured interview. If there was difficulty contacting the teacher, questionnaire measures, Conner's Teacher Rating Scale (Conners *et al.*, 1998) and DuPaul teacher rating scales (DuPaul, 1981), were sent to teachers. Pervasiveness was defined as present if the teacher endorsed one symptom from each of the core clinical dimensions and presence of impairment in at least one of these symptoms.

For each section of the CAPA, for any symptoms endorsed as present in the child, parents were asked to rate if their child's symptoms interfered with function in eight

different areas of life. These included impairment present at home, school, sports / clubs, activities in the community, during social interactions, learning to take care of oneself, play / leisure activities and handling of daily chores / responsibilities. This was rated as 'never', rarely', 'sometimes' or 'often'. Impairment scores of 'sometimes' or 'often' were taken as indicating presence of impairment in that area of the child's life. In deriving a continuous ADHD impairment score, a total summed impairment score out of eight was obtained. For a research diagnosis of ADHD, impairment was counted as being present if ADHD impairment was endorsed in any area.

2.1.3.3 Parental Psychopathology

Parental psychopathology was assessed using questionnaire measures. 546 mothers and 280 fathers completed questionnaires. The sample consisted of many (58% - mostly mothers) single parent families. Overall, 51% of families had no father questionnaire data available.

Parent ADHD

Mothers and fathers each completed a questionnaire regarding the presence of their own ADHD symptoms at ages 7-11 years (childhood) and in the last six months (current), using an 18 item checklist of DSM ADHD symptoms (American Psychiatric Association, 2000). Symptom presence was rated on a likert scale from 0 to 3, ('not at all', 'just a little', 'pretty much' and 'very much'). Ratings of 'pretty much' or 'very much' were taken to indicate the presence of a symptom. Total scores were generated for childhood and current symptoms separately.

There are many controversies and uncertainties in defining adult ADHD as there are no criteria laid out specifically for adults (McGough and Barkley, 2004). In the absence of

well-validated and universally accepted diagnostic criteria, it was decided that the symptom diagnostic criteria in the DSM-IV would be used to define adult ADHD for the first aim of this thesis, (chapter 3, analyses completed 2012); parent ADHD was rated as present if symptom criteria were met for any DSM-IV ADHD subtype (e.g. six inattentive symptoms, six hyperactive/impulsive symptoms or both in both childhood and current ratings). Cronbach's alpha reliability for parental ADHD symptom measures ranged from 0.91-0.94.

Following the publication of DSM-5 (American Psychiatric Association, 2013), the criteria for DSM-5 were utilised. Parent ADHD was assessed using symptom criteria for DSM-5; (six symptoms present in childhood and five symptoms present in adulthood) and this measure was used in the analyses for thesis aims 2 and 3 (chapters 4 and 5). Table 2.1 provides symptom diagnostic criteria for DSM-IV and DSM-5 ADHD. A binary measure of parent ADHD was used in this thesis instead of a continuous parent ADHD measure as it is difficult to generate a continuous measure using both child and current ADHD symptoms.

Table 2.1: ADHD diagnostic criteria for DSM-IV and DSM-5 ADHD (changes to criteria highlighted in **bold**).

Attention-Deficit/Hyperactivity Disorder Criteria A and B of the DSM	
DSM-IV	DSM-5
<ul style="list-style-type: none"> • Six or more of the symptoms of inattention and/or hyperactivity-impulsivity have persisted for at least six months to a degree that is maladaptive and inconsistent with developmental level • Some inattentive or hyperactive-impulsive symptoms that caused impairment were present before age 7 years 	<ul style="list-style-type: none"> • A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development • Six or more of the symptoms have persisted for at least six months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities • For older adolescents and adults (age 17 and older), five or more symptoms are required • Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years

Parent Depression

To measure parental depression, parents completed the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) which has been used widely to assess symptoms and caseness of depression and anxiety in non-psychiatric hospitals (Snaith, 2003). The HADS requires individuals to respond to questions in relation to how they have felt in the past week. It consists of 14 items divided into 2 subscales, depression and anxiety subscales (7 items each). The HADS scale has been used extensively and has been shown to be able to be a useful indicator of possible depression and anxiety in clinic as well as population samples (Lisspers, Nygren and Söderman, 1997; Bjelland *et al.*, 2002). In previous validation studies, a cut-off score of 11 or higher indicated the presence of a mood disorder (Bjelland *et al.*, 2002) and this

is what is used to define presence of depression in parents in this study. This thesis looked only at depression in parents but not anxiety in parents and therefore only the depression scale from the HADS was used. In the HADS, some of the anxiety items were similar to ADHD symptoms, for example 'restlessness' and 'being on the move'. Furthermore there is significant similarity of anxiety and depressive symptoms as anxiety and depression are thought to index the same underlying liability. Therefore parental anxiety was not included in any study investigation in this thesis. Cronbach's alpha for the HADS depression scale in this study is 0.83 which lies in the range reported in previous studies (0.67 to 0.90) (Bjelland 2002).

Parental Conduct problems in childhood

Parents also completed a DSM-IV/5 conduct symptom checklist on the presence of conduct disorder symptoms in themselves at age 7-11 years (ODD symptoms were not included in this checklist). Symptom presence was rated on a likert scale from 0 to 3, ('never', 'rarely', 'sometimes' and 'often'). Ratings of 'sometimes' or 'often' were taken to indicate the presence of a symptom. The number of symptoms present were then summed to calculate a total symptoms score of self-reported conduct symptoms in childhood for mothers and fathers separately.

2.1.3.4 Family Factors

Family environment

Parents completed questionnaires rating the family environment and parent warmth and hostility at home. Two subscales from The Family Environment Scale (FES) were used to assess family environment; nine items on family conflict and nine items on family cohesion (Moos and Moos, 1974). The alpha for the conflict and cohesion scale

in the FES manual is 0.75 and 0.78 respectively (Moos and Moos, 1981). The items were rated on a likert scale from 1 - 4 (strongly disagree to strongly agree). Items rated as 'agree' or 'strongly agree' were taken as indicating the item as present. Family environment measures were coded to reflect negative outcomes; higher scores indicate high conflict and low cohesion. For the cohesion scale, items 1, 3, 5, 7, 11, 15 and 17 were reverse coded so higher scores would indicate lower cohesion. For the conflict scale, items 4, 6, 8, 10, 12, 14, 16 and 18 were reverse coded so higher scores indicate reflect high conflict.

Warmth and Hostility

Parents were also asked to complete a 10 item questionnaire (Iowa Youth and Families Project Interaction Ratings Scales) containing two subscales; warmth and hostility (Melby *et al.*, 1993). Children aged 12 years and above (n=235) were also asked to rate their relationship with their mothers and fathers separately using the same measure (Melby *et al.*, 1993; Lifford, Harold and Thapar, 2009). These were rated on a likert scale of 1-7. Items were summed up to obtain a total score for each scale. The warmth and hostility measures were also coded to reflect negative outcomes; higher scores reflect higher levels of hostility and low levels of warmth. Cronbach's alpha for the warmth and hostility scale for child reports ranged from 0.85 to 0.93 and for parent report 0.81 – 0.87.

In general it was mostly mothers who completed these questionnaires. Data collected on the family environment and warmth and hostility measures are included in analyses in chapter 3.

Demographics and other factors

Information on family background including family income, parental educational attainment, employment status and history of mental health problems was obtained from each family. Socioeconomic status was classified according to the occupation of the main family wage earner, using the UK Standard Occupation Classification 2000 (*Standard Occupational Classification, 2000*). Families were then categorised as having a lower social economic status or not, with lower socioeconomic status defined as being in unskilled employment/unemployment. Low parent education was defined as having left school without any qualifications (including GCSE or equivalent). Data on education and social class relates to a combination of information from both the mother and father. Families were asked to indicate their household earning based on income bandings ranging from less than £10,000 to more than £60,000. These were split into a total of seven bands. According to the Office of National Statistics, the median household income in the UK is approximately £26,000, (<https://www.ons.gov.uk/>). Based on the data available according to the different bandings, low income was defined as annual family income < £20,000 which was the banding that fell below the median income. Information on current child medication use was also collected and children were classified according to whether or not they had a current prescription for ADHD medication.

2.1.3.5 Neurocognitive measures

Cognitive ability

All cognitive assessments were administered by trained psychologists. It was requested that children stop taking their stimulant medication 24 hours prior to testing, so performance on cognitive tests would not be influenced by effects of medication.

Cognitive ability was assessed using the Wechsler Intelligence Scale for Children version IV (WISC-IV) where a measure of full scale IQ was obtained (Wechsler, 2003). The full scale IQ is obtained from 10 subtests which comprise of four different components/ indices. The WISC-IV comprises of the following indices: Verbal Comprehension Index, Perceptual Reasoning Index, Working Memory Index and Processing Speed Index. The digit span subtest is a measure of verbal working memory and generated from the WISC (Wechsler, 2003).

Children are verbally given sequences of numbers and asked to repeat them, as heard and then in reverse order. It is simple and easy to administer but one limitation is that this test is limited to measuring working memory capacity related to verbal material only. This task has been used in previous research to assess working memory in children with ADHD (Gau and Shang, 2010).

Set Shifting

Children were also assessed using selected tasks from the Cambridge Neuropsychological Test Automated Battery (CANTAB) a computerised battery of nonverbal visually-presented neuropsychological tests (Cambridge Cognition, 1996). The Intra / Extra Dimensional Set Shift (IED) task is a computerised analogue version of the Wisconsin Card Sorting test and largely used as an executive functioning measure of visual discrimination, set shifting and attention flexibility. One of the strengths of the IED task is that it measures flexibility in a systematic fashion that allows for controlled increases in shifting demands

Participants are presented with two types of dimensions/shapes; 1) simple - white line or colour-filled shapes and 2) compound – white lines overlying coloured shapes (figures 2.2 and 2.3). The computer initiates a rule to determine a “correct” and

“incorrect” pattern presentation. Participants are asked to choose a pattern they think is correct. This rule continues until a participant has correctly identified the correct shape 6 times. The computer will then change the rule without informing the participant. The participant will now need to shift his/her attention to the new rule set by the computer. Feedback from the computer teaches the participant which is the correct rule and they need to follow it until the rule changes again, where they will need to shift to the new rule. There are a total of nine stages and at each stage the participant has to learn the relevant visual discrimination rule. Progress on to the next stage is dependent on a criterion of six consecutive correct responses (Downes *et al.*, 1989; Syngelaki *et al.*, 2009).

Figure 2.2: IED test screen example showing two simple colour-filled shapes (Taken from CANTABeclipse Test Administration Guide, manual version 3.0.0, 2006 Cambridge Cognition Limited)

(This figure has been removed by the author for copyright reasons)

There are two key stages here; 1) Stage 6- Intra dimensional shift (ID), which requires the participants to maintain attention to a previously relevant dimension and 2) Stage 8- Extra dimensional shift (ED) where the participants then need to shift their attention to a previously irrelevant dimension. The outcome measures are the total number of errors made throughout the task (adjusted for any stage that was not attempted) and the number of errors made in the ED shift stage (stage 8). A binary measure of whether the participant had successfully completed stage 8/9 (ED stage- ability to shift attention to the irrelevant stimuli) or not was also derived.

Figure 2.3: IED test screen example showing two overlapping dimensions (Taken from CANTABeclipse Test Administration Guide, manual version 3.0.0, 2006 Cambridge Cognition Limited)

(This figure has been removed by the author for copyright reasons)

Motivational Deficits

The Cambridge Gambling task (CGT), also part of the CANTAB assesses decision making and risk taking behaviour outside a learning context. Unlike other gambling tasks, it separates the decision-making (where participants choose what to bet on) from risk-taking (where participants decide how much then to bet on that choice) (figure 2.4) (Rogers *et al.*, 1999). On each trial, participants were presented with different ratios of 10 red and blue boxes in one of which a yellow token is hidden. Participants must guess if the yellow token is concealed behind a red or blue square (see figure 2.5). The participants start with a number of points displayed on the screen and must then select or bet a proportion of these points, (which are presented in either ascending or descending order) to gamble on their confidence of their chosen colour. The aim is to accumulate as many points as possible (see figure 2.5). The outcome measures used were *quality of decision making*, which looks at the proportion of trials where the majority colour was chosen (a higher score is favourable); *delay aversion* which is difference in percentage bets on the descending vs ascending trials (higher scores indicate impulsivity and intolerance of waiting); *risk taking* which is the mean proportion of points bet on trials where the most likely outcome was chosen; and *risk adjustment* which is the rate at which subjects increase the bet proportion in response to more favourable ratios (low scores are unfavourable) (DeVito *et al.*, 2008; Groen *et al.*, 2013).

Figure 2.4: The CGT task screen for the decision stage (Taken from CANTABeclipse Test Administration Guide, manual version 3.0.0, 2006 Cambridge Cognition Limited)

(This figure has been removed by the author for copyright reasons)

Figure 2.5: The CGT task screen for the gambling trial. (Taken from CANTABeclipse Test Administration Guide, manual version 3.0.0, 2006 Cambridge Cognition Limited)

(This figure has been removed by the author for copyright reasons)

2.1.4 Sample characteristics and demographics

The demographics and characteristics of the sample are presented here as this sample is mostly used across the thesis. The sample consisted of 570 children for cross-sectional analyses in chapters 3 and 5, with a mean age of 10.8 years (SD 3.0 years). Table 2.2 shows socio-demographic characteristics of children and families. The mean IQ for the whole sample was 82 (SD 13.6) and the male to female proportion is typical of a clinical ADHD sample (Gaub and Carlson, 1997).

Table 2.2: Demographics and characteristics of families (n=570)

	Total n		n	%
Child gender:	570	Male	482	85
		Female	88	15
Social class:	515	Low	279	54
		High & Medium	236	46
Income:	493	Low	174	35
		High & Medium	319	65
Parent Education:	527	GCSEs and above	382	72
		Below GCSEs	145	28
Child IQ:	540	IQ of 70 and above	463	86
		IQ below 70	77	14
On ADHD medication:	565	No	118	21
		Yes	447	79

Approximately 72% of children had a diagnosis of ADHD DSM-IV Combined type, 6% with DSM-IV inattentive subtype or DSM-5 predominantly inattentive presentation, 9% with DSM-IV hyperactive-impulsive subtype or DSM-5 predominantly hyperactive-impulsive presentation and 13% ADHD DSM-III-R (Children were classified as DSM-III-R where teacher reports were unobtainable but evidence of pervasiveness was present from parent reports). With regards to comorbidity, 40.2% had met research diagnostic criteria for ODD, 21.2% for CD, 7.7% for any anxiety disorder (separation, social and general anxiety disorders) and 0.9% for any depression diagnosis. More than one comorbid disorder could apply here apart for comorbidity of CD and ODD. Children who met research diagnostic criteria for bipolar disorder did not overlap with those that met research diagnostic criteria for depression. Table 2.3 shows the breakdown of DSM ADHD research diagnoses and comorbidity in the sample. The review and update of ADHD diagnoses and comorbidities from DSM-IV to DSM-5 criteria, showed that proportions of ADHD and comorbidities remained unchanged apart from rates of Oppositional Defiant Disorder (ODD) (Eyre *et al.*, 2017). A higher number of children met criteria for ODD using the DSM-5 criteria (51.8%), as Criterion D in the DSM-IV had an exclusion criterion preventing ODD diagnosis in the presence of CD which has been removed in the DSM-5. However in this thesis, analyses using ODD symptoms and diagnoses were only used in chapter 3 which is based on the DSM-IV criteria.

Table 2.3: ADHD diagnosis and comorbidity in children

	n (%)
ADHD Diagnosis: Combined	411 (72)
Inattentive	35 (6)
Hyperactive/Impulsive	49 (9)
DSM-III-R	75 (13)
Oppositional Defiant Disorder (ODD)	226 (40.2)
Conduct Disorder (CD)	119 (21.2)
Any Anxiety diagnosis	42 (7.7)
Any Depression diagnosis	5 (0.9)
Bipolar disorder	7 (1)
Tic disorder (transient/ chronic)	57 (11.4)

Table 2.4 Percentages of parent ADHD and depression in the SAGE sample (n=570)

	Mother	Father	Parent (either mother or father)	Both (mother and father)
	n = 543	n = 277	n = 568	
	n (%)	n (%)	n (%)	n (%)
ADHD DSM-IV	102 (18.8%)	70 (25.3%)	164 (28.9%)	8 (1.4%)
ADHD DSM-5	117 (21.5%)	80 (28.9%)	186 (32.7%)	11 (1.9%)
Depression	113 (21%)	30 (10.9%)	135 (24%)	8 (1.4%)

The rates of parent ADHD using DSM-IV and DSM-5 criteria and parent depression are shown in table 2.4. Despite the stringent research criteria used for parent ADHD, high rates of ADHD were found in parents for this sample. Using the DSM-5 criteria slightly increased the rates by approximately 3% for both mothers and fathers. With regards to depression, 21% of mothers met the cut-off score for depression on the HADS whereas only 11% of fathers met the cut-off score criterion. Analyses using small sample size can affect results in many ways; reducing the chances of detecting a true effect (false negatives) or can overestimate the magnitude of an effect if true effect is found (false positives) (Button *et al.*, 2013). Given the low proportion of paternal depression in this sample, it was decided that paternal depression on its own would not be included in the investigation of the aims in this thesis.

2.2 Follow up sub-sample

2.2.1 Recruitment procedure

For analyses in chapter 4 of this thesis, a subgroup of the SAGE sample was utilised. This group who had previously completed all of the assessment procedures detailed earlier (Time 1) took part in a follow up study (Time 2) on average two and a half years later. This section details the sample recruitment and procedures for the follow up study, herein referred to as Time 2. Male participants aged between 10-17 years with an IQ > 70 were invited to take part at this follow up. Amongst those who were traceable and invited to take part at Time 2 (n=240), 72% agreed to participate. In total, 174 participants from the SAGE study took part at Time 2. Of these, 143 participants had complete parent questionnaire data from the initial SAGE study. Figure 2.1 (page 44) shows details of the recruitment process for Time 2. Ethical approval was obtained from the Wales Multicentre Research Ethics Committee (reference number: 11/WA/0050). Written informed consent was obtained from parents and adolescents aged 16 years and over and written assent was obtained for younger adolescents. Information about the follow up study has also been published in the following reference (van Goozen *et al.*, 2016)

2.2.2 Assessment and measures at Time 2

All baseline measures (Time 1) for these participants are detailed in section 2.1.3 of this chapter. Child psychopathology at Time 2 was re-assessed using the Development and Well Being Assessment (DAWBA) structured diagnostic interview (Goodman *et al.*,

2000). The DAWBA was used rather than the CAPA to reduce the assessment and time burden on families. Parents completed the ADHD, ODD and CD sections and young people the ODD and CD sections (there is no child report section for ADHD in the DAWBA). ODD and CD symptoms were rated as present when endorsed by either the parent or young person. All interviews were administered by trained psychologists supervised weekly by a child psychiatrist and a psychologist. Symptom scores and diagnoses were generated from the DAWBA using DSM-5 criteria. The follow up study did not obtain any information from teachers.

2.3 Summary

As detailed in the beginning of this chapter, results in chapters 3 and 5 are based on the SAGE clinical sample of children with ADHD, and the results within chapter 4 are based on the follow up of a subsample of SAGE study that were reassessed a couple of years later. Further information on the relevant assessment measures, predictor and dependent variables as well as analyses are described again briefly in each subsequent chapter as relevant.

Chapter 3

Are parent ADHD problems associated with a more severe clinical presentation and greater family adversity in children with ADHD?

Chapter description

This chapter will address the first aim of this thesis which is to investigate the association between parent ADHD, child clinical presentation and family functioning in a clinical sample of children with ADHD. The sample and measures used have been explained in detail in chapter 2 but are briefly presented in the methods sections of this chapter. This chapter is based on the publication '*Are parental ADHD problems associated with a more severe clinical presentation and greater family adversity in children with ADHD?*' in the European Child and Adolescent Psychiatry Journal 2013 Jun; 22(6):369-77.

3.1 Introduction

As discussed in chapter 1, it is well established that Attention Deficit Hyperactivity Disorder (ADHD) is a familial and highly heritable disorder (Thapar *et al.*, 2013). Previous studies have also shown elevated rates of ADHD in the parents of children with ADHD and vice versa (Chronis *et al.*, 2003; Minde *et al.*, 2003). Little is known about the relationship between parent ADHD, the severity of child ADHD and other clinical and family factors. There is increasing recognition of the significance of ADHD symptoms in adults; adults with ADHD are reported to have much impairment in the form of repeated life failures such as academic underachievement, frequent job changes, marital breakdown and high rates of divorce (Wilens, Faraone and Biederman, 2004; Asherson *et al.*, 2007). The impairments and difficulties faced by a parent with ADHD could impact on family functioning and the presentation of ADHD in their children.

As discussed in chapter 1, the family environment is thought to be an important aspect in development, outcomes and manifestation of a disorder in children (Johnston and Mash, 2001). Previous literature shows that families of children with ADHD encounter greater difficulties such as family conflict, negative parent-child relationship and higher rates of parental psychopathology (Barkley and Murphy, 1998; Biederman, Faraone and Monuteaux, 2002). Parenting studies have linked parent ADHD to less effective parenting (Murray and Johnston, 2006; Banks *et al.*, 2008). High levels of mother ADHD symptoms were found to interfere with improvement shown by children with ADHD following parent training (Sonuga-Barke, Daley and Thompson, 2002). It has

also been found that one predictor of persistent ADHD in children was exposure to maternal psychopathology (Biederman *et al.*, 2011).

Parental psychopathology is clearly important, not only as an index of inherited risk but because of the role a parent plays in providing care and in becoming a role model for the child. Having a parent with ADHD may index additional risk to the child, influencing the ADHD severity and pattern of comorbidity in the child. Unfortunately, few studies have investigated the relationship between parent ADHD and child's clinical presentation and findings have so far been inconsistent. Two studies found parent ADHD to be associated with child ADHD severity whereas one other study did not find support for this association (Biederman, Faraone and Monuteaux, 2002; Goos, Ezzatian and Schachar, 2007; Takeda *et al.*, 2010). This difference could be due to different definitions and timing of parental ADHD used in each study. Parent ADHD has been either measured only during childhood or only currently in adult life (Goos, Ezzatian and Schachar, 2007; Takeda *et al.*, 2010). In a family study of ADHD probands and controls, children and their siblings were categorized into groups based on presence of parental ADHD before and after the birth of the child, but not necessarily concurrent to child ADHD assessment (Biederman, Faraone and Monuteaux, 2002). Given that ADHD persists into adulthood for some but not all individuals and because associations with child clinical presentation may be due to the child's exposure to the parenting (e.g. via environment) or the parent's underlying traits (e.g. via genetic risk) or both (via gene-environment correlation), it is not clear whether having a parent with just history of childhood ADHD or persistent/current ADHD symptoms may be relevant or associated with child clinical presentation.

To diagnose ADHD in adults, clinicians often use the symptom criteria outlined in the DSM-IV as a guideline. One of the requirements is to establish the presence of symptoms both during childhood and 6 months before interview (Weiss and Murray, 2003). This definition of 'adult' ADHD will be used in this study. Given the inconsistency of results and definitions of parent ADHD, it would be useful to explore how differences in the timing of the presence of parental ADHD symptoms relate to child and family functioning specifically by comparing persistent parental ADHD ('adult' ADHD criterion) with remitted ADHD (symptom criteria only met during childhood).

Understanding the influence of parent ADHD has important clinical relevance; if having a parent with ADHD indexes a more severe child clinical presentation, regardless of whether these links are inherited and/or environmental, then it may be important to ask about parental history during clinical assessment and consider addressing parental ADHD as part of the treatment plan.

As discussed in chapter 1, literature on familial models has suggested gender differences in prevalence of ADHD exist due to the different burden of risk in males and females (Rhee *et al.*, 1999). It is suggested that females with ADHD require a greater load of genetic risk than males before manifesting symptoms (Cloninger *et al.*, 1978; Faraone *et al.*, 1995). By extending this into adulthood, the literature suggests that females transmit a greater genetic risk to their offspring than affected males (Rhee *et al.*, 1999; Goos, Ezzatian and Schachar, 2007). Thus a mother with ADHD may convey a greater risk to her offspring compared to a father with ADHD. Evidence reveals mixed findings regarding different risk effect of parental gender. Biederman and colleagues (2002) found no significant differences in the effect of parent gender

on association between parent ADHD and child clinical outcome (Biederman, Faraone and Monuteaux, 2002). Conversely in a study by Goos et al (2007), maternal ADHD was found to have greater influence on child impairment, but on the other hand Takeda et al (2010) found paternal ADHD to have greater influence instead (Goos, Ezzatian and Schachar, 2007; Takeda *et al.*, 2010). Therefore it may be important to clarify if there are differences related to having a mother or father with ADHD.

3.2 Study Aims

In a sample of children with ADHD, this chapter aims to investigate:

1. Associations between mother and father ADHD and clinical presentation of the child
2. Associations between mother and father ADHD and family adversity
3. If there are any differences according to which parent has ADHD (mother or father)

It was hypothesised that children with a parent with ADHD problems will have a more severe clinical presentation of the disorder compared to children without a parent with ADHD and that there will be greater conflict and hostility in this subgroup of children. It was also hypothesised that there would be no difference according to which parent (mother or father) had ADHD. A secondary aim of this study is to explore the differences between how persistent parent ADHD (adult ADHD criterion) and parent ADHD childhood-only (symptom criteria only met during childhood) relate to observed associations with child clinical presentation and family function.

3.3 Methods

3.3.1 Sample

This chapter utilises the cross-sectional sample of children with ADHD obtained from the Study of ADHD Genes and Environment – SAGE. Recruitment procedures and assessments / measures used in this sample are discussed in detail in chapter 2. The measures specifically used in this chapter are outlined below briefly.

3.3.2 Measures

Predictors

Parent ADHD

Mothers and fathers each completed a questionnaire regarding the presence of ADHD symptoms in themselves at age 7-11 years (childhood) and in the last six months (current), using an 18 item checklist of DSM ADHD symptoms (American Psychiatric Association, 2000). Positive ADHD status was assigned if symptom criteria were met for any DSM-IV ADHD subtype (e.g. six inattentive symptoms, six hyperactive/impulsive symptoms or both). The predictor measures used in this study are:

- Mother adult ADHD (DSM-IV)
- Father adult ADHD (DSM-IV)

The term 'adult ADHD' refers to persistent ADHD in adults/ parents and will be used throughout this chapter. ADHD childhood-only status was generated separately for mothers and fathers who met ADHD status in childhood, but not currently. These

variables were utilised for further analyses to explore differences between adult ADHD status (persistent) and ADHD status during childhood-only.

Outcome measures

Child Psychopathology

Child psychopathology was assessed using a semi structured research diagnostic interview; the Child and Adolescent Psychiatric Assessment (CAPA) (Angold and Costello, 2000). Symptom scores and diagnosis were generated from the CAPA according to DSM-IV criteria. ADHD severity in this study refers to the sum of ADHD symptoms that were endorsed by parent report. Impairment of ADHD symptoms across eight different settings (e.g. home, school, leisure activities) was obtained from the parent interview. Teacher reports of child symptoms were obtained and used to assess pervasiveness of ADHD symptoms across settings. Symptoms of oppositional defiant disorder, conduct disorder, anxiety and depression were counted as present when endorsed by either the parent or child and were summed separately to calculate severity scores for each disorder. Below is a list of the clinical outcome measures:

- ADHD subtype
- ADHD severity
- ADHD impairment
- Conduct Disorder (CD) diagnosis and severity
- Oppositional Defiant Disorder (ODD) diagnosis and severity
- Depression severity
- Anxiety severity

Family Factors

The family measures were obtained from the Family Environment Scale (Moos and Moos, 1974) and the Iowa Youth and Families Project Interaction Ratings Scales (Melby *et al.*, 1993). Items on the family environment measures were reverse coded so that higher scores reflect negative outcomes; higher scores reflect high conflict and hostility, low cohesion and warmth. Listed below are the family outcome measures that were used:

- Conflict (parent reported); Family Environment Scale
- Low cohesion (parent reported); Family Environment Scale
- Low warmth (parent and child report); Iowa Youth and Families Project Interaction Ratings Scales
- Hostility (parent and child report); Iowa Youth and Families Project Interaction Ratings Scales

3.3.3 Analysis

Analyses were conducted using linear regression for continuous outcomes and logistic regression for binary outcomes. For variables that were not normally distributed (with scores of skewness and kurtosis of above 1 and 3 respectively) scores were transformed using the square root (ADHD total severity, inattention severity, hyperactive-impulsive severity, ADHD impairment, conduct symptom severity, depression symptom severity and parent report of low warmth) or natural logarithmic (anxiety symptom severity) transformations. As ADHD symptoms are expected to

decline with age and because of a high male preponderance in clinical samples of ADHD (see discussion in chapter 1), child age and gender were included as covariates. To investigate the relationship between parental psychopathology and child clinical presentation, data were analysed using the DSM-IV adult measure of parental ADHD for mothers and fathers separately. These were binary predictors in all analyses. Analysis was also conducted to explore differences in timing of parental ADHD by investigating associations using parental ADHD status during childhood-only. Direct comparisons between mother and father ADHD groups as well as between the adult ADHD group and parent ADHD childhood-only group were also conducted. As low social class is highly correlated with parent ADHD and it is difficult to distinguish if social class is a confounder or a mediator between parent and child presentation, further analysis was conducted to examine to what extent all observed associations changed after adjustment for social class. All results are presented using unstandardized coefficients. All analyses were performed using SPSS version 20.

It is important to note here that there was no adjustment for multiple comparisons as this was an exploratory study setting out to investigate the associations between parent psychopathology and clinical presentation in children with ADHD. The findings would not withstand correction for multiple testing and are in need of replication. Additionally, given that outcomes are correlated, some have suggested that correction for multiple testing such as the Bonferroni method may be overly conservative.

3.4 Results

The sample consisted of 570 children, 88 (15.4%) females and 482 (84.6%) males, with a mean age of 10.78 years (SD 3.01 years). Details of sample demographics and characteristics are provided in section 2.1.4 in chapter 2.

High rates of parental ADHD problems were found in this sample; 29% (95%CI 25-33%) of children had a parent who met DSM-IV criteria for adult ADHD, where 18.8% (95%CI 16-22%) of mothers and 25% (95%CI 20-31%) of fathers met criteria for adult ADHD. The rates of ADHD in fathers were high despite there being many missing fathers and possible selective attrition. There also seemed to be little overlap where both parents have ADHD (1.4%). Rates of parent ADHD are shown in more detail in table 3.1.

Child age and gender did not significantly differ between those with or without a mother (age: $t = 0.35$ (541), $p=0.72$; gender: $\chi^2 = 1.08$ (1), $p=0.30$) or father (age: $t = 1.05$ (275), $p=0.30$; gender: $\chi^2 = 0.19$ (1), $p=0.66$) with ADHD. Both mother and father adult ADHD were significantly associated with lower social class (mother ADHD, $\chi^2 = 8.92$ (1), $p=0.003$; father ADHD, $\chi^2 = 4.57$ (1), $p=0.03$). Child ADHD medication use did not differ across groups (mother ADHD, $\chi^2 = 0.03$ (1), $p=0.86$; father ADHD, $\chi^2 = 0.11$ (1), $p=0.75$).

Table 3.1: ADHD problems in mothers and fathers.

Parent ADHD Status:	Adult ADHD	No Adult ADHD	ADHD Childhood- <u>only</u>
Mother	102 (18.8%)	441 (81.2%)	54 (10.1%)
Father	70 (25.3%)	207 (74.7%)	68 (25.2%)
<u>Either</u> Parent*	164 (28.9%)	404 (71.1%)	115 (20.5%)
<u>Both</u> Mother <u>and</u> Father**	8 (2.9%)	269 (97.1%)	7 (2.5%)

*either mother or father with an 'Adult' ADHD status

**Both mother and father with an 'Adult' ADHD status

3.4.1 Child Clinical Presentation

As detailed in table 3.2, Mother ADHD was associated with greater child total ADHD ($B = 0.14$, 95%CI 0.004, 0.28, $p=0.044$) and inattention symptom severity ($B = 0.11$, 95%CI 0.001, 0.22 $p=0.048$). Children with mothers in the adult ADHD group were more likely to have a diagnosis of CD (OR = 1.79, 95%CI 1.06, 3.02 $p=0.029$) and increased conduct symptom severity (table 3.2). Father ADHD was associated with children's total conduct symptom scores ($B = 0.15$, 95%CI 0.02, 0.29 $p=0.026$) and the odds ratio for a diagnosis of CD in the paternal ADHD group was OR = 1.85 (95%CI 0.93, 3.69 $p=0.08$) (table 3.3). Both mother and father ADHD were not found to be associated with ADHD impairment in the offspring.

As discussed in section 2.1.3.3 of chapter 2, the analyses for this chapter (accompanying journal article submitted in January 2013) were conducted based on DSM-IV criteria. To assess potential differences due to diagnostic criteria, sensitivity analyses were re-run using DSM-5 criteria. Results did not differ between the two. The analysis from this chapter using DSM-5 criteria is included in the appendices (appendix 3.1 to 3.4)

Table 3.2: Mother ADHD and child clinical presentation

Child Clinical Presentation	Mother ADHD		Unadjusted			Adjusted for child age and gender		
	No ADHD n=441	ADHD n=102	B	95% CI	p	B	95% CI	p
	Mean (SD)	Mean (SD)						
ADHD severity ^a	15.05 (2.77)	15.62 (2.42)	0.15	0.003, 0.29	0.046	0.14	0.004, 0.28	0.044
Inattention severity ^a	7.42 (1.70)	7.75 (1.66)	0.11	0.002, 0.22	0.046	0.11	0.001, 0.22	0.048
Hyperactive-Impulsive severity ^a	7.63 (1.65)	7.87 (1.51)	0.07	-0.03, 0.18	0.17	0.07	-0.03, 0.17	0.15
ADHD impairment ^a	6.70 (1.56)	6.99 (1.37)	0.09	-0.01, 0.19	0.07	0.09	-0.01, 0.19	0.08
CD symptom severity ^a	1.17 (1.64)	1.59 (2.06)	0.11	0.004, 0.22	0.042	0.11	0.01, 0.22	0.042
Oppositional Defiant Disorder severity	3.66 (2.32)	4.00 (2.27)	0.34	-0.16, 0.84	0.18	0.33	-0.17, 0.82	0.19
Depression severity ^a	1.47 (1.47)	1.68 (1.51)	0.07	-0.03, 0.17	0.15	0.07	-0.03, 0.16	0.15
Anxiety severity ^a	0.88 (1.70)	1.06 (1.73)	0.08	-0.06, 0.22	0.25	0.08	-0.06, 0.22	0.26
	<i>n (%)</i>	<i>n (%)</i>	<i>OR</i>	<i>95% CI</i>	<i>p</i>	<i>OR</i>	<i>95%CI</i>	<i>p</i>
ADHD DSM-IV Combined	305 (72.1)	76 (78.4)	1.38	0.82, 2.35	0.23	1.40	0.81, 2.40	0.22
ADHD DSM-IV Inattentive	26 (6.0)	5 (4.9)	0.77	0.29, 2.06	0.61	0.77	0.28, 2.09	0.60
ADHD DSM-IV Hyperactive-Impulsive	37 (8.5)	9 (8.8)	0.98	0.46, 2.09	0.96	1.02	0.47, 2.18	0.97
CD Diagnosis	68 (15.6)	25 (24.8)	1.78	1.06, 2.99	0.031	1.79	1.06, 3.02	0.029
Oppositional Defiant Disorder Diagnosis	180 (41.4)	38 (37.6)	0.85	0.55, 1.33	0.49	0.84	0.54, 1.32	0.45

^aTransformed scores

Table 3.3: Father ADHD and child clinical presentation

Child Clinical Presentation	Father ADHD							
	No ADHD n=207	ADHD n=70	Unadjusted			Adjusted for child age and gender		
	<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>B</i>	<i>95% CI</i>	<i>p</i>	<i>B</i>	<i>95% CI</i>	<i>p</i>
ADHD severity ^a	14.75 (2.62)	14.97 (3.38)	0.08	-0.10, 0.27	0.38	0.06	-0.12, 0.24	0.50
Inattention severity ^a	7.41 (1.61)	7.35 (1.87)	-0.01	-0.15, 0.12	0.87	-0.02	-0.15, 0.12	0.81
Hyperactive-Impulsive severity ^a	7.34 (1.71)	7.62 (2.11)	0.12	-0.02, 0.26	0.10	0.10	-0.04, 0.24	0.17
ADHD impairment ^a	6.68 (1.66)	6.66 (1.38)	-0.03	-0.16, 0.10	0.67	-0.04	-0.17, 0.09	0.55
CD symptom severity ^a	0.98 (1.49)	1.53 (2.13)	0.15	0.02, 0.28	0.026	0.15	0.02, 0.29	0.026
Oppositional Defiant Disorder severity	3.50 (2.37)	3.73 (2.44)	0.23	-0.42, 0.89	0.48	0.19	-0.46, 0.84	0.57
Depression severity ^a	1.32 (1.24)	1.44 (1.31)	0.04	-0.07, 0.15	0.46	0.05	-0.06, 0.16	0.37
Anxiety severity ^a	1.01 (1.87)	0.79 (1.40)	-0.06	-0.23, 0.12	0.54	-0.05	-0.23, 0.13	0.58
	<i>n (%)</i>	<i>n (%)</i>	<i>OR</i>	<i>95% CI</i>	<i>p</i>	<i>OR</i>	<i>95% CI</i>	<i>p</i>
ADHD DSM-IV Combined	131 (66.8)	47 (69.1)	1.09	0.60, 1.97	0.79	1.02	0.55, 1.90	0.96
ADHD DSM-IV Inattentive	20 (9.8)	3 (4.3)	0.40	0.11, 1.37	0.14	0.45	0.13, 1.59	0.21
ADHD DSM-IV Hyperactive-Impulsive	20 (9.8)	4 (5.9)	0.73	0.27, 2.04	0.55	0.61	0.20, 1.86	0.39
CD Diagnosis	28 (13.7)	16 (22.9)	1.86	0.94, 3.70	0.08	1.85	0.93, 3.69	0.08
Oppositional Defiant Disorder Diagnosis	75 (36.8)	25 (35.7)	0.96	0.54, 1.68	0.88	0.93	0.53, 1.64	0.80

^aTransformed scores

3.4.2 Family environment

Higher levels of conflict and lower levels of cohesion were reported by parents in the mother ADHD group, there was a similar pattern but no evidence of association ($B=2.29$, 95%CI -0.02 , 4.60 , $p=0.05$) for higher levels of mother hostility reported by children in these families (table 3.4). Children reported significantly higher levels of mother warmth when fathers had ADHD (table 3.5). Contrary to what was found in the mother ADHD analyses, there was no evidence of high levels of family conflict (parent-reported) found in the father ADHD group. To further investigate this, these associations were examined in a subset of families where information on family environment was available from both parents ($n=96$). Higher levels of mother hostility (child-reported) were found when mothers had ADHD compared to when fathers had ADHD ($p<0.01$) (table 3.6). There was no evidence of any differences between mother and father ADHD groups in terms of parent-reported conflict ($p=0.08$) and cohesion ($p=0.65$) in the family.

Table 3.4: Associations between mother ADHD and family environment

Family Environment	Mother ADHD		Unadjusted			Adjusted for child age and gender		
	No ADHD n = 441	ADHD n = 102	B	95% CI	p	B	95% CI	p
	Mean(SD)	Mean(SD)						
Parent report Low Warmth ^a	10.82 (5.29)	11.47 (5.18)	0.11	-0.06, 0.27	0.20	0.11	-0.04, 0.27	0.16
Parent report Hostility	15.35 (4.37)	16.23 (4.67)	0.88	-0.09, 1.84	0.08	0.89	-0.08, 1.85	0.07
Child report Mother Low Warmth ^a	11.32 (6.62)	12.61 (6.47)	0.19	-0.13, 0.50	0.24	0.21	-0.08, 0.50	0.16
Child report Mother Hostility	18.18 (6.63)	20.49 (6.69)	2.31	-0.01, 4.63	0.05	2.29	-0.02, 4.60	0.05
Child report Father Low Warmth	14.87 (8.84)	17.93 (8.61)	2.89	-0.61, 6.39	0.11	2.89	-0.61, 6.39	0.11
Child report Father Hostility	17.59 (7.57)	19.52 (7.50)	1.93	-1.13, 4.99	0.22	1.86	-1.22, 4.94	0.24
Parent report Conflict	4.02 (2.36)	5.07(2.37)	1.06	0.54, 1.57	<0.01	1.06	0.54, 1.57	<0.01
Parent report Low Cohesion	2.18 (1.91)	2.68 (2.13)	0.51	0.08, 0.94	0.02	0.51	0.08, 0.94	0.02

^a Transformed scores

Table 3.5: Associations between father ADHD and family environment

Family Environment	Father ADHD		Unadjusted			Adjusted for child age and gender		
	No ADHD n=207	ADHD n=70	B	95% CI	p	B	95% CI	p
	<i>Mean(SD)</i>	<i>Mean(SD)</i>						
Parent report Low Warmth ^a	11.93 (5.96)	10.12 (4.52)	-0.25	-0.47, -0.03	0.03	-0.21	-0.42, 0.00	0.06
Parent report Hostility	15.34 (4.40)	15.32 (4.81)	-0.02	-1.29, 1.25	0.98	0.01	-1.26, 1.29	0.98
Child report Mother Low Warmth ^a	13.11 (7.68)	8.96 (4.20)	-0.56	-0.99, -0.13	0.01	-0.49	-0.90, -0.07	0.02
Child report Mother Hostility	18.39 (7.02)	15.36 (7.33)	-3.03	-6.27, 0.21	0.07	-2.88	-6.18, 0.42	0.09
Child report Father Low Warmth	14.45 (8.87)	13.48 (7.68)	-0.97	-4.91, 2.97	0.63	-0.32	-4.23, 3.59	0.87
Child report Father Hostility	18.52 (7.47)	17.56 (7.86)	-0.96	-4.43, 2.51	0.58	-0.54	-4.07, 2.98	0.76
Parent report Conflict	4.11 (2.42)	4.20 (2.46)	0.09	-0.60, 0.77	0.80	0.10	-0.59, 0.79	0.78
Parent report Low Cohesion	2.16 (1.86)	2.40 (2.04)	0.24	-0.30, 0.78	0.38	0.24	-0.30, 0.78	0.38

^aTransformed scores

Table 3.6 Means and comparison of parent ADHD group in those with complete information on both mothers and fathers n=96

Child report on parent warmth and hostility	Parent ADHD groups			
	No parent ADHD (n = 60)	Mother ADHD only (n = 12)	Father ADHD only* (n = 21)	Both parents with ADHD (n = 3)
Mother - low warmth	12.41 (7.38)	13.17 (7.37)	9.05 (4.30)	7.67 (4.62)
Mother - hostility	18.26 (6.53) ^b	20.85 (8.15) ^a	13.57 (6.25) ^{a, b}	23.67 (6.11) ^b
Father - low warmth	14.03 (9.35)	16.92 (7.89)	12.57 (6.41)	20.00 (15.00)
Father - hostility	18.61 (7.74)	20.08 (7.05)	16.38 (7.19)	24.00 (11.53)

*Father ADHD only as comparison group

^a significant p<0.01

^b significant p<0.05

3.4.3 Childhood-only parental ADHD vs adult parental ADHD

Analyses were conducted to examine if there were associations between parental childhood-only ADHD status and child clinical presentation and family environment. There was no evidence of associations between mother and father childhood-only ADHD and child clinical presentation (table 3.7). Children in the mother childhood-only ADHD group reported mothers as showing less warmth (B = 2.89, 95% CI 0.23, 5.54 p=0.03). In the father childhood-only ADHD group, associations were found with better cohesion (B = -0.77, 95% CI -1.32, -0.23, p=0.01) in the family as reported by parents (table 3.8). Mothers and fathers in the childhood-only ADHD group were not completely without current ADHD symptoms; few symptoms were present though not sufficient to meet symptom criteria for current diagnosis of any DSM-IV subtype (mean current ADHD symptoms: mothers 5.98 (SD 2.69), fathers 4.46 (SD 2.75)). Direct comparisons between the two groups (parent adult ADHD and parent childhood-only

ADHD) showed that children in the mother adult ADHD group had higher symptom severity and more parent-reported conflict and parent-reported hostility in families compare to those in the mother childhood-only group. In the father adult ADHD group, there was evidence of lower parent-reported cohesion (tables 3.9 and 3.10).

Table 3.7: Mother and father childhood-only ADHD and child clinical presentation

Child Clinical Presentation	Mother childhood-only ADHD ^b			Father childhood-only ADHD ^c		
	<i>B</i>	<i>95% CI</i>	<i>p</i>	<i>B</i>	<i>95% CI</i>	<i>p</i>
ADHD severity ^a	0.19	-0.001, 0.38	0.05	0.06	-0.13, 0.25	0.55
Inattention severity ^a	0.13	-0.01, 0.28	0.07	-0.01	-0.15, 0.13	0.93
Hyperactive-Impulsive severity ^a	0.11	-0.03, 0.24	0.13	0.09	-0.06, 0.23	0.25
ADHD impairment ^a	0.01	-0.13, 0.14	0.94	-0.03	-0.16, 0.10	0.61
CD symptom severity ^a	-0.08	-0.22, 0.06	0.28	-0.06	-0.20, 0.08	0.43
Oppositional Defiant Disorder severity	-0.63	-1.29, 0.30	0.06	0.28	-0.39, 0.95	0.41
Depression severity ^a	-0.07	-0.20, 0.06	0.27	0.01	-0.10, 0.12	0.85
Anxiety severity ^a	-0.15	-0.34, 0.03	0.10	0.12	-0.07, 0.30	0.21
	<i>OR</i>	<i>95% CI</i>	<i>p</i>	<i>OR</i>	<i>95% CI</i>	<i>p</i>
CD Diagnosis	1.26	0.62, 2.55	0.52	0.88	0.41, 1.89	0.74
Oppositional Defiant Disorder Diagnosis	0.55	0.29, 1.02	0.06	1.60	0.91, 2.83	0.10

^a Transformed scores

^b Linear regression analyses: presence of mother childhood-only ADHD status vs mothers without childhood-only ADHD

^c Linear regression analyses: presence of father childhood-only ADHD status vs fathers without childhood-only ADHD

Table 3.8: Mother and father childhood-only ADHD and family environment

Family Environment	Mother childhood-only ADHD ^b			Father childhood-only ADHD ^c		
	<i>B</i>	<i>95% CI</i>	<i>p</i>	<i>B</i>	<i>95% CI</i>	<i>p</i>
Parent report Low Warmth ^a	0.17	-0.04, 0.37	0.12	-0.17	-0.40, 0.05	0.13
Parent report Hostility	-1.10	-2.35, 0.16	0.09	-1.26	-2.53, 0.01	0.05
Child report Mother Low Warmth ^a	2.89	0.23, 5.54	0.03	-3.17	6.45, 0.12	0.06
Child report Mother Hostility	-1.15	-4.13, 1.82	0.45	-1.48	-4.81, 1.85	0.38
Child report Father Low Warmth	1.11	-3.38, 5.60	0.63	-1.07	-5.12, 2.98	0.60
Child report Father Hostility	-1.96	-5.79, 1.87	0.31	-0.60	-4.16, 2.97	0.74
Parent report Conflict	-0.07	-0.75, 0.61	0.84	-0.29	-0.99, 0.41	0.42
Parent report Low Cohesion	0.10	-0.46, 0.65	0.73	-0.77	-1.31, -0.23	0.01

^a Transformed scores

^b Linear regression analyses: presence of mother childhood-only ADHD status vs mothers without childhood-only ADHD

^c Linear regression analyses: presence of father childhood-only ADHD status vs fathers without childhood-only ADHD

Table 3.9: Comparisons between mother childhood-only ADHD vs mother adult ADHD

Child clinical symptoms	Mother childhood- only ADHD (n = 54)	Mother adult ADHD (n = 102)	<i>t (df) / χ^2</i>	<i>p</i>
Total ADHD	14.48 (3.24)	15.62 (2.42)	2.52 (151)	0.01
Inattention severity	7.09 (1.87)	7.75 (1.66)	2.42 (151)	0.02
Hyperactive-Impulsive severity	7.38 (1.78)	7.87 (1.51)	1.87 (151)	0.06
CD severity	1.04 (1.56)	1.59 (2.06)	-1.74 (152)	0.08
ODD severity	3.17 (2.33)	4.00 (2.28)	-2.14 (152)	0.03
CD Diagnosis	11 (20.8%)	25 (24.8%)	0.685 (1)	0.41
ODD Diagnosis	15 (28.3%)	38 (37.6%)	1.34 (1)	0.25
Family environment			<i>t (df)</i>	<i>p</i>
Parent report Low Warmth	11.94 (5.83)	11.47 (5.18)	0.45 (152)	0.66
Parent report Hostility	14.54 (4.45)	16.23 (4.67)	-2.18 (152)	0.03
Child report Mother Low Warmth	14.05 (6.23)	12.61 (6.47)	0.98 (58)	0.33
Child report Mother Hostility	17.50 (5.88)	20.49 (6.69)	-1.74 (59)	0.09
Child report Father Low Warmth	16.41 (8.02)	17.93 (8.61)	-0.592 (44)	0.56
Child report Father Hostility	16.18 (3.58)	19.52 (7.50)	-2.04 (43)	0.05
Parent report Conflict	4.15 (2.41)	5.07 (2.37)	-2.28 (150)	0.02
Parent report Low Cohesion	2.35 (2.23)	2.68 (2.13)	-0.904 (150)	0.37

Table 3.10: Comparisons between father childhood-only ADHD vs father adult ADHD

Child clinical symptoms	Father childhood-only	Father adult ADHD	<i>t (df) / χ^2</i>	<i>p value</i>
	(n = 68)	(n = 70)		
Total ADHD	14.69 (2.62)	14.97 (3.38)	0.86 (132)	0.39
Inattention severity	7.46 (1.44)	7.35 (1.87)	-0.18 (132)	0.86
Hyperactive-Impulsive severity	7.23 (1.72)	7.62 (2.11)	1.61 (132)	0.11
CD severity	0.97 (1.45)	1.53 (2.13)	-1.69 (134)	0.09
ODD severity	3.76 (2.30)	3.73 (2.44)	0.07 (134)	0.94
CD Diagnosis	10 (15.2%)	16 (22.9%)	1.30 (1)	0.25
ODD Diagnosis	29 (43.9%)	25 (35.7%)	0.96 (1)	0.33
Family environment			<i>t (df)</i>	<i>p value</i>
Parent report Low Warmth	10.46 (5.02)	10.12 (4.52)	0.39 (128)	0.70
Parent report Hostility	14.37 (4.30)	15.32 (4.81)	-1.19 (128)	0.24
Child report Mother Low Warmth	9.72 (5.65)	8.96 (4.20)	0.44 (48)	0.66
Child report Mother Hostility	16.56 (6.00)	15.36 (7.33)	0.63 (48)	0.53
Child report Father Low Warmth	13.42 (8.99)	13.48 (7.68)	-0.03 (47)	0.98
Child report Father Hostility	17.88 (8.06)	17.56 (7.86)	0.14 (47)	0.89
Parent report Conflict	3.90 (2.40)	4.20 (2.46)	-0.69 (124)	0.49
Parent report Low Cohesion	1.67 (1.34)	2.40 (2.04)	-2.39 (126)	0.02

3.4.4 Further analysis with social class as a covariate

As a separate analysis, the study examined to what extent all observed associations changed after adjustment for social class. Adjusting for social class attenuated associations between mother ADHD and child total ADHD symptoms, conduct symptoms, conduct disorder and child-reported mother hostility by approximately 20-30%. However, associations for inattention symptoms, family conflict, cohesion and maternal warmth were relatively unchanged. Table 3.11 shows comparison of estimates for significant associations found in the primary analysis, before and after adjustment for social class.

Table 3.11: Comparison of estimates for associations unadjusted and adjusted for social class

Mother ADHD (No ADHD vs ADHD present)						
	Unadjusted			Adjusted for age, sex and social class		
	<i>B</i>	<i>95% CI</i>	<i>p</i>	<i>B</i>	<i>95% CI</i>	<i>p</i>
Total ADHD severity	0.14	-0.01, 0.28	0.07	0.11	-0.04, 0.25	0.16
Inattention severity	0.10	-0.01, 0.22	0.07	0.11	-0.01, 0.22	0.07
CD severity	0.15	0.03, 0.26	0.01	0.10	-0.01, 0.22	0.07
Child report mother hostility	2.67	0.25, 5.15	0.03	2.16	-0.30, 4.63	0.09
Conflict	1.21	0.68, 1.74	<0.01	1.09	0.55, 1.62	<0.01
Low Cohesion	0.62	0.17, 1.06	0.01	0.62	0.12, 1.01	0.01
	<i>OR</i>	<i>95% CI</i>	<i>p</i>	<i>OR</i>	<i>95% CI</i>	<i>p</i>
CD Diagnosis	2.01	1.18, 3.44	0.01	1.70	0.98, 2.95	0.06
Father ADHD (No ADHD vs ADHD present)						
	Unadjusted			Adjusted for age, sex and social class		
	<i>B</i>	<i>95% CI</i>	<i>p</i>	<i>B</i>	<i>95% CI</i>	<i>p</i>
CD severity	0.13	-0.01, 0.27	0.07	0.10	-0.04, 0.23	0.17
Child report mother low warmth	-0.43	-0.84, -0.02	0.04	-0.43	-0.85, -0.01	0.04

* Unadjusted estimates do not match those in primary analysis (tables 3.2-3.5) as unadjusted estimates here were conducted on the sample with no missing data on social class (n=515) to enable clear comparison with adjusted results. All associations were adjusted for age and gender.

3.5 Discussion

This is one of the first studies to investigate the association between parent ADHD and clinical presentation and family environment in a large clinical sample of children with ADHD in the UK. It includes the investigation in both mothers and fathers and explores differences in the timing of the presence of parent ADHD; adult ADHD compared to ADHD in childhood-only.

A recent pooled prevalence of adult ADHD is estimated to be around 2.5% in the general population (Simon *et al.*, 2009). In this sample, high rates of parental ADHD problems were found, which were consistent with rates found in other studies of children with ADHD and behavioural disorders (Chronis *et al.*, 2003; Goos, Ezzatian and Schachar, 2007). Approximately a third of parents in this sample met criteria for the adult definition of ADHD (questionnaire assessed). This is noticeably high despite the relatively stringent criterion set for the definition of adult ADHD although ADHD impairment was not assessed for parents.

The findings in this study suggest that having a parent with ADHD, particularly persistent ADHD (as reported by parents), is associated with a more severe clinical presentation in children with ADHD. Mother ADHD was associated with increased severity of total ADHD, inattention and conduct symptoms and increased likelihood of CD in children. Paternal ADHD was found to be associated with increased severity of children's CD symptoms. The effect sizes of associations were relatively small (ranging from 0.11 to 0.15). This may perhaps be due to less variability in the sample as all children have a diagnosis of ADHD. In other words, the association between parental ADHD and child characteristics might be stronger in general population (non-ADHD)

samples. Studies that were subsequently published after the publication of findings in this chapter have shown similar results in support of the findings that parent ADHD is associated with child ADHD severity (Segenreich *et al.*, 2014; Middeldorp *et al.*, 2016a).

Thus it appears that having a parent with persistent ADHD problems provides additional risk for a more severe clinical presentation of ADHD that could represent inherited or environmental risks as well as gene-environment interplay. Previous offspring of twin studies suggest that antisocial behaviour in parents is a genetic risk factor for hyperactivity in children, whilst it is both an environmental and genetic risk factor for conduct disturbance in children (Silberg, Maes and Eaves, 2012). The transmission between parent ADHD and child problems however, has not been explored beyond the investigation of inherited influences found in adoption studies (Sprich *et al.*, 2000). It is suggested that the effects of parent ADHD on child outcome could be transmitted through genetic effects as well as family environment through mechanisms such as parenting (Johnston *et al.*, 2012) but this requires investigation. This study is not genetically informative and thus does not allow one to identify whether associations are inherited or environmentally mediated.

This study also investigated the differential effects of parent gender on offspring clinical presentation. There have been mixed findings on parent gender differences (Biederman, Faraone and Monuteaux, 2002; Goos, Ezzatian and Schachar, 2007; Takeda *et al.*, 2010). Our results seem to imply stronger evidence for influences of mother ADHD. However there were many missing fathers in this sample, and therefore power to find paternal effects was limited, whilst there may also be selection bias where more fathers with ADHD are missing. Direct comparisons of mother and father

ADHD in a subset of complete families (families with both parents) suggest that there are no differences on child clinical presentation between mother and father ADHD. Although this sample is small, it was adequately powered to identify associations with effect sizes similar to those presented in this thesis (sample size $n=96$, 80% at $p=0.05$ to detect a small effect size of 0.08).

The study also investigated if parent ADHD was associated with adverse family environment. Mother ADHD was associated with higher levels of conflict and lower levels of cohesion in the family. Although these are based on parent reports, there was a similar trend for higher levels of mother hostility reported by the children in this group. In a sample of affected sibling pairs, both mother history of mood disorder and current ADHD was a predictor of impairment in family functioning (Pressman *et al.*, 2006).

One explanation for the effects of mother ADHD on family environment could be because mothers are frequently the main caregiver and primarily responsible for the day-to-day organising for the family. Parenting a child with ADHD is already in itself challenging; parenting a child with ADHD when the parent has ADHD symptoms themselves could be very stressful. This added stress may result in more conflict and hostility in the family. Parenting studies have found that parental ADHD symptoms are associated with decreased positive and involved parenting and more negative expressed emotion (Harvey *et al.*, 2003; Psychogiou *et al.*, 2008). Parental ADHD symptoms were found to be the strongest predictor of parental distress compared to other contextual factors such as marital status, parental education and social support (Theule *et al.*, 2011).

Interestingly, mothers were reported to be warmer to their children when fathers have ADHD. This may indicate that mothers living with a spouse with ADHD may be more empathic to their child's ADHD symptoms. This is supported by findings from Minde and colleagues (2003), who reported differences between perceptions of men and women who have a spouse with ADHD. Men appeared to be more critical and less tolerant if they were married to a woman with ADHD whereas, women were much more supportive and more tolerant of husbands with ADHD. One study supports the idea that there are differences in the effect of mother and father ADHD in types of parenting problems where mothers with high ADHD symptoms offered more child blaming attributions when their child had ADHD whilst fathers with high ADHD symptoms offered fewer (Johnston and Lee-Flynn, 2011).

Low social class has previously been found to be associated with child mental health problems including ADHD (Russell, Ford and Russell, 2015). As low social class is also highly correlated with parent ADHD, the study explored if any observed associations would attenuate by including social economic status as a covariate. Comparison of estimates showed that some associations were attenuated by 20-30% and some remained relatively unchanged. However, it is not possible to distinguish whether social class is a confounder or acts as a mediator of the relationship between parent ADHD and child presentation and family functioning in this cross-sectional sample. For example, adults with persistent ADHD have functional impairments which lower their ability to achieve both educationally and occupationally. Thus, it is feasible that these individuals end up in a lower social class as a result of this. Consequently, growing up in this environment could increase the severity of ADHD in offspring (e.g. insufficient resources or support). Even if social class is a confounder the associations were not

completely attenuated by adjustment for this. However, as with any observational study, the study is unable to exclude the possibility of residual confounding for example by other characteristics associated with parent ADHD.

3.5.1 Limitations

Firstly, this is a cross-sectional study; therefore it was difficult to determine the direction of transmission from parent to child. Secondly, whilst these results suggest that having a parent with persistent ADHD is associated with greater severity in children with ADHD, these findings are in need of replication as associations may not withstand correction for multiple testing. However given that the study of parent ADHD and child clinical presentation is an under-researched area, the investigations in this study were very much exploratory. Findings add potential insight into how parent ADHD may be associated with presentation of ADHD in children. It was found that having parents with only a childhood history of parent ADHD was not associated with more severe clinical presentation in children. This might suggest that exposure to parent ADHD behaviours during the child's lifetime is more relevant. However a further limitation is that, this needs to be explored further in studies with a genetically sensitive design.

The definition of adult ADHD in this study may be overly restrictive; therefore the percentage of children with a parent with ADHD may have been underestimated. How this may have affected the results is unclear; it may be that associations were not found as children with a parent with ADHD were not classified as such. Conversely, by identifying a more severe group of parents with ADHD, observed associations may be relevant only to those with a more severe phenotype. Unfortunately there is no formal

definition to diagnose ADHD in adults. Given controversy and uncertainty in this area, it was decided that the diagnostic criteria in the DSM-IV was most reasonable to define adult ADHD. There was however, no measure of symptom impairment for parents in this study and therefore this definition could also be considered too broad. Measures of parent ADHD were based on self-report and retrospective measures for parent childhood ADHD. Nevertheless, evidence from previous studies has suggested that adults can give a reasonable account of their own childhood and current symptoms (Murphy and Schachar, 2000).

There may be possible shared rater bias as mostly mothers had rated child symptoms, family environment and parent-child relationships. It has been suggested that ADHD in parents can influence the way they report their children's ADHD symptoms and this may differ by parent ADHD status (Mayfield *et al.*, 2016). Due to a greater awareness of their own symptoms and knowledge about the disorder, parents may be more likely to report similar traits in their child which may lead to overestimation. On the other hand, parents could be desensitised to their child's ADHD symptoms and this could therefore lead to underreporting of symptoms (Faraone, Monuteaux, *et al.*, 2003). A study examining the possibility of reporting bias amongst parents with ADHD found that rates of reporting were similar between groups of families with and without a parent with ADHD (Faraone, Monuteaux, *et al.*, 2003). Therefore ADHD status of parents did not appear to bias maternal reports of ADHD symptoms. In this study, child reports of parent warmth and hostility showed similar directions of associations to parent reports. The study also obtained teacher reports of child symptoms but these were used mainly to assess pervasiveness of ADHD symptoms across settings. A decision was made not to use these reports as an alternative measure of symptoms as

three different measures were utilised to obtain teacher reports. , However sensitivity analyses were conducted using teacher ratings of ADHD as an outcome with adjustment for medication status. Results showed no associations between mother and father ADHD using teacher ratings but associations were found with medication status. About 79% of children in the sample were on medication for their ADHD. Teacher-rated ADHD severity was associated with child medication status. Mean teacher rated ADHD severity for children prescribed with ADHD medication was lower (4.64 (SD 4.85)) than teacher-rated ADHD severity for those without ADHD medication (6.53 (SD 5.24)) ($t=3.03$ (377), $p=0.003$). ADHD medication is perhaps more effective during school hours depending on the preparation of the prescription (long or short acting), and thus the effects of medication may have worn off by the time the child is home, therefore making teacher ratings less accurate of the home situation.

Most families ascertained in this sample were not complete families as there were many single parent families (mostly mothers). Therefore there was not as much data available for fathers which limits the power to examine whether father ADHD has more or less influence on child clinical presentation compared to mother ADHD. However including data from single parent families makes this sample more representative of families of children with ADHD. Children from single parent families had significantly higher total ADHD and conduct symptoms than children in families with both parents present, which are similar findings to those reported by West and colleagues (West *et al.*, 2002). This study could not examine the influences of parent ADHD separately by child gender as there were only a small number of girls, which is typical in clinically ascertained samples such as this.

3.5.2 Clinical implications

This study highlights the importance of considering parent ADHD during clinical assessment. Results indicate that children with more severe behavioural symptoms are more likely to have a parent with persistent ADHD. Having a parent with ADHD problems could exacerbate or impede improvement in child symptoms through parenting and inconsistent treatment administration for the child. Screening parents during assessment of the child could help identify families where parents may have more difficulties. It may be important to consider current treatment needs or interventions for the family as a whole. If further studies provide evidence that persistent parental ADHD is associated with the severity of child ADHD, this would encourage parenting programmes to cater for parents with ADHD, offering more support and coping strategies. Perhaps treatment strategies can be extended to parents who have current symptoms of ADHD as previous studies have found that treatment of other forms of parental psychopathology, notably depression might result in improvement in child symptoms (Pilowsky *et al.*, 2008).

3.6 Conclusion

On the whole, the results suggest children of parents with ADHD have more severe symptoms of the disorder compared to children without an affected parent. Family environment is also more adverse in these families especially when mothers have ADHD. The study in this chapter however is based on a cross-sectional sample, and it is not clear if parent ADHD is associated with child clinical presentation over time. Furthermore, it is also not known if clinical presentation or family differences are due to parent ADHD *per se* rather than other parental psychopathology, like depression.

As the initial focus of this chapter was to explore associations between parent ADHD and child clinical presentation, parent depression was not included. There is however evidence of elevated rates of depression amongst parents of children with ADHD (Faraone and Biederman, 1997). These gaps in the literature lead to the next chapter which will discuss the second aim of the thesis; to investigate the influences of parental ADHD or depression on the longer term outcome of psychopathology in a longitudinal sample of children with ADHD.

Chapter 4

Maternal psychopathology and offspring clinical outcome: a follow-up of boys with ADHD

Chapter description

Findings from chapter 3 and previous research have demonstrated that parental ADHD is associated with child clinical presentation of ADHD and comorbidity. However, it is not clear what influence parental psychopathology has on the course and persistence of ADHD and comorbidity in children across time. The aim of this current chapter is to investigate the influences of 1) maternal ADHD and 2) maternal depression on the longer term clinical outcome in a longitudinal sample of children with ADHD. The analyses in this chapter will be based on the follow up subsample described in chapter 2. Following the publication of the DSM-5 manual and in keeping with current trends, analyses for this chapter and the subsequent, chapter 5, utilised criteria set in DSM-5 for both parent and child psychopathology. The chapter is based on the publication *'Maternal psychopathology and offspring clinical outcome: a four year follow-up of boys with ADHD'* in the peer reviewed journal, *European Child and Adolescent Psychiatry* 2016 July; 26(2):253-262.

4.1 Introduction

Within samples of children with ADHD, a number of cross-sectional studies, including the study in chapter 3, have demonstrated that parental ADHD is associated with a more severe clinical presentation of the disorder in offspring, including higher ADHD symptom severity (Takeda *et al.*, 2010; Agha *et al.*, 2013; Segenreich *et al.*, 2014) and comorbid conduct problems (Chronis *et al.*, 2003; Pressman *et al.*, 2006; Humphreys, Mehta and Lee, 2012; Agha *et al.*, 2013). There is also evidence that parental depression is associated with more severe clinical presentation and impairment in children (Chronis *et al.*, 2003; Pressman *et al.*, 2006; Humphreys, Mehta and Lee, 2012) and that maternal psychopathology may be especially important (Pressman *et al.*, 2006). Given these findings suggesting that parental psychopathology, specifically ADHD and depression, is associated with a more severe offspring ADHD clinical presentation cross-sectionally, and considering the importance of ADHD persistence and comorbid conditions over time discussed in Chapter 1, the next question, is to what extent does parental psychopathology longitudinally predict a) ADHD persistence and b) long term presence of conduct disorder symptoms in a clinical sample of children with ADHD?

There is some indication that parental ADHD may be associated with persistence of offspring ADHD longitudinally; one study found that a family history of ADHD was associated with ADHD persistence (Biederman *et al.*, 1996). Whether this was specific to mother's or father's ADHD was not reported, although the same group did find that maternal history of comorbid psychopathology (presence of at least two psychiatric disorders) predicted ADHD persistence (Biederman *et al.*, 2011). A family history of

mood disorders may also predict persistent ADHD (Biederman *et al.*, 2010) although an initial study of a community sample suggests that this may be explained by paternal rather than maternal mood (Lara *et al.*, 2009). These initial studies demonstrate that this is an interesting area of research, but further investigation is needed to assess the association between persistence of ADHD and parental ADHD or parental depression, especially looking at mothers and fathers separately. Given that in chapter 3 parental ADHD is associated with clinical presentation of ADHD in childhood, it is also important to investigate whether ADHD persistence at follow up is not a consequence of greater severity at diagnosis.

Whilst studies of parental ADHD have looked at links with offspring ADHD persistence over time, they have not looked at associations between parent ADHD and the development of comorbid conduct disorder, despite the fact that children with ADHD with comorbid CD are known to have poorer outcomes than those without (Langley *et al.*, 2010; Sibley *et al.*, 2011). Conversely, in the only study to date looking at the long-term outcomes for children with ADHD where mothers have depression, Chronis and colleagues (2007) found, as part of an eight year longitudinal study of 108 families, that children of mothers with depression have higher risk of developing comorbid conduct problems when adjusting for baseline conduct severity (Chronis *et al.*, 2007). This study did not look at persistence of child ADHD and mothers were asked about their lifetime history of depression and therefore it was not possible to tell if maternal depressive episodes had occurred during their child's lifetime. This means that it is unclear whether there are associations with the child being exposed to maternal depression. Therefore, there is a need for further work to investigate the associations

between parent depression and offspring ADHD persistence and comorbidity over time.

4.2 Study Aims

These initial studies indicate the potential importance of parental ADHD and depression as markers of offspring ADHD prognosis in adolescence and potentially into adult life, although further work is needed to replicate these findings and investigate the area further. This study aimed to address this by building upon previous work described in chapter 3 by using follow-up data from the clinical subsample of adolescent males described in chapter 2. The aims of the current study are to investigate whether mother ADHD and mother depression predicts:

- a. persistence of ADHD symptoms and diagnoses, taking childhood ADHD severity into account
- b. presence of conduct disorder symptoms in adolescence, taking childhood conduct severity into account

This study hypothesised that mother ADHD and mother depression at baseline would be a predictor of worse outcome, greater persistence and less improvement in symptoms over time. As mentioned in chapter 2, few fathers met study criteria for depression (6%, n=5) and so it was decided that it was not reasonable to investigate associations with father psychopathology. Therefore, analyses conducted in this chapter focused on mother psychopathology, namely mother ADHD and mother depression. Parental psychopathology and family environment was only assessed at baseline and not at follow up. Offspring anxiety and depression symptoms are not

included in the analyses here as there was unfortunately no measure of child mood or anxiety problems at this follow up.

4.3 Method

4.3.1 Sample

This chapter utilises the follow up sample described in detail in chapter 2 which consists of 143 males aged between 10-17 years. Measures and assessments relevant to this study are outlined below briefly. More details of these measures are discussed in chapter 2.

4.3.2 Measures

Predictors

Mother psychopathology

Mother psychopathology was assessed at Time 1. Mother ADHD was measured using an 18 item checklist of DSM-5 ADHD symptoms (see chapter 2 for further details). Positive ADHD status was assigned if symptom criteria both in childhood and currently were met for a DSM-5 ADHD diagnosis. Mother depression was assessed using the Hospital Anxiety and Depression Scale (HADS), where presence of depression was determined using a validated cut off score of 11 or higher (Bjelland *et al.*, 2002; Snaith, 2003). The predictor measures used in this study are as follows:

- Mother adult ADHD
- Mother Depression

Mothers were also asked to complete a DSM-IV/5 conduct symptom checklist to rate the presence of CD symptoms (not ODD) in themselves at age 7-11 years. A total

symptom score of self-reported conduct symptoms in childhood for mothers was derived from this. This measure was used as a covariate in the regression model to test if associations between mother psychopathology and child symptoms were independent of mother's symptoms of conduct disorder in childhood, as previous studies have highlighted the shared genetic liability between depression and antisocial behaviour (O'Connor *et al.*, 1998; Kim-Cohen *et al.*, 2005).

Outcome measures

Child psychopathology (assessed at Time 1 and 2)

Child psychopathology at Time 1 was assessed using the Child and Adolescent Psychiatric Assessment (CAPA) (see Chapter 2 for further details) (Angold and Costello, 2000). At time 2, child psychopathology was assessed using the Development and Well Being Assessment (DAWBA) structured interview (Goodman *et al.*, 2000). For both time points, parents completed the ADHD and CD sections and young people the CD section. CD symptoms were rated as present when endorsed by either the parent or young person (Rutter, Giller and Hagell, 1998). Information from the CAPA and DAWBA were used to define Time 1 and Time 2 ADHD and CD symptom scores and diagnoses using the DSM-5 criteria.

ADHD persistence

Young people were defined as having persistent ADHD if they met DSM-5 diagnostic criteria for ADHD at both Time 1 and 2, and remitted ADHD if they did not meet diagnostic criteria for ADHD at Time 2 (all individuals met diagnostic criteria for ADHD at Time 1).

ADHD and CD symptom change

ADHD symptom and conduct symptom change scores were calculated to observe the changes in these symptoms over time. Total symptoms at Time 1 were subtracted from total symptoms at Time 2. Negative scores indicate symptom reduction over time and positive scores indicate symptom increase over time.

Listed below are the following outcome measures used in this analyses:

- ADHD diagnosis at Time 2 - persistent or remitted ADHD
- ADHD symptom change score
- ADHD symptom severity at Time 2
- CD symptom change score
- CD symptom severity at Time 2

Analysis

Mother ADHD and mother depression were considered as predictors using binary scores (presence of ADHD diagnosis status (meeting DSM-5 criteria during childhood and current ADHD) and presence of depression (using the HADS cut-point)). As

different assessment tools were used at Time 1 (CAPA) and Time 2 (DAWBA), the symptom scores for ADHD and CD were standardised and used in all the analyses. All continuous outcome variables were normally distributed. Logistic regression analysis was used to estimate odds ratios and 95% confidence intervals to predict ADHD persistence in the child at Time 2 in relation to mother psychopathology. Linear regressions were used to estimate differences (and 95% confidence intervals) in child ADHD and conduct symptom severity scores at Time 2 in relation to mother psychopathology at Time 1. Estimates were adjusted for child age, child ADHD and CD symptoms at Time 1 (except when analysing the symptom change score in ADHD and CD respectively) and mother self-reported childhood conduct symptoms (recall of their own conduct symptoms in childhood) to test if associations were not explained by severity of child symptoms or presence of conduct symptoms in mothers during childhood. Estimates were also adjusted for the period between Time 1 and Time 2 as the length of time children were followed-up between the two assessments ranged from one to five years, which means that some children may have been followed up much sooner than others. ADHD medication status at Time 2 was also included as a potential confounder in the final model to determine if any associations found were not also explained by effects of being on ADHD medication. Linear regressions were also conducted between symptom score change from Time 1 to Time 2 and mother psychopathology at Time 1. Although, using both the change score and severity score as an outcome may produce similar outcomes, however both methods are known to cause biased estimates. Therefore it is recommended that both methods are conducted to ensure robustness of results (Allison, 1990). All analyses were performed using STATA (version 13). Low social class was found to be correlated with mother

ADHD and depression. As mentioned in chapter 3, because it is difficult to distinguish if social class is a confounder or a mediator between parental psychopathology and child presentation, separate analysis was conducted to examine to what extent all observed associations changed after adjustment for social class.

4.4 Results

The sample consisted of 143 males aged 10-17 years (mean age of 13.73 (SD 1.74)) with a confirmed diagnosis of ADHD who were assessed at baseline (Time 1) and reassessed on average two and a half years later (Time 2). The mean age of children at Time 1 was 10.7 years (SD 2.1) with an age range of 6-15 years. The mean time between the two assessments was 2.59 years (SD 0.91), range 1–5 years.

Clinical and demographic data were compared between families who took part at both time points and those participants recruited at Time 1 only (table 4.1). As expected, because of the eligibility criteria for the follow up study (males, aged 10-18 years with IQ > 70), there were systematic differences found on gender and IQ between participants who took part at Time 1 only and those who took part at both time points. Families that took part at Time 1 only were more likely to be in the lower social class and have lower education compared to families that took part at both time points. There were no differences between these groups with regards to ADHD and conduct symptom severity or prevalence of mother ADHD or depression at Time 1.

Table 4.1: Comparison of Time 1 measures between those who took part at both times vs those in Time 1 only.

	Range scores	Time 1 only n = 427	Both Time 1 & Time 2 n = 143		
		<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>t-test</i>	<i>p value</i>
Child Age	6-18	10.81 (3.25)	10.71 (2.14)	0.39	0.70
Child IQ	41-119	81.41 (14.44)	85.13 (10.25)	-3.26	0.001*
ADHD symptom severity	0-18	15.08 (2.79)	15.41 (2.52)	1.15	0.25
CD symptom severity	0-9	1.29 (1.74)	1.25 (1.78)	0.38	0.71
		<i>n (%)</i>	<i>n (%)</i>	<i>χ²</i>	<i>p value</i>
Gender (male)		339 (79%)	143 (100%)	34.85	0.001*
Low social class		227 (58%)	52 (41%)	11.19	0.001
Low income		241 (66%)	76 (59%)	2.04	0.15
Low parental education		116 (30%)	26 (20%)	5.44	0.02
ADHD medication (child)		330 (78%)	117 (83%)	1.70	0.19
Mother ADHD		91 (22%)	26 (19%)	0.15	0.70
Mother Depression		85 (21%)	28 (21%)	0.01	0.93

* Study inclusion criteria at Time 2 accounts for these differences (males and IQ >70)

In this sample, we found that 19% (n=26, 95%CI 0.13, 0.27) of mothers met the study criteria for ADHD and 21% (n=28, 95%CI 0.14, 0.28) of mothers met the study criteria for depression. Only 6.6% (n=9) of mothers met study criteria for both ADHD and depression.

At Time 2, 82% (n=112) of the young people continued to meet full criteria for DSM-5 ADHD diagnosis and were classified with persistent ADHD (mean symptom score 14.29, SD 2.87). The remaining 18% (n= 25) of young people did not meet full diagnostic ADHD criteria at Time 2 and were classified as having remitted ADHD.

Although they no longer met criteria for ADHD, these young people still had some ADHD symptoms (mean 5.76, SD 2.77) and 19 (76%) young people from this group were still being treated with ADHD medication. Six participants did not have any data on their ADHD symptoms at Time 2.

At Time 1, 20% (n=28) of young people had a DSM-5 diagnosis of CD (mean symptom score 1.39 (SD 1.69)). The prevalence of CD at Time 2 was 53% (n=74/139, mean symptom score 3.70, SD 3.19). A total of 36% (n=50/139) of young people had developed new onset CD at Time 2 and 17% (n=24) had conduct disorder persisting between both time points. Only 3% (n=4) of those with CD at Time 1 no longer fulfilled diagnostic criteria at Time 2 (mean CD symptoms 1.17, SD 0.41). Four participants did not have complete data on their CD symptoms.

4.4.1 Mother ADHD and offspring outcomes

Mother ADHD status did not predict ADHD persistence in adolescents (unadjusted model: OR 1.16, 95%CI 0.36, 3.78, p=0.80). There was also no evidence of an association between mother ADHD status and child ADHD symptom severity at Time 2 (unadjusted model: B = 0.23, 95%CI -0.19, 0.66, p=0.28) (table 4.2). In relation to symptom change, although mean ADHD symptom score change was lower over time amongst young people who had a mother with ADHD compared to those without (-1.88 vs -2.66 respectively), there was no substantial evidence to support this difference (p = 0.35) (table 4.3).

With regards to CD symptoms, there was no evidence of an association between mother ADHD status and conduct symptom severity at Time 2 (unadjusted model: B =

0.23, 95%CI -0.22, 0.68, $p=0.32$) (table 4.2) or with conduct symptom change score (unadjusted model: $B = 0.71$, 95%CI -0.54, 1.96, $p=0.26$).

In this follow-up sample, there were no associations found between mother ADHD status and child ADHD and conduct symptoms at Time 1, even though these associations were previously found in chapter 3. This could be due to smaller sample size compared to the study at Time 1. Appendix 4.1 shows associations between mother ADHD status and child ADHD and conduct symptoms at time 1 using the follow-up sample (time 2).

4.4.2 Mother depression

Mother depression status did not predict ADHD diagnostic persistence in adolescents (OR 1.93 95%CI 0.53, 7.08, $p=0.32$). It was also found that mother depression status did not predict child ADHD severity at Time 2 or ADHD symptom change score (tables 4.2 and 4.3). Mother depression status was found to be associated with child conduct symptom severity at Time 2, and this persisted after adjusting for severity of child CD symptoms at Time 1 (model 1; $B = 0.54$, 95%CI 0.14, 0.93, $p=0.008$) (Table 4.2). Mother depression status was also found to be associated with a higher mean CD change score in children compared to mothers who did not have depression (3.36 vs 1.97, $p=0.02$) (table 4.3).

Table 4.2: Associations between maternal psychopathology and (a) child ADHD symptoms at Time 2 and (b) child conduct symptoms at time 2

	Unadjusted Model			Model 1			Model 2		
	<i>B</i>	<i>95%CI</i>	<i>p</i>	<i>B</i>	<i>95%CI</i>	<i>p</i>	<i>B</i>	<i>95%CI</i>	<i>p</i>
(a) Child ADHD symptoms at Time 2^a									
Mother ADHD	0.23	-0.19, 0.66	0.278	0.16	-0.20, 0.52	0.383	0.22	-0.16, 0.59	0.249
Mother depression	0.18	-0.23, 0.59	0.381	0.003	-0.35, 0.36	0.984	-0.02	-0.39, 0.35	0.912
(b) Child conduct symptoms at Time 2^b									
Mother ADHD	0.23	-0.22, 0.68	0.319	0.24	-0.16, 0.65	0.236	0.11	-0.34, 0.55	0.635
Mother depression	0.78	0.37, 1.20	<0.001*	0.54	0.14, 0.93	0.008*	0.47	0.05, 0.88	0.027*

^a Model 1: Adjusted for ADHD severity Time 1 (standardised score). Model 2: Adjusted for ADHD severity Time 1 (standardised score), period between Time 1 & 2, ADHD medication Time 2, child age.

^b Model 1: Adjusted for CD severity Time 1 (standardised score). Model 2: Adjusted for CD severity Time 1 (standardised score), maternal childhood CD symptoms, period between Time 1 & 2, ADHD medication Time 2, child age.

* standardised score.

Table 4.3: Mean scores for child ADHD symptom change scores and child conduct symptom change

	Child ADHD symptom change <i>Mean (SD)</i>	Child conduct symptom change <i>Mean (SD)</i>
Mother ADHD:		
None	-2.66 (3.80)	2.13 (2.80)
Present	-1.88 (3.63)	2.84 (3.10)
Mother depression:		
None	-2.52 (3.87)	1.97 (2.69)
Present	-2.54 (3.37)	3.36 (3.25)*

*p<0.05

After adjusting for child age and the covariates mentioned previously, the effect of mother depression status on child conduct outcome at Time 2 was slightly attenuated but the association still remained (model 2; B = 0.47, 95%CI 0.05, 0.88, p=0.03) (table 4.2). Adjusting for baseline medication and oppositional defiant disorder symptoms at Time 1 did not alter the association between mother depression status and child conduct disorder.

At Time 1, mother depression status was associated with child conduct disorder symptoms and there was weak evidence of an association with child ADHD symptoms (table 4.1 in the appendix). Similar results for associations between maternal depression and offspring clinical severity were found in the larger cross-sectional sample (n=570).

4.4.3 Further analysis with social class as covariate

As a separate analysis, this study examined to what extent the observed associations changed after adjustment for low social class. Adjusting for low social class had slightly attenuated associations between mother depression and child conduct symptoms at Time 2 by approximately 6–12%. (Mother depression status ($B = 0.44$, 95%CI -0.02, 0.90, $p=0.06$) (table 4.4).

Table 4.4: Further adjustment for low social class: associations between mother psychopathology and child ADHD and CD symptoms at Time 2

Associations with child ADHD symptoms Time 2 ^a	Model 3		
	<i>B</i>	95%CI	<i>p</i>
Mother ADHD	0.19	-0.20, 0.58	0.346
Mother depression	-0.05	-0.45, 0.36	0.820
Associations with child CD symptoms Time 2 ^b	Model 3		
	<i>B</i>	95%CI	<i>p</i>
Mother ADHD	0.21	-0.26, 0.68	0.381
Mother depression	0.44	-0.02, 0.90	0.061

^a Adjusted for ADHD severity Time 1 (standardised score), period between Time 1 & 2, ADHD medication Time 2, child age, low social class

^b Adjusted for CD severity Time 1 (standardised score), maternal childhood CD symptoms, period between Time 1 & 2, ADHD medication Time 2, child age.

* standardised score

4.5 Discussion

The present study aimed to investigate whether mother ADHD and mother depression at baseline predicted clinical outcome of adolescent boys with ADHD across time. The prevalence of mother ADHD and mother depression in this sample is high compared to rates reported in a general population sample (Kessler *et al.*, 2006) but similar to other studies of clinical samples (Chronis *et al.*, 2003; Vidair *et al.*, 2011). Looking at clinical outcomes at Time 2, there was a high prevalence of young people who still met full DSM-5 diagnostic criteria of ADHD. The pattern of symptom change over time was as expected; ADHD symptoms reduced with age and CD symptoms increased into adolescence. However the prevalence of ADHD and CD highlights the fact that these young people are still very much symptomatic and impaired.

Contrary to the study hypothesis, there were no associations found between mother self-reported ADHD and the course or persistence of clinical symptoms of ADHD or conduct disorder across adolescence, even though the study described in chapter 3 had previously found associations between mother ADHD and these clinical measures cross-sectionally. However, mean ADHD symptom change was lower in those with a mother with ADHD which implies that this group showed less improvement of ADHD symptoms over time. However, the study may have been underpowered to detect an effect of this size. This is reinforced by the negative findings for baseline associations in this follow-up group. Additionally the length of time (mean 2.5 years) for which children were followed up was possibly not long enough to distinguish individuals who would persist and remit.

The results however show that mother depression is associated with CD symptoms in adolescent boys with ADHD at time 2, which is consistent with the study hypothesis. The results of the present study are in keeping with previous findings from Chronis and colleagues (2007), who found that a history of maternal depression predicted later development of conduct problems. This study adds to these findings by investigating the influences between mother ADHD and the development of comorbid conduct disorder which has not been investigated previously. Previous studies have looked at associations with maternal history of depression. This study extends these findings by investigating associations with concurrent mother depression.

Unlike the findings from Biederman and colleagues (Biederman *et al.*, 1996, 2010, 2011) on ADHD persistence, mother ADHD or mother depression in this study was not found to predict ADHD persistence. These differences could be due to the inclusion of a broad range of psychopathology (e.g. depressive disorders, anxiety disorders, substance misuse) in any first degree relative in the studies by the Biederman group including fathers and siblings (Biederman *et al.*, 1996, 2010) or the lack of specificity regarding maternal diagnoses (mother psychopathology was defined in this study as having any two psychiatric diagnoses) (Biederman *et al.*, 2011). Therefore previous findings are perhaps not specific to mother self-reported depression or ADHD. In this regard, the findings in this study do concur with those of Lara and colleagues (2009) who did not find an association between maternal mood and anxiety and ADHD persistence. In addition, differences in defining ADHD using DSM-5 criteria may have contributed to differences in findings although similar results were found within this sample when defining ADHD using DSM-IV criteria. Rates of ADHD persistence in this study were also high, possibly because the follow up period was only on average after

two and a half years (mean age of 13.7 years). Future studies investigating associations with ADHD persistence should include larger samples of young people over a longer period of time.

Parents play a significant role in providing the caregiving environment and have the earliest influences on a child's development. The association between depression in mothers and child conduct symptom severity are likely to have come about for a variety of reasons. Parents of children with ADHD are at heightened genetic risk of depression (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013) and experience chronic stress from their children's symptoms. Parents of children with ADHD are also reported to experience economic strain such as work loss for family members and cost of medical care which are potent risk factors for depression (Sayal, Taylor and Beecham, 2003; Swensen *et al.*, 2003; D'Amico *et al.*, 2014). Parenting difficulties and the quality of parent-child relationship could also be another possible mechanism which might explain the link between depression in mothers and CD in offspring (Lovejoy *et al.*, 2000). One study suggests that responsiveness in parenting acts as a mediating mechanism in the relationship between parent depressive symptoms and conduct problems in children with ADHD (Johnston *et al.*, 2002). Several studies in families of children with ADHD have found that currently depressed mothers face more parenting challenges relative to non-depressed mothers and that they are more susceptible to child characteristics which can affect the quality of parent-child relationships (Gamble *et al.*, 2013; Lee *et al.*, 2013; Thomas *et al.*, 2014). This study did not investigate if the association between mother depression and later development of child conduct symptoms could be explained by family measures mentioned in chapter 3 (family environment or parental warmth and hostility). This

was due to the fact that the family measures were assessed at the same time as mother depression and therefore it would have been difficult to determine any direction of effects of the family variables.

Another possible explanation for associations between depression in mothers and child conduct symptom severity is direct child effects on the parent. A recent adoption design suggested the importance of child ADHD on mother-child relationship, where genetically influenced child ADHD characteristics elicit hostility in parenting (Harold *et al.*, 2013). Treatment studies have shown that mother-child relationships improve following treatment of child ADHD symptoms (Schachar *et al.*, 1987). However, adjusting for medication status (and therefore current treatment) made no difference to the findings reported here. This suggests that treatment per se does not explain the associations between mother depression and child conduct symptoms, although we do not have information regarding efficacy of medication (especially in regard to conduct problems).

Paternal psychopathology is another important consideration when examining the association between maternal depression and child presentation. One cannot rule out the possibility that the association between mother depression and child conduct problems are explained by paternal mental health as well as other unmeasured confounders. Like most observational studies, genetic factors may also contribute to residual confounding.

In this sample many families were classed as being in the low social class category (41%) and it was found that social class was associated with both mother psychopathology and child ADHD. It is difficult to distinguish whether social class is a

confounder or acts as a mediator for the relationship between parental psychopathology and child outcome. Therefore, in separate analyses, observed associations were adjusted for by social class to investigate if any of these associations would change as a result. Comparison of estimates showed that the associations were attenuated by about 6-12%. It appears that adjusting for social class has minimal impact and is therefore unlikely to explain the associations observed. Of course there are likely to be errors in measurement of social class and therefore it is difficult to rule out any stronger effects of confounding or mediation that might have been missed as a result of this. As for any observational study, this study is unable to exclude the possibility of residual confounding.

To my knowledge (at the time this manuscript was submitted to the journal) this is the first study investigating the different influence of mother self-reported ADHD and concurrent depression in mothers on future outcomes in a clinical sample of boys with ADHD, taking baseline symptoms into account. The study looks at symptom change over time and includes measures of child and mother psychopathology using DSM-5 criteria. It also takes into account both mother and child reports of child CD symptoms. Since the publication of this study, evidence from prospective longitudinal studies of children with and without ADHD recruited both from schools and child services have found that maternal ADHD predicted later ADHD symptoms in preschool children (Breux, Brown and Harvey, 2017) and in young adolescence after adjusting for parent depression (Moroney *et al.*, 2017). There are several methodological differences in these studies compared to the study in this chapter. The study by Breux and colleagues (2017) was conducted on a community sample (rather than a clinical sample) of preschool children and a measure of current parental ADHD was used

(rather than a combination of current and childhood symptoms). The study by Moroney and colleagues was also based on a community sample and measured parent ADHD using current symptoms. Additionally they also had a longer follow up period (6-7 years) compared to 2.5 years of follow up in this study. These might account for why findings differ from what was found in this study.

4.5.1 Limitations

This study however, should be considered in view of certain limitations. Firstly, we could not look at the effects of paternal psychopathology, as there was insufficient data available from fathers. Many families ascertained in this sample were single-parent families (mostly mothers) and we did not want to reduce the sample size by excluding such families and including only intact families. There is evidence to suggest that inclusion of only intact families may result in a sample with a less severe clinical presentation of ADHD. Had we included only intact families (and therefore looking at both mother and father psychopathology) we may not have had a very representative sample of children with (clinically diagnosed) ADHD (West *et al.*, 2002). In the analyses, whilst this study controlled for current medication use of the children, there was no information collected on any psychological or non-pharmacological treatments. Therefore it was not possible to determine if any associations might have been explained by any non-pharmacological treatments.

Unfortunately there was no measure of child mood or anxiety problems at follow up and therefore the outcome of these disorders in this sample could not be examined. There was also no current measure of maternal psychopathology at Time 2; therefore this study was unable to test specific timing effects of depression in parents in relation

to child disorder. In addition, it is not possible to rule out measurement error effects that might have biased any findings in relation to mother ADHD or depression and change in child outcome over time.

Depression status for parents in this study was obtained from the HADS which was initially developed for screening purposes and therefore does not represent definitive diagnosis of depression. However, the HADS has been widely used and is reported to have good validity and performs well in predicting caseness of depression in psychiatric and primary care patients as well as the general population (Bjelland *et al.*, 2002). Questionnaire measures of parent mental health are also likely to be more practical in settings that focus primarily on child mental health, enhancing the applicability of our investigation to clinical practice. There are concerns that parental depression can bias the reporting of child behaviour. Some studies have reported that mothers with depression can have distorted cognitions or judgements and may therefore exaggerate behavioural problems in their children (Fergusson, Lynskey and Horwood, 1993; Najman *et al.*, 2001; Goodman *et al.*, 2011). There has also been evidence to suggest that parents with depression can reliably report on child psychopathology and behaviour (Richters and Pellegrini, 1989; Rice *et al.*, 2007; Lewis *et al.*, 2012). The measure of CD symptoms here includes child self-reports, possibly reducing the effect of any such biases. Sensitivity analysis was carried out to look at the associations between maternal depression at Time 1 and the child's own ratings of CD symptoms at Time 2. Similar associations were found when using child ratings of CD symptoms ($B=1.17$ 95%CI 0.14-2.21, $p=0.03$).

Another limitation is that child psychopathology at Time 2 was assessed using the DAWBA, a structured interview, which was different to assessment at Time 1 where

the CAPA, a semi-structured interview was used. Some do consider the DAWBA to be relatively conservative and rates might be higher when using the CAPA. However a study comparing three different psychiatric interviews (CAPA, DAWBA & DISC) found ADHD reported at 9.2% using the DAWBA and 10.6% using the CAPA. The DAWBA generated significantly fewer cases of depression and anxiety than the CAPA, but similar rates of behavioural disorders (ADHD, ODD and CD). (Angold *et al.*, 2012). Furthermore, to account for this change in assessment instrument, standardised scores were used in the analyses.

Adults with ADHD are reported to have high rates of comorbid anxiety and depression (Simon, Czobor and Bitter, 2013). It would have been interesting to investigate the influence of comorbid parental psychopathology. However, there was little overlap in this sample of mothers who had both ADHD and depression [6.6 % (n=9)], and therefore, there was insufficient power to further investigate this. Mothers of children with ADHD are also reported to have higher anxiety symptoms compared to controls (Segenreich *et al.*, 2014). In this sample, there was considerable overlap observed between some of the anxiety items of the HADS questionnaire and ADHD symptoms, such as restlessness and 'being on the move'. Therefore, it was decided that this questionnaire measure of anxiety might not be valid in parents of children with ADHD. This would, however, be interesting to study in the future.

This analysis was conducted on a sample of boys and therefore this study could not investigate if the effect of parental psychopathology on child outcomes would be the same in sample of girls with ADHD. Several studies examining intergenerational patterns of transmission by gender have suggested that maternal depression may have stronger adverse effect for girls. These studies however examined associations

between maternal depression and child depression (Cortes *et al.*, 2006; Lewis *et al.*, 2011; Sellers *et al.*, 2016), so it is not clear if the findings would be the same for ADHD. The findings and conclusions from this study are specific to young adolescent boys with ADHD. Future research should consider investigating the differences of effect on boys and girls.

4.5.2 Clinical Implications

Findings from the present study have important clinical implications. When assessing children with ADHD in clinic, it is important for clinicians to be aware of the high prevalence of parent mental health problems. Given that mother depression is associated with adverse clinical outcomes in children with ADHD, it may be especially important to screen for depression in mothers. It is important to consider the multiple impairments or difficulties faced by families especially if the parent has mental health difficulties (Deault, 2010) and therefore treatment and interventions can be planned and tailored accordingly. Preliminary evidence in a recent trial, revealed that an integrated intervention based treatment incorporating parenting training and cognitive behavioural depression treatment had slightly better beneficial effects compared to parenting training alone in a sample of children with ADHD (Chronis-Tuscano *et al.*, 2013). Treatment of parent depression in randomised controlled trials has been found to result in improvements in child mental health, especially conduct problems (Weissman *et al.*, 2015). Though treatment studies on parental ADHD are still in the early stages, evidence so far suggests that although medication helps to improve ADHD symptoms in parents, more intensive treatments are needed to target improvement in parenting behaviour (Chronis-Tuscano *et al.*, 2011; Wietecha *et al.*,

2012; Babinski, Waxmonsky and Pelham, 2014; Wang, Mazursky-Horowitz and Chronis-Tuscano, 2014; Waxmonsky *et al.*, 2014; Jans *et al.*, 2015). Additionally, given that social class may play a role in the association between maternal depression and child symptoms, perhaps improving the socio economic status of the family could be considered as a form of intervention as well.

4.6 Conclusion

Overall, the results of this study suggest that depression but not ADHD in mothers, is associated with adverse clinical outcomes in terms of CD symptoms in a sample of boys with ADHD. Further work is needed to understand the processes that contribute to this association, given the global impairment in functioning associated with CD in ADHD. The study also suggests that the influence of mother psychopathology on longer term outcomes in boys with ADHD may differ by specific parental psychopathology. However we are not able to test this directly due to our limited sample size, and this needs to be investigated further.

Thus evidence has so far shown that parent ADHD and depression are associated with clinical presentation in children with ADHD. However ADHD is also characterised by neurocognitive deficits, which is another marker of severity. Given that neurocognitive domains are heritable and may share familial and genetic risks with ADHD, understanding more about associations between parental psychopathology and neurocognitive functioning may help identify a subgroup of children who are more impaired and contribute to understanding the etiological heterogeneity of ADHD. This will be explored in the next chapter.

Chapter 5

Parental psychopathology and neurocognitive functioning in children with ADHD

Chapter description:

In chapters 3 and 4, associations between parental psychopathology and clinical presentation in children with ADHD were investigated and results suggest that parent ADHD and depression is associated with a more severe clinical presentation of ADHD in children. Following on from this, the study in the current chapter will examine whether parental psychopathology is associated with neurocognitive variation in the children with ADHD, a further marker of disorder severity. The sample used in this chapter is the cross-sectional sample derived from the SAGE study that was previously used in chapter 3. The neuropsychological measures used have been described in detail in chapter 2 of this thesis, but are briefly described here. The chapter is based on the manuscript '*Parent psychopathology and neurocognitive functioning in children with ADHD*', which has been submitted to the Journal of Attention Disorders in February 2017. This manuscript is currently under review.

5.1 Introduction

Previous research on children with ADHD, including the study in chapter 3, has shown that parental ADHD is associated with a more severe clinical presentation of the disorder in offspring, including higher ADHD symptom severity and comorbid conduct symptoms and diagnoses (Humphreys, Mehta and Lee, 2012; Agha *et al.*, 2013; Segenreich *et al.*, 2014). Since the publication of findings described in chapter 3, these findings have been replicated by other groups (Middeldorp *et al.*, 2016b; Breaux, Brown and Harvey, 2017; Moroney *et al.*, 2017). There is also evidence that maternal depression is associated with a more severe ADHD clinical presentation and impairment in children with ADHD (Pressman *et al.*, 2006; Chronis *et al.*, 2007; Humphreys, Mehta and Lee, 2012) and results from chapter 4 show that maternal depression is associated with later development of conduct disorder symptoms in children.

5.1.2 ADHD and neurocognitive deficits

ADHD is characterised by neurocognitive deficits as well as by its core clinical features (Willcutt *et al.*, 2005). Research has also shown that children with ADHD score lower in overall cognitive ability compared to typically developing children (Crosbie and Schachar, 2001; Rucklidge and Tannock, 2002). These findings have important implications as lower IQ is itself related to higher levels of psychopathology, conduct problems, criminality in adulthood, lower ranking occupations and deficits in social skills (Mannuzza and Klein, 2000; Satterfield *et al.*, 2007).

Children with ADHD manifest deficits in various key neurocognitive domains including executive function (Willcutt *et al.*, 2005; Seidman, 2006) and delay aversion (Sonuga-

Barke, 2002). Just as the clinical presentation of ADHD is heterogeneous, there is heterogeneity in neurocognitive performance amongst children with ADHD (Nigg *et al.*, 2005; Doyle, 2006). Furthermore, number of studies have demonstrated that variability in neurocognitive performance among children with ADHD is associated with comorbidity and worse outcomes such as higher rates of repeated grades, lower education and occupational attainment in adolescence and adulthood (Biederman *et al.*, 2004; Doyle, 2006; Biederman, Petty, *et al.*, 2008; van Lieshout *et al.*, 2016). Thus, as discussed in chapter 1, such deficits provide an alternative index of ADHD severity. Many of the studies looking at associations between parental psychopathology and offspring ADHD phenotype characteristics utilise subjective reports of clinical severity in the child that in many cases have been provided by the parent. It is possible therefore, that the parents' own mental state and psychopathology may influence their reporting of the child's behaviour. Neurocognitive measures provide a more objective and non-behavioural measure of impairment in children with ADHD compared to subjective parent reports. Therefore, investigating the relationship between parental psychopathology and neurocognitive variability in ADHD provides an additional opportunity to empirically assess the relevance of parental mental health to the clinical severity of offspring ADHD.

5.1.3 Parental psychopathology and neurocognitive deficits in ADHD offspring: previous evidence

5.1.3.1 Parent ADHD

Very few studies have specifically investigated how parental psychopathology might be associated with neuropsychological variation in offspring within a sample of children with ADHD. The few studies to date that have undertaken this type of investigation have shown somewhat mixed findings.

Seidman and colleagues found that children with ADHD and a family history of ADHD (in first degree relatives including siblings) performed significantly worse than children with ADHD without a family history of ADHD on a set shifting task (Wisconsin Card sorting task) and another task measuring selective attention (Stroop Task) (Seidman *et al.*, 1995, 1997). Another study found that children with ADHD and poor inhibition had significantly higher rates of family history of ADHD (first degree relatives – mother, father and sibling) (48%) in comparison to ADHD children with good inhibition (18.5%) and controls (7.7%), which suggests that children with ADHD and a deficit in response inhibition may represent a familial subtype of ADHD (Crosbie and Schachar, 2001). Thissen and colleagues found that mother ADHD was associated with poorer offspring inhibition and motor control/functioning whereas father ADHD was found to be associated with motor timing problems (temporal organisation of motor outputs) and lower verbal and total IQ, with this latter finding restricted to girls (Thissen, Rommelse, Altink, *et al.*, 2014). However it was reported that there were no differences between the effect sizes between father and mother ADHD for any of the measures except for associations with inhibition and motor control measures. Furthermore the effect sizes found in this study were small with the exception of the association between mother

ADHD and inhibition, which was moderate (Thissen, Rommelse, Altink, *et al.*, 2014). Conversely, two other studies investigating response inhibition in families of children with ADHD, found no specific associations of maternal and paternal ADHD in relation to offspring response inhibition (Crosbie and Schachar, 2001; Goos *et al.*, 2009) perhaps due to smaller sample sizes in these studies. It is difficult to draw any conclusions from the current evidence as studies to date are small (ranging from 54 to 238 participants), results are inconsistent and include different domains of neurocognitive functioning, using different task measures.

5.1.3.2 Parent Depression

Previous research has shown evidence of association between parent depression and offspring neurocognitive difficulties in a community sample of children of mothers with mental health problems (depression and bipolar disorder) (Cogill *et al.*, 1986; Klimes-Dougan *et al.*, 2006). In a longitudinal study of a sample of low income families, depression in mothers was found to be associated with the development of executive function in children at age six years; mothers with fewer symptoms at baseline and reduction of maternal symptoms over time were associated with improvement in executive functioning (Hughes *et al.*, 2013). However, two separate studies of older children (age 6 to 17 years) at risk for depression, did not find any associations between mother depression and neurocognitive difficulties (Klimes-Dougan *et al.*, 2006; Micco *et al.*, 2009). Whilst evidence from this thesis (chapter 4) and other studies with ADHD samples show evidence that maternal depression is associated with increased behavioural problems (Chronis *et al.*, 2007; Harvey, Stoessel and Herbert, 2011; Agha *et al.*, 2016), what is not known is if parent depression is associated with

neurocognitive variation in children with ADHD. To date, only one small, pilot study to date has investigated the association between parental depression and neurocognitive profiles in children with ADHD (Park *et al.*, 2014). In a sample of 38 children with ADHD, these authors found significantly poorer performance on tasks measuring visuospatial organisation, processing speed and visual attention in those children with a parent who had a history of mood disorder compared to those without, but no differences on a range of other neurocognitive domains (Park *et al.*, 2014).

5.1.3.3 Clinical relevance

Recent evidence from treatment trials in children with ADHD suggests that treatment strategies targeting improvement of executive functioning through parent involvement can help improve symptoms of ADHD (Halperin *et al.*, 2013; Tamm, Nakonezny and Hughes, 2014). The delivery of psychosocial or parent administered treatment are usually dependent on parent well-being (Cortese *et al.*, 2015; Tarver, Daley and Sayal, 2015) and therefore it is important to understand more about the association between parent mental health and severity of neuropsychological deficits in children with ADHD as this could help identify a subgroup of patients who are more impaired and who may not respond to treatment as well.

5.2 Study aims

Given the somewhat inconsistent and limited body of evidence to date, this study will explore associations between parental ADHD and parent depression and neurocognitive performance in a sample of children with a clinical diagnosis of ADHD. General cognitive ability and three domains of neurocognition, previously shown to be associated with ADHD in a large meta-analysis (Willcutt *et al.*, 2005), were chosen for examination: working memory, set shifting ability and motivational deficits. Working memory is the ability to temporarily hold and manipulate information in the mind for the purpose of completing a task or action. Baddeley (2003) had proposed a three component model of working memory which consists of two storage components, phonological loop (verbal storage system) and visuospatial information (visual storage system) and a central executive system where the information stored is controlled and manipulated (Baddeley, 2003). Evidence shows that children with ADHD show impairments across these different components (Martinussen *et al.*, 2005). Attention set shifting, which is also found to be impaired in children with ADHD, involves the ability to shift attention between one task / concept and another (Kempton *et al.*, 1999; Mehta, Goodyer and Sahakian, 2004). Motivational deficits such as risky behaviour and abnormal reward processing have also been identified as one of the core neurocognitive deficits in ADHD (Barkley, 1997; Sonuga-Barke, 2002). Delay aversion can be described as intolerance of waiting that can result in a tendency to select immediate rewards over larger rewards for which one has to wait. This can also manifest in poor decision-making as the decisions we make involve the ability to integrate experience of rewards and losses over time (Garon, Moore and Waschbusch,

2006). Children with ADHD have been shown to exhibit aversions to delay, preferences for smaller and immediate rewards and impaired decision-making (Toplak, Jain and Tannock, 2005; Garon, Moore and Waschbusch, 2006; DeVito *et al.*, 2008; Groen *et al.*, 2013).

The primary aim of this study was to investigate the influence of parent ADHD and depression on neurocognitive performance in three domains of offspring neurocognitive functioning; working memory, set shifting and motivational deficits. Secondary analysis examined the association separately for mother and father ADHD and mother depression.

5.3 Methods

5.3.1 Sample

For the current chapter, analysis is based on a sample of 570 children from the SAGE study at Time 1 (detailed in chapter 2) with information obtained from both mothers and fathers. Measures used in this chapter are briefly listed below, details of the sample and measures are described in chapter 2.

5.3.2 Measures

5.3.2.1 Predictors

In chapter 3, mother and father ADHD were separately examined, whereas in this chapter a combined measure of parent ADHD and parent depression was used for the primary analysis. This was to increase statistical power and because there was no evidence of assortative mating for ADHD parent status; ADHD symptoms were not

correlated between mothers and fathers for either current ($r = -0.04$, $p < 0.52$) or childhood symptoms ($r = -0.08$, $p < 0.22$). There was little evidence to demonstrate the presence of assortative mating between mother and father depression symptoms for parent depression ($r = 0.19$, $p < 0.01$). However, sensitivity analyses were conducted to investigate associations with mother ADHD, depression and father ADHD separately. Due to the small number of fathers with depression, this sensitivity analyses was not performed on father depression alone. The predictor measures used in this study are:

- Parent ADHD (either mother or father meeting study criteria for adult ADHD)
- Parent depression (either mother or father meeting study criteria for depression)

5.3.2.2 Outcome measures

- Cognitive ability was measured using the full scale IQ. This was assessed using the Wechsler Intelligence Scale for Children version IV (WICS-IV) (Wechsler, 2003)
- Verbal working memory was measured using the Digit Span task which is a subtest from the WISC-IV
- Attention set shifting measured by Intra / Extra Dimensional Set Shift task (IED) taken from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Cambridge Cognition, 1996). Participants are presented with two types of dimensions / shapes and are asked to choose a pattern they think is correct. Further details of this task are explained in section 2.3.1 in chapter 2.

The outcome measures are as follows:

- Total errors made throughout the set shifting task (adjusted for any stage that was not attempted)
- Errors made during the Extra Dimensional Shift stage (ED Stage 8 – the ability to shift attention to the irrelevant stimuli)
- Motivational deficits measured by the Cambridge Gambling Task (CGT), which is also part of the Cambridge Neuropsychological Battery (CANTAB). It assesses decision making and risk taking behaviour. Participants were presented with different ratios of 10 red and blue boxes in one of which a yellow token is hidden. Participants must guess if the yellow token is concealed behind a red or blue square. Further details of this task are explained in section 2.3.1 in chapter

2. The outcomes measure are as follows:

- Quality of decision making (proportion of trials where the majority colour was chosen - a higher score is favourable)
- Delay aversion (difference in percentage bets on the descending vs ascending trials - higher scores indicate impulsivity and intolerance of waiting)
- Risk taking (mean proportion of points bet on trials where the most likely outcome was chosen)
- Risk adjustment (rate at which subjects increase the bet proportion in response to more favourable ratios - low scores are unfavourable)

5.3.3 Analysis

Linear regressions were used to examine associations between predictors (parent ADHD and depression) and outcomes (child scores on the neurocognitive tasks). All neurocognitive outcome scores were normally distributed and were standardised for ease of interpretation and comparison across different tasks. Estimates were then further adjusted for child age, low social class and low parent education to test if associations found were explained by parent level of education and social class (as proxy measures of parent IQ). Child IQ was included as a covariate in the subsequent model except for the analyses looking at IQ and Digit Span (it is one of the subtests used to assess full scale IQ). In the final model, child ADHD and CD severity were included as covariates to determine if associations between parental psychopathology and child neurocognitive performance were independent of child psychopathology. Post estimation tests identified two outliers for the digit span scores. As these outliers had higher than average leverage and residual values, these two individuals were excluded from the analyses. As mentioned in section 5.3.2.1 sensitivity analyses were conducted to examine associations for mothers and father ADHD separately. In view of the high proportion of missing information on fathers, this study examined if performance on neurocognitive tasks differed by comparing children with complete parent information and those without. All analyses were performed using STATA (version13).

5.4 Results

The sample consisted of 568 children, 480 (84.5%) males and 88 (15.4%) females with a mean age of 10.77 (SD 3.01). All children had a research diagnosis of ADHD. Rates of ADHD subtypes and comorbidities in this sample are reported in more detail in section 2.1.4 of chapter 2.

As mentioned previously in Chapter 3, high rates of parental psychopathology were found; 33% (n=186) of children in the sample had a parent meeting symptom criteria for adult ADHD as defined by DSM-5. There were only a few children where both parents had ADHD in the same family (1.9%, n=11). Looking at parent depression, 23.8% (n=133) of children had a parent who met the cut-point for depression based on the HADS. Only 1.4% (n=8) of children had both parents meeting study criteria for depression.

Child age, gender, child ADHD medication use and parent education level did not differ between those with and without a parent with ADHD or depression. The study found that 62% of families with a parent with ADHD were classified as being of low social class compared to 50% of families without an ADHD parent ($\chi^2(1) = 6.69, p=0.01$). Similarly, 61% of families with a parent with depression were more likely to be classified in the lower social class compared to 52% of families without a parent with depression (61% vs. 52%; $\chi^2(1) = 3.04, p=0.081$).

5.4.1 Correlations between child clinical and neurocognitive measures

The pattern of correlations between child clinical symptoms and neuropsychological tasks is shown in table 5.1. ADHD symptom severity was found to be positively correlated with errors in the set shifting task, where those with more symptoms had more errors during the task. ADHD symptom severity was also negatively correlated with quality of decision making and risk taking scores. Conduct disorder symptoms on the other hand, were negatively correlated with IQ and digit span. However, these correlation coefficients were small to medium ranging between $r = 0.17 - 0.25$.

Table 5.1: Correlation matrix between child clinical symptoms and neuropsychological tasks

		1	2	3	4	5	6	7	8	9
Child clinical symptoms	1. Child ADHD symptoms									
	2. Child CD symptoms	.17*								
Cognitive ability	3. IQ	-.04	-.25*							
Working memory	4. Digit Span	-.04	-.12*	.62*						
Attention set-shifting	5. Total errors during set shifting task	.15**	.01	-.16*	-.17*					
	6. Errors during ED stage ^a	.11	.01	-.15**	-.15**	.84*				
Motivational deficits	7. Quality of decision making	-.15**	.01	.11	.14**	-.31*	-.25*			
	8. Delay aversion	.11	.001	-.16**	-.10	.23*	.25*	-.32*		
	9. Risk adjustment	-.10	-.06	.08	.07	-.11	-.09	.17*	-.39*	
	10. Risk taking	-.18*	-.02	.05	.08	-.15**	-.15**	.45*	-.73*	.08

^a ED – Extra dimensional Shift Stage (Stage 8)

*Correlation is significant at the 0.01 level (2-tailed)

**Correlations is significant at the 0.05 level (2-tailed)

The mean scores for each task for the whole sample are presented in table 5.2. In the set shifting task, the mean number of stages passed was 7.90 (SD 0.96). Most children in the sample completed the Intra dimensional shift stage (ID - stage 6) but just less than half the sample (49%) was unable to complete the Extra dimensional shift (ED) stage of the task (stage 8).

5.4.2 Parent ADHD and offspring neurocognitive outcomes

Parent ADHD was found to be associated with lower offspring scores on the Digit Span subtest ($B = -0.25$, 95%CI $-0.42, -0.07$, $p = 0.006$) and higher scores for the total number of errors made in the EDS shift stage ($B = 0.26$, 95%CI $0.02, 0.50$, $p = 0.035$). When comparing parental psychopathology groups, it was found that only 44% of children with a parent with ADHD completed stage 8 / 9 of the set shifting task compared to 55% in the group of children without a parent with ADHD ($\chi^2(1) = 3.10$ $p = 0.08$). Parent ADHD was not associated with total errors made by offspring on the set shifting task and any of the measures from the gambling task (delay aversion, quality of decision making, risk adjustment and risk taking behaviour) (table 5.2). The effect sizes and pattern of results remained similar after adjusting for the covariates which indicates that the associations are independent of and not explained by child ADHD severity and all other variables adjusted for (table 5.3).

Table 5.2: Associations between parent ADHD (mother/father) and child neurocognitive performance

Neurocognitive outcome		Total sample		Parent ADHD		Unadjusted Model**		
		n	Mean (SD)	NO n = 380 Mean (SD)	YES n = 186 Mean (SD)	B	(95%CI)	p
Working memory	Digit Span	520	7.14 (2.72)	7.35 (2.81)	6.66 (2.81)	-0.25	-0.42, -0.07	0.006
Cognitive ability	IQ	521	82.30 (13.54)	82.62 (13.59)	81.51 (13.43)	-0.08	-0.26, 0.10	0.383
Attention set shifting	Total errors - set shifting task	278	44.29 (21.22)	43.01 (21.45)	46.53 (20.22)	0.17	-0.08, 0.41	0.183
	ED* shift errors	278	16.57 (10.50)	16.93 (10.14)	19.56 (9.63)	0.26	0.02, 0.50	0.035
Motivational deficits	Quality of decision making	296	0.76 (0.19)	0.77 (0.20)	0.76 (0.18)	-0.04	-0.28, 0.20	0.750
	Delay aversion	207	0.57 (0.20)	0.57 (0.21)	0.57 (0.20)	0.01	-0.28, 0.29	0.971
	Risk taking	294	0.54 (0.17)	0.54 (0.17)	0.55 (0.16)	-0.05	-0.19, 0.29	0.689
	Risk adjustment	294	0.31 (0.89)	0.31 (0.93)	0.32 (0.80)	-0.01	-0.23, 0.25	0.960

*Extra dimensional Shift Stage (Stage 8)

**All neurocognitive outcome variables are standardized scores

Table 5.3: Associations between parent ADHD (mother/father) and child neurocognitive performance adjusting for covariates (low parent education status, low social class, child age, child IQ, ADHD severity, and conduct symptom severity)

Neurocognitive outcome		Model 1 (Low parent education (n=525), low social class (n=513) & child age (n=568))			Model 2 + (IQ (n=523))			Model 3 +(ADHD & CD severity (n=560))		
		<i>B</i>	(95%CI)	<i>P</i>	<i>B</i>	(95%CI)	<i>p</i>	<i>B</i>	(95%CI)	<i>p</i>
Working memory	Digit Span ^a	-0.24	-0.43, -0.05	0.013				-0.24	-0.43, -0.04	0.017
Cognitive ability	IQ	-0.05	-0.24, 0.14	0.622				-0.02	-0.21, 0.17	0.819
Attention set shifting	Total errors -set shifting task	0.20	-0.05, 0.45	0.119	0.18	-0.08, 0.43	0.170	0.21	-0.05, 0.47	0.107
	ED* shift errors	0.30	0.03, 0.55	0.027	0.27	0.004, 0.53	0.047	0.29	0.02, 0.55	0.034
Motivational deficits	Quality of decision making	-0.03	-0.27, 0.21	0.800	-0.03	-0.28, 0.22	0.821	-0.04	-0.29, 0.22	0.785
	Delay aversion	0.03	-0.27, 0.32	0.866	0.03	-0.27, 0.33	0.830	0.04	-0.27, 0.35	0.802
	Risk taking	0.06	-0.18, 0.30	0.607	0.08	-0.16, 0.32	0.507	0.07	-0.18, 0.32	0.563
	Risk adjustment	0.03	-0.23, 0.28	0.825	0.03	-0.23, 0.29	0.808	0.06	-0.20, 0.32	0.658

*Extra dimensional Shift Stage (Stage 8)

^a Digit Span subtest is included as part of the full scale IQ estimate therefore this was not adjusted for
All neurocognitive outcome variables are standardized scores

Table 5.4: Associations between parent depression (mother/father) and child neurocognitive performance

Neurocognitive outcome		Parent Depression			Unadjusted Model		
			NO n = 425	YES n = 133			
		n	Mean (SD)	Mean (SD)	<i>B</i>	(95%CI)	<i>p</i>
Working memory	Digit Span	512	7.11 (2.86)	7.22 (2.26)	0.04	-0.16, 0.23	0.721
Cognitive ability	IQ	513	82.72 (13.81)	81.46 (12.17)	-0.09	-0.30, 0.11	0.372
Attention set shifting	Total errors - set shifting task	271	43.63 (21.50)	46.42 (19.34)	0.13	-0.14, 0.40	0.335
	ED* shift errors	271	17.55 (10.12)	19.28 (9.54)	0.17	-0.10, 0.44	0.211
Motivational deficits	Quality of decision making	289	0.75 (0.20)	0.78 (0.17)	0.17	-0.10, 0.43	0.221
	Delay aversion	203	0.56 (0.21)	0.62 (0.19)	0.29	-0.02, 0.60	0.068
	Risk taking	287	0.54 (0.17)	0.55 (0.15)	0.07	-0.20, 0.33	0.628
	Risk adjustment	287	0.31 (0.90)	0.27 (0.87)	-0.05	-0.32, 0.22	0.716

*ED – Extra dimensional Shift Stage (Stage 8)

All neurocognitive outcome variables are standardized scores

Table 5.5: Associations between parent depression (mother/father) and child neurocognitive performance adjusting for covariates (low parent education status, low social class, child age, child IQ, ADHD and conduct symptom severity)

Neurocognitive outcome		Model 1 (Low parent education (n=525), low social class (n=513) & child age (n=568))			Model 2 + (IQ (n=523))			Model 3 +(ADHD & CD severity (n=560))		
		B	(95%CI)	P	B	(95%CI)	p	B	(95%CI)	P
Working memory	Digit Span	0.13	-0.08, 0.34	0.219				0.16	0.06, 0.38	0.154
Cognitive ability	IQ	0.01	-0.20, 0.23	0.901				0.05	-0.16, 0.27	0.619
Attention set shifting	Total errors -set shifting task	0.15	-0.12, 0.43	0.277	0.11	-0.16, 0.39	0.427	0.14	-0.14, 0.43	0.311
	ED* shift errors	0.20	-0.09, 0.48	0.182	0.14	-0.15, 0.43	0.344	0.16	-0.13, 0.46	0.273
Motivational deficits	Quality of decision making	0.28	0.01, 0.54	0.043	0.26	-0.02, 0.53	0.066	0.25	-0.03, 0.53	0.083
	Delay aversion	0.20	-0.12, 0.52	0.222	0.17	-0.15, 0.49	0.297	0.18	-0.14, 0.52	0.274
	Risk taking	0.16	-0.10, 0.42	0.238	0.17	-0.09, 0.43	0.197	0.16	-0.10, 0.44	0.228
	Risk adjustment	0.04	-0.24, 0.32	0.799	0.02	-0.27, 0.30	0.910	0.06	-0.23, 0.35	0.671

* ED – Extra dimensional Shift Stage (Stage 8)

All neurocognitive outcome variables are standardized scores

5.4.3 Parent Depression and offspring neurocognitive outcomes

As detailed in table 5.4, we did not observe associations between parent depression and any of the offspring neurocognitive outcome scores, apart from weak evidence of association with the delay aversion score ($B= 0.29$, 95%CI $-0.02, 0.60$, $p=0.068$). After adjustment for covariates, the pattern of associations did not change (table 5.5). In the parent depression groups, 42% of offspring with a parent with depression completed stage 8/9 compared to 53% of children whose parent did not have depression ($\chi^2(1) = 2.31$ $p=0.13$).

5.4.4 Sensitivity analysis

Associations with Mother ADHD

There were no significant associations found between mother ADHD and offspring performance on neuropsychological tasks, apart from weak evidence of association between mother ADHD and scores on digit span ($B = -0.18$, 95%CI $-0.39, -0.03$, $p=0.09$) (table 5.6).

Associations with Father ADHD

Father ADHD was not found to be strongly associated with child performance on digit span ($B = -0.25$, 95%CI $-0.51, 0.003$, $p=0.05$) and IQ ($B = -0.27$, 95%CI $-0.54, 0.01$, $p=0.05$) (table 5.7). Father ADHD was not associated with performance on the set shifting task and any of the measures from the gambling task.

Table 5.6: Associations between mother ADHD and child neurocognitive performance

		Mother ADHD		Unadjusted Model		
		NO (n=423) Mean (SD)	YES (n=117) Mean (SD)	<i>B</i>	<i>95%CI</i>	<i>p</i>
Working memory	Digit Span	7.28 (2.81)	6.77 (2.41)	-0.18	-0.39, -0.03	0.09
Cognitive ability	IQ	82.45 (13.57)	82.45 (13.30)	-0.0008	-0.21, 0.21	0.99
Attention set shifting	Total errors during the whole set shifting task	43.54 (21.23)	45.67 (20.08)	0.10	-0.17, 0.37	0.47
	ED* shift errors	17.30 (10.12)	19.39 (9.57)	0.21	-0.07, 0.48	0.14
Motivational deficits	Quality of decision making	0.77 (0.20)	0.75 (0.18)	-0.06	-0.33, 0.22	0.69
	Delay aversion	0.57 (0.21)	0.57 (0.20)	-0.03	-0.35, 0.30	0.88
	Risk taking	0.54 (0.18)	0.55 (0.14)	0.08	-0.19, 0.35	0.58
	Risk adjustment	0.32 (0.90)	0.29 (0.86)	-0.03	-0.31, 0.24	0.81

*ED – Extra dimensional Shift Stage (Stage 8)
All neurocognitive outcome variables are standardized scores

Table 5.7: Associations between father ADHD and child neuropsychological performance

		Father ADHD		Unadjusted Model		
		NO (n=196)	YES (n=80)			
		Mean (SD)	Mean (SD)	<i>B</i>	<i>95%CI</i>	<i>p</i>
Working memory	Digit Span	7.22 (2.61)	6.51 (2.59)	-0.25	-0.51, 0.003	0.05
Cognitive ability	IQ	84.05 (13.05)	80.34 (14.22)	-0.27	-0.54, 0.01	0.05
Attention set shifting	Total errors during the whole set shifting task	44.51 (21.35)	47.32 (21.25)	0.13	-0.24, 0.50	0.48
	ED* shift errors	18.17 (9.92)	19.32 (9.64)	0.11	-0.25, 0.48	0.54
Motivational deficits	Quality of decision making	0.76 (0.19)	0.76 (0.20)	0.01	-0.35, 0.37	0.95
	Delay aversion	0.57 (0.20)	0.58 (0.21)	0.01	-0.42, 0.44	0.95
	Risk taking	0.54 (0.16)	0.54 (0.18)	-0.02	-0.39, 0.34	0.90
	Risk adjustment	0.33 (0.89)	0.40 (0.73)	0.07	-0.28, 0.42	0.69

*ED – Extra dimensional Shift Stage (Stage 8)

Table 5.8: Associations between mother depression and child neurocognitive performance

		Mother Depression		Unadjusted Model		
		NO (n=420)	YES (n=111)			
		Mean (SD)	Mean (SD)	<i>B</i>	(95%CI)	<i>p</i>
Working memory	Digit Span	7.16 (2.85)	7.19 (2.29)	-0.01	-0.20, 0.23	0.92
Cognitive ability	IQ	82.77 (13.75)	81.43 (12.28)	-0.10	-0.32, 0.12	0.38
Attention set shifting	Total errors during the whole set shifting task	43.29 (20.94)	46.92 (19.61)	0.17	-0.11, 0.45	0.23
	ED* shift errors	17.45 (10.07)	19.51 (9.60)	0.20	-0.08, 0.49	0.16
Motivational deficits	Quality of decision making	0.75 (0.20)	0.79 (0.17)	0.04	-0.02, 0.10	0.178
	Delay aversion	0.56 (0.21)	0.61 (0.19)	0.21	-0.11, 0.53	0.20
	Risk taking	0.53 (0.17)	0.56 (0.15)	0.18	-0.10, 0.45	0.21
	Risk adjustment	0.31 (0.90)	0.28 (0.88)	-0.04	-0.32, 0.25	0.80

*ED – Extra dimensional Shift Stage (Stage 8)

All neurocognitive outcome variables are standardized scores

Associations with Mother Depression

There were no significant associations found between mother depression and offspring performance on neuropsychological tasks (table 5.8.). As discussed previously, there were too few fathers with depression to analyse any associations separately.

5.4.5 Further analysis with complete families

In view of the high proportion of missing information on fathers, this study examined if there were differences in associations between children with complete parent information and those without. Mean scores of performance on neurocognitive tasks did not differ between children with and without complete parent information (table 5.9).

Table 5.9: Comparison of neurocognitive task performance between children from complete families (information from both parents) and families where information is available for one parent only

Neurocognitive task	Single parent families n=333	Complete families n=235	t-test (df)	p value
	Mean (SD)	Mean (SD)		
IQ full scale	81.69 (13.59)	83.30 (13.59)	-1.23 (521)	0.22
Digit Span	7.15 (2.81)	7.11 (2.61)	0.19 (520)	0.85
IED Total errors (adjusted)	44.56 (21.81)	43.94 (20.51)	0.24 (276)	0.81
Errors ED stage of task	17.64 (10.15)	18.20 (9.89)	-0.46 (276)	0.64
Quality of decision making	0.76 (0.19)	0.76 (0.19)	0.19 (294)	0.85
Delay aversion	0.57 (0.20)	0.57 (0.21)	-0.16 (205)	0.88
Risk adjustment	0.30 (0.93)	0.33 (0.83)	-0.26 (292)	0.79
Risk taking	0.54 (0.17)	0.54 (0.17)	0.13 (292)	0.90

5.5 Discussion

This study aimed to build upon previous findings presented in chapter 3 and 4 of this thesis, and in other literature, that parental ADHD and depression are associated with a clinically more severe presentation of offspring ADHD as defined by reported symptoms (Chronis *et al.*, 2003; Pressman *et al.*, 2006; Humphreys, Mehta and Lee, 2012; Agha *et al.*, 2013, 2016; Segenreich *et al.*, 2014). As previously described, rates of parental psychopathology were high; 33% of children had a parent with ADHD and 24% had a parent with depression. I was interested in whether associations previously described in this thesis between parental psychopathology and offspring ADHD clinical severity extended to alternative, more objective, measures of offspring difficulty; that is, impaired neurocognitive performance.

These are the main findings from this chapter. Children who had a parent with ADHD performed more poorly in measures of working memory (the digit span task) and set-shifting ability (number of errors in the ED shift stage). However, no differences were found in the domains of general cognitive ability (full scale IQ) or motivational deficits in decision making (measured by the Cambridge Gambling Task). These findings for set-shifting ability are similar to those reported by Seidman and colleagues (Seidman *et al.*, 1995, 1997) where family history of ADHD (in first degree relatives including siblings) was found to predict impairment in the Wisconsin card sorting tasks (WCST) which is akin to the IE / ED set shifting task.

In the set shifting tasks, most children completed stage 6 (IED) of the task which is as expected, as it has been reported that stages prior to the ED shift are easier to complete compared to the ED shift stage (Luciana and Nelson, 2002). Although most

children were able to complete stage 6 of the task, about half the children in this sample were unable to complete the next crucial stage, ED shift stage (stage 8). Although it appears that children with a parent with ADHD were less likely to complete stage 8 when compared to children without a parent with ADHD, there was no strong evidence to support this.. The ED shift stage of the set shifting tasks is said to be more difficult than the earlier stages of the task as it requires the need to use more resources on focused attention and working memory to integrate information from previous stages of the tasks, which might imply impairments in other processes (Luciana and Nelson, 2002). The findings of this study suggest that having a parent with ADHD might reflect heterogeneity of children with ADHD with more compromised deficits in attention set shifting ability compared to those without a parent with ADHD. This is however only preliminary and further investigation is needed.

The results of an association between parent ADHD and poorer offspring working memory differ from those of Thissen and colleagues who found no association in their study of 259 families of adolescents with ADHD (Thissen, Rommelse, Hoekstra, *et al.*, 2014). As there were no estimates provided for non-significant findings, I was unable to compare the magnitude of effect and direction of association with the findings in this study. The differences in findings may be due to the slightly different task measures used between these two studies and the different ages (mean age 17.3 years vs 10.8 in this study) of the individuals studied, which highlights the need to take such task and sample characteristics into account. Working memory was measured in both studies using the Digit Span task; however the study by Thissen and colleagues (2014) used the digit span backwards score whereas the scaled scores of digit span (forward & backwards) was used in this study (Thissen, Rommelse, Hoekstra, *et al.*, 2014).

Unfortunately, separate scores of digit span forwards and backwards were not available in the dataset of this study. Although cognitive tasks, are perhaps more objective than subjective reports, one problem is that there is no single gold standard method for assessing specific neurocognitive constructs.

Nonetheless, there has been recent evidence which found ADHD polygenic risk scores associated with lower IQ and working memory performance as well as ADHD symptom levels in children in the general population (Martin *et al.*, 2015). This suggests that the genetic risk for ADHD is also relevant to lower IQ and working memory abilities; however the present study focuses on variation within ADHD patients only. Taken together, the findings indicate that association between parent ADHD and lower performance in working memory might be an indicator of higher genetic risk.

Another study by Thissen and colleagues (2014) found that there may also be different influences of mother and father ADHD on the child's neurocognitive task performance (inhibition) (Thissen, Rommelse, Altink, *et al.*, 2014). However results on parent gender differences are not consistent as there are other studies that failed to show any differences between mother and father psychopathology on offspring performance of tasks (Crosbie and Schachar, 2001; Goos *et al.*, 2009). In this study, a combined parental measure was used; that is for either mother or father to have ADHD or depression. This was decided *a priori* to increase statistical power and because there was no evidence of assortative mating for parent ADHD or depression. This procedure is also similar to ones used in endophenotype studies of ADHD where parents are combined for main analyses (Asarnow *et al.*, 2002; Nigg *et al.*, 2004). Sensitivity analyses were conducted to investigate associations with mother ADHD, depression

and father ADHD separately. Results showed some weak evidence between mother and father ADHD and working memory.

In contrast to the findings for children with parents who have ADHD, no associations were found between parent depression status and offspring neurocognitive performance. These findings support and extend those of a much smaller pilot study (Park *et al.*, 2014) which found no evidence of differences in working memory, cognitive ability or set-shifting for children with ADHD between those with and without a parent with a history of mood disorder. Motivational decision making was not investigated by that group. It is important to note that the measure of parent ADHD in the present study perhaps indexes more longstanding symptoms from childhood to the present, whereas parent depression is only measured currently. This perhaps might explain why associations were found with parent ADHD and not parental depression; the parent ADHD measure is indexing more severe or more persistent psychopathology, and depression can be a relapsing and remitting disorder, unlike ADHD. Additionally, the aetiology of depression is different to ADHD, as the familial overlap between ADHD and neurocognitive deficits had been shown generally. However, this is not the case for depression and the types of cognitive measures that were used in this study.

This study is one of the first studies to investigate the links between parental psychopathology and variation in offspring neurocognitive performance in a large clinical sample of children with ADHD. It includes the analysis of both parent ADHD and depression within the same sample and explores associations with variation in offspring neurocognitive functions implicated as being affected in ADHD including delay aversion and decision making, that have not been examined previously. Overall,

the results of this study highlight that children with ADHD who already have neurocognitive deficits relative to the general population and who have a parent with ADHD may experience even greater neurocognitive problems, which underscores the importance of considering parent mental health during clinical assessment. Parent mental health problems appear to be linked to both cognitive as well as clinical indices of ADHD severity in clinic children; this is in the context of elevated social adversity that commonly accompanies parental psychopathology. Mechanisms that account for these cross-generational links likely include genetic, biological and social ones (Johnston and Mash, 2001; Stein and Harold, 2015).

5.5.1 Limitations

As with any investigation, this study should be considered in view of certain limitations. Measures of parent ADHD were based on self-report and retrospective recall of childhood ADHD symptoms, although evidence from previous studies has suggested that adults can give a reasonable account of their own childhood and current symptoms (Murphy and Schachar, 2000). Depression status for parents in this study was obtained using a cut-point on a widely used, validated scale, the HADS which was initially developed for screening purposes and therefore does not represent a DSM-5 diagnosis of major depressive disorder. However, the HADS has been reported to have good validity and performs well in predicting caseness of depression in both psychiatric and primary care patients as well as the general population (Bjelland *et al.*, 2002). Unfortunately there was no measure of parental IQ and parents were not assessed on the same neurocognitive tasks as their children. However adjusting for parent education in the analyses is a proxy measure of parent IQ, and associations

between parental ADHD and child performance on neurocognitive tasks remained unchanged.

A large proportion of individuals ascertained in this sample were from single parent families (mostly mothers), typical of referrals to many services in the UK where health care is free of charge so those from high-risk backgrounds are well represented in clinics. Therefore information on a substantial number of fathers was missing and there was not as much data available for fathers. Sensitivity analyses were conducted in the sample and it was found that there were no differences in associations for children with data available from both parents and those from single parent families.

Finally, the findings of this study are in need of replication considering that there were no corrections for multiple testing. The outcomes for each task in this study are correlated with each other, although some have suggested that traditional methods of correcting for multiple testing, such as the Bonferroni method, would be overly conservative in situations like this (Perneger, 1998). This was an exploratory study and findings help add potential insight into how parent ADHD and depression is related to some aspects of offspring neurocognitive performance, another important manifestation of the ADHD phenotype, but these findings require further investigation.

5.5.2 Clinical implications

There have been a few advances in the development of intervention strategies for children with ADHD that target neuropsychological impairments (Halperin *et al.*, 2013; Tamm, Nakonezny and Hughes, 2014; Tarver, Daley and Sayal, 2015). These interventions encourage parental involvement in adopting strategies and techniques

aimed at improving aspects of executive functioning deficits and abnormal reward processing (Tarver, Daley and Sayal, 2015). Examples include play and exercise activities to develop inhibitory control, (eg Simon says games), working memory and altering reward processing (immediate parental reinforcement). Preliminary evidence from this has shown improvements in EF performance and ADHD severity post treatment (Halperin *et al.*, 2013; Tamm, Nakonezny and Hughes, 2014). However interventions such as these depend heavily on parental involvement and optimal engagement from parents depends very much on many factors including parent mental health (Tarver, Daley and Sayal, 2015). Therefore, understanding the association between parental psychopathology and neurocognitive deficits in children with ADHD is important and relevant for the development of intervention and treatment plans specifically tailored for subgroups of high-risk children. It might be important for clinicians to be aware that children who present at clinic with neurocognitive difficulties and severe clinical presentation may have a parent with ADHD. This highlights that there may be a subgroup of patients that are more impaired and may not respond to treatment as well those without a parent with ADHD. This can help inform treatment interventions, which can be catered according to the child's cognitive strengths and weaknesses and parent mental health difficulties.

5.6 Conclusion

In conclusion, the results of this study suggest that parental ADHD is related to poorer performance in set shifting and working memory in their offspring with ADHD, but that parental depression is not associated with impaired offspring neurocognitive functioning. This further extends findings that parental ADHD is associated with offspring ADHD severity and again highlights the importance of considering parental mental health when assessing child ADHD.

Chapter 6

Discussion

6.1 Summary of findings

The main aim of this thesis was to examine links between parental psychopathology, and offspring phenotype in children with ADHD. Chapter 3 investigated the association between parent ADHD and offspring clinical features in a cross-sectional clinical sample of children with a diagnosis of ADHD. In this clinical sample of children with ADHD, a high number of parents (either mother or father) met study criteria for ADHD; 29% (DSM-IV) and 33% (DSM-5). This rate is much higher than rates of parental ADHD found in general population samples of children, but similar to those in community and clinical samples of children with ADHD (Murray and Johnston, 2006; Goos, Ezzatian and Schachar, 2007). Parent ADHD was found to be associated with severity of ADHD and conduct disorder symptoms; mother ADHD associated with total ADHD and inattention symptoms as well as CD symptoms and diagnosis whilst father ADHD was associated with CD symptoms. There was some weak evidence of associations between mother ADHD and child ADHD impairment but no evidence of association between father ADHD and child ADHD impairment. As all the children in the sample had a diagnosis of ADHD, there may have been insufficient variation in impairment scores; mean impairment score for the whole sample was 6.78 (SD 1.51) with scores ranging from 0 to 8. This could possibly account for the lack of association found between father ADHD and child ADHD impairment but presence of weak evidence between mother ADHD and impairment scores may indicate that perhaps the sample was

underpowered as well. In examining the timing of parental ADHD, parent adult ADHD (persistent) was associated with significantly higher offspring symptom severity than childhood-only ADHD (i.e. 'remitted' ADHD). Higher levels of family conflict and hostility as well as lower levels of cohesion were found to be related to mother ADHD. Up to 59% of the sample consisted of single parent families (mostly mothers). Higher levels of maternal warmth were reported by children who had a father with ADHD which indicates mothers are warmer to their children if their partner has ADHD.

As findings from chapter 3 suggested that parent ADHD is associated with a more severe offspring clinical presentation, the next step was to understand what influences parental psychopathology have on the course and persistence of ADHD and presence of CD in children across time. The study in chapter 4 set out to address this aim in a follow up of a subsample of participants who took part in the cross-sectional study used in chapter 3. It also examined associations with maternal depression. Mother ADHD was not associated with a change in child ADHD or conduct symptom severity over time. Maternal depression on the other hand predicted an increase in child conduct symptoms over time but did not contribute to ADHD symptom levels, after adjusting for conduct symptom severity at baseline. This study suggests that maternal depression is a predictor of worsening conduct symptoms in children with ADHD as they move into adolescence.

Finally the third aim of this thesis was to investigate associations between parental ADHD and depression and neurocognitive variation in children with ADHD, as a further marker of severity and impairment in children with ADHD. Here, parent ADHD, but not parent depression was found to be associated with lower scores on tasks assessing

working memory (digit span) and set shifting abilities (Extra Dimensional (ED) shift errors).

6.2 Interpretation of findings

6.2.1 Parent ADHD

The findings of this study suggest that even within a sample of children all of whom have ADHD, having a parent with ADHD may index a higher severity of symptoms. It also highlights that persistent / adult ADHD may be more relevant to the severity of offspring ADHD symptoms than remitted parent ADHD. This is inconsistent with the results of one study which did not find differences in child dysfunction between remitted and persistent groups (Biederman, Faraone and Monuteaux, 2002). There are other studies however which suggest that persistent ADHD is a more familial and genetic form of the disorder than remitted ADHD (Biederman *et al.*, 1996; Faraone, Biederman and Monuteaux, 2000b; Larsson *et al.*, 2011; Franke *et al.*, 2012; Pingault *et al.*, 2015; Riglin *et al.*, 2016) which would support our finding that persistent ADHD was associated with a poorer child clinical profile. Discrepancies between studies are perhaps due to different definitions of persistence in different studies (as discussed in chapter 1). The findings of this study add support for the evidence that ADHD in parents, especially with continuing symptoms of ADHD that manifest during the child's lifetime, may be important to the severity of ADHD in children.

Overall it was found that parent ADHD was associated with greater hostility, less cohesion, more conflict and less warmth in families of children with ADHD, with stronger associations found particularly with mother ADHD, possibly due to different involvement mothers and fathers have in child rearing. This is similar to what was

found in another study, where mothers with ADHD were reported to have higher levels of conflict with adolescents with ADHD compared to mothers without ADHD (Babinski *et al.*, 2016). One explanation for this is because mothers frequently play a more central role especially with the day to day management of a child (Connell and Goodman, 2002). The results of the study in this thesis also found that mothers were warmer towards their child when fathers have ADHD. This is quite interesting as it indicates that mothers may be more tolerant towards their children, if they have a partner / spouse with ADHD. As discussed in chapter 3, a study by Minde and colleagues also had similar findings suggesting different perspectives of men and women who have a spouse with ADHD (Minde *et al.*, 2003). Men who were married to women with ADHD were found to be more critical and reported more distress compared to women who were married to men with ADHD (Minde *et al.*, 2003). One other important point here is that this finding may be different depending on whether that father is the mother's current or ex-partner. This was not investigated in this thesis but will be interesting to be examined in future studies with a more qualitative design.

A small number of studies investigating parent ADHD and parenting have proposed a 'similarity-fit hypothesis' which suggest that there is less conflict when both the parent and child have high levels of ADHD as they share the same attributes and are therefore more empathic to their child's behaviour (Psychogiou *et al.*, 2007, 2008; Griggs and Mikami, 2011). On the other hand the 'similarity-misfit hypothesis' proposes that a parent and child with ADHD would experience more conflict due to difficulties the parents face when managing both the child's and their own behaviour (Psychogiou *et al.*, 2007, 2008). There is a suggestion that the similarity fit / misfit models might apply

differently for mothers and fathers. (Psychogiou *et al.*, 2007, 2008; Mikami *et al.*, 2010; Babinski *et al.*, 2016). A recent study testing these two hypotheses found evidence for similarity–fit process in fathers and similarity-misfit in mothers with regards to conflict levels between parent and adolescent with ADHD, which is similar to what was found in this thesis (Grimbos and Wiener, 2016). One reason why no associations were found with father ADHD may perhaps be because there were many single parent families in this sample, most of whom were lone mothers, thus there might be insufficient data on fathers and inadequate power to make any conclusion on associations between father psychopathology and family environment. Alternatively, it might be that there are differences in family environment between those families that are intact and those where parents are separated (for example more conflict within families / between parents where the parents split up, in comparison to those who stay together). This study was unable to address such potential differences.

Following on from the findings from chapter 3, the next study (chapter 4) investigated if parent ADHD was associated with child clinical presentation over time using a subset of the previous sample. As mentioned previously, due to the low number of fathers in the sample, this chapter was focused on mother psychopathology (mother ADHD and depression). Although associations were found with mother ADHD cross-sectionally, results in the follow up study did not find an association between mother ADHD and the course of the disorder (within an affected ADHD sample) over time. Parent ADHD can influence offspring phenotype via genes and environmental risk as well as the interaction between genes and environment. The combination of higher genetic susceptibility and exposure to parent ADHD symptoms (e.g. inattention) may both contribute to offspring outcome (Biederman, Faraone and Monuteaux, 2002).

Biederman and colleagues proposed that exposure to parent ADHD may not add additional risk for dysfunction of the offspring reflecting a ceiling effect where the severity of the child's own ADHD cannot be made much worse by effects of exposure to parent ADHD beyond inherited factors (Biederman, Faraone and Monuteaux, 2002). Other more recent studies have suggested that ADHD genetic liability predicts ADHD persistence and that persistent ADHD is more strongly familial (Franke *et al.*, 2012; Pingault *et al.*, 2015; Riglin *et al.*, 2016). Several studies have shown that parent mental health or family history of psychopathology is one of the most important childhood predictors of persistence in ADHD (Lara *et al.*, 2009; Biederman *et al.*, 2011; Roy *et al.*, 2016). In this thesis, there was no strong evidence of association between mother psychopathology and ADHD persistence in children, which was quite surprising. However, a trend in the results does imply that children with a mother with ADHD may show less improvement of ADHD symptoms over time. This study was perhaps underpowered to detect any effects due to a smaller sample in the follow up sample. This also could be due to the over restrictive definition of parent ADHD that was used in this study and that perhaps a wider range of outcomes should be assessed for the child. Additionally the length of time (mean 2.5 years) for which children were followed was possibly not long enough to distinguish individuals who persist and remit. Most of the participants in the follow-up period were still in early adolescence stage. It would be interesting to replicate this study in a much larger sample and for a longer follow up period.

6.2.2 Mother depression

Findings in this thesis suggest that maternal depression is associated with the severity of ADHD over time, specifically with severity of conduct disorder in children with ADHD. Over time, mother depression was found to predict an increase of CD symptoms in young adolescents after adjusting for child baseline symptoms. There are many studies which have documented the link between maternal depression and externalising problems in offspring (Downey and Coyne, 1990; Goodman *et al.*, 2011). Few have investigated this in samples of children with ADHD (Pressman *et al.*, 2006; Chronis *et al.*, 2007; Humphreys, Mehta and Lee, 2012; Segenreich *et al.*, 2014). The results of this study add to this growing body of evidence that in families of children with ADHD, current maternal depression is associated with severity of CD problems in offspring. It is not possible however to draw any conclusions about the mechanisms underlying this association. The mechanisms or pathway by which maternal depression increases risk of psychopathology are complex and still not fully understood. Behavioural genetics studies have suggested that inherited, non-inherited pathways or both, play an important role. For example, some have proposed that it may be environmental influences (e.g. parenting) that mediate the link between maternal depression and conduct disorder in children (Kim-Cohen *et al.*, 2005; Silberg, Maes and Eaves, 2010). In a sample of children with ADHD, Chronis and colleagues found that both parenting and a history of maternal depression appeared to be unique predictors of the development of conduct problems (Chronis *et al.*, 2007). Though findings from this thesis showed association between maternal depression and child conduct symptoms across time, association does not necessarily imply the direction of effects, not least because this study assessed maternal depression only at Time 1. It is difficult

to tell if depression in parents occurred as a result of child ADHD traits or vice versa. Additionally it would have been interesting to investigate if current family environment partially mediated the associations between maternal depression and development of child conduct disorder. Unfortunately because family environment was measured at the same time as parental psychopathology and at only one time point, it was not possible to determine the direction of effects.

6.2.3 Neurocognitive factors – alternative index of severity

Associations between parental psychopathology and offspring neurocognitive variation were only found for parent ADHD and not parent depression. These results suggest that having a parent with ADHD may indicate a more compromised neurocognitive function in the child, which is also an alternative index of severity. Identification of children with ADHD with neurocognitive difficulties can be useful to understand the child's behaviour and difficulties they may have at school. This can help inform treatment interventions, for example interventions can be planned according to child's cognitive strengths and weaknesses (Seidman *et al.*, 1995; Rajendran *et al.*, 2013; Chacko, Kofler and Jarrett, 2014).

The results of the study also suggest that exposure to parent depression may not be relevant to differences in the types of neurocognitive functioning measured in this thesis, in children with ADHD. Studies of children who have a mother with depression (non ADHD samples) have found links between mother depression and impaired neurocognitive functioning in younger children (mean age 6 years SD 0.4) (Hughes *et al.*, 2013) but not in adolescents (mean age 15.6 years SD 2.6) (Klimes-Dougan *et al.*,

2006) which indicate that maternal depression influences may be attenuated as children get older. In samples of children with ADHD, the relationship between parent depression and neurocognitive functioning has only been investigated in one pilot study, which similarly did not find any associations between parental depression and neurocognitive functioning (Park *et al.*, 2014).

6.3 Implications

Findings from this study highlight that it is important for clinicians including referrers such as general practitioners (GPs) to be aware of and consider parent mental health difficulties when assessing children with ADHD, given the high prevalence of ADHD and depression found in parents. The results indicate that children with a parent with ADHD, particularly persistent ADHD, may have more severe symptoms and adverse family environments compared to those without an affected parent. The results also highlight that maternal depression may be an important factor in the development of later conduct disorder. It may therefore be important to screen for ADHD or depression in parents during child ADHD assessment as this could help identify families who may be facing more difficulties and require additional support.

These findings may have further implications for the treatment of children with ADHD, beyond just identifying those at risk of a more severe presentation. The use of parenting programs for children with ADHD has been recommended in the NICE guidelines (NICE, 2008), but there are many difficulties faced with the implementation of parenting programs, one of which is parent mental health difficulties (Kazdin and Wassell, 1999; Reyno and McGrath, 2006). One study recommends that it is important

to provide support for parents' mental health needs in order for them to be able to successfully follow a parenting program (Smith *et al.*, 2015). Knowledge about parent mental health may help inform decisions when implementing treatment or interventions for different families. Perhaps treating parents with mental health problems in parallel to children may be helpful. Recent treatment trials have shown emerging evidence that integrated intervention including treatment of mother depression and mother ADHD is associated with improvements of mother symptoms, parenting and child disruptive behaviour in samples of children with ADHD (Chronis-Tuscano *et al.*, 2013; Jans *et al.*, 2015). However treatment for parents can be difficult as links between children's and adult services are not necessarily good. Even though these treatment studies are still in their early stages, these findings indicate the likely importance of considering parental psychopathology when planning treatment for children with ADHD (Chronis-Tuscano *et al.*, 2013; Jans *et al.*, 2015).

6.4 Strengths of studies within this thesis

The investigations in this thesis utilised a large and well characterised clinical sample of children with ADHD. Detailed information was obtained on clinical symptoms and diagnoses of ADHD and comorbidity as well as information on family characteristics, family environment and neurocognitive constructs. The sample size of the study compares favourably to other clinical ADHD studies. The measures of parent mental health in this study were concurrent to child assessments and also included the investigation of both mother and father ADHD which few studies have done. Indeed many studies put together information from all first degree relatives including mothers, fathers and siblings. Both childhood and current symptoms of parent ADHD

were measured and this enabled the study to examine differences between parents who meet criteria in adulthood and those that only met criteria in childhood. All the measures were well validated measures and the study took into consideration and applied updates of diagnostic changes from DSM-IV to DSM-5. All analyses included adjustment for multiple known confounders (e.g. social class, medication use). A subsample of children from the cross-sectional study was followed up into adolescence and longitudinal data were available which enabled the study to investigate association of parental psychopathology and ADHD persistence and severity of symptoms over time. Although children stopped taking medication for neurocognitive testing, this group was not restricted to a medication naive sample and so is more representative of a clinical ADHD population.

6.5 Limitations

The limitations have been discussed separately in each chapter, but general limitations that apply to the thesis as a whole are discussed here again. Firstly the clinical sample used is predominantly a cross-sectional sample (chapters 3 & 5) and therefore it is difficult to determine the direction of effects from parent to child. A subsample of participants was followed up and results seem to suggest that maternal depression predicts later severity of CD in children (chapter 4). However as mentioned before it is difficult to clarify whether or not maternal depression had occurred as a consequence of ADHD in the child and therefore this influences the child's disorder trajectory. Longitudinal studies measuring parental psychopathology prior to the birth of a child

are needed to further understand this; however it may be difficult to get a clinical representative sample with a similar size and power as this study.

Secondly as there is limited research on the influences of parental psychopathology in children with ADHD, much of this research is exploratory and therefore some associations found may not withstand correction for multiple testing. Furthermore much work has been focused on cross-sectional studies with emphasis on mother psychopathology. Additionally as the study sample had only included children of British Caucasian origin and mostly included the oldest child in the family, findings may not generalise to other ethnic populations or younger children in the family.

Thus, these findings are in need of replication. More longitudinal studies are needed to examine the associations between parental psychopathology and child behaviour throughout the child's development. As the effects of parental psychopathology are likely to transmit to a child through both genetic and environmental mechanisms, it would be interesting to examine these findings in a more genetically sensitive design (Silberg and Eaves, 2004; Silberg, Maes and Eaves, 2012). A number of different research designs like an adoption study design can help disentangle environment from shared genes effects.

In view of the controversy and uncertainty in defining adult ADHD, the diagnostic criteria in DSM-IV were seen to be the most reasonable approach to define adult ADHD at the beginning of this research. Following the release of the DSM-5, adult ADHD in this study was subsequently defined using the DSM-5 symptom criteria (6 symptoms present in childhood and 5 symptoms present in adulthood) and used in chapters 4 and 5. This definition however is not without limitations. The definition of

parent ADHD may have been over restrictive as requirements were to meet full DSM symptom criteria both in childhood and currently. It has been suggested that using a strict DSM symptom threshold can lead to false negatives as the defined symptoms (checklist of DSM symptoms) were developed mainly for school aged children, and are not age appropriate or developmentally sensitive to adults (Sibley *et al.*, 2012). As sample collection was prior to the release of DSM-5, the measures did not include the adult specific symptom description as proposed in the DSM-5. As a result this measure may have missed picking up symptoms that are more relevant in adulthood and rates may have been underestimated. Using the DSM-5 criteria increased the percentage of parents meeting study criteria for ADHD from 29% to 33%. This did not substantially change the overall findings in this thesis, as can be seen when results in chapter 3 were repeated using the DSM-5 criteria (appendix 3.1 to 3.4).

The measure of parent ADHD was based on self-report and retrospective recall of childhood ADHD. There are several concerns raised about the ability of adults to report their own symptoms, particularly childhood symptoms, which may cause inaccuracies and is subject to recall bias (Miller, Newcorn and Halperin, 2010; Moffitt *et al.*, 2015). Evidence shows that adults with ADHD tend to underestimate their symptoms compared to other informant reports (Sibley *et al.*, 2012, 2016). However, others have also demonstrated that adults are able to give a reasonable account of their own childhood and current symptoms (Murphy and Schachar, 2000; Magnusson *et al.*, 2006). Despite concerns of self-report, it can be argued that this method may be more practical and be the only source for those who may not have an alternative informant that is reliable (Sibley *et al.*, 2016). Perhaps future studies investigating ADHD in parent or adults should incorporate prospective measures and include information from

multiple informants, although the former may be practically impossible especially when recruiting an offspring clinical sample. Finally the measure of adult ADHD in this thesis did not unfortunately include a measure of symptom impairment. Including the presence of impairment can help reduce false positive diagnoses and should therefore be considered. Research on how to optimally define ADHD in adults is ongoing and until a standardised approach is agreed upon, the definition of adult ADHD will continue to vary between studies. A review by Sibley and colleagues propose that to minimise misclassification of adult ADHD, future studies should consider incorporating a combination of self and informant ratings, including a measure of impairment and using age appropriate symptom thresholds (Sibley, Mitchell and Becker, 2016)

The measure of parent depression is taken from the HADS which has been previously developed for screening depression (Snaith, 2003), rather than assessing for a diagnosis of depression. Additionally the questions in the HADS relate to how the parent had been feeling in the last week therefore only captures depression at one point in time and does not take into account past history of depression, thus the prevalence here may have been underestimated. A diagnostic interview would perhaps capture a more clinical diagnosis of depression based on diagnostic criteria. However, this thesis aimed to investigate current depression and the HADS has been reported to have good validity and performs well at predicting caseness of depression in psychiatric patients and in the general population (Bjelland *et al.*, 2002). Additionally, when assessing children in clinics, questionnaire measures of parent mental health would be easier and more practical to administer than diagnostic interviews.

Adults with ADHD are often reported to have high rates of comorbidities including anxiety and depression. In this sample, there seemed to be little overlap in ADHD and depression in both mothers and fathers. One reason for this could be because the HADS only measures recent depression rather than lifetime history of depression. In view of this low overlap, I was unable to investigate the influences of comorbid parent ADHD and depression on offspring. As previously mentioned in chapters 1 and 4, although parent anxiety was measured, it was observed that there was considerable overlap between anxiety items in the HADS and ADHD symptoms. Removing these items from HADS checklist would mean that the validated cut-off established would not accurately apply. Moreover there is significant similarity of anxiety and depressive symptoms as anxiety and depression are thought to index the same underlying liability (Kendler *et al.*, 1987; Mathew *et al.*, 2011). The parental anxiety measure was therefore not included in any investigation in this thesis. It would however be interesting to examine this in future studies.

Some studies have also reported that parents of children with ADHD, especially fathers, are commonly reported to have high rates of antisocial personality disorder (Johnston and Mash, 2001; Chronis *et al.*, 2003). The investigation of parental psychopathology in this sample however was limited to parent ADHD and depression. Information on parents' symptoms of conduct disorder in childhood was obtained but this was a retrospective measure and there was unfortunately no measure of current parent antisocial disorder in this study. However this measure was included as a covariate in the regression analysis in chapter 4. Adjusting for parental childhood conduct symptoms did not seem to attenuate effects of maternal depression on offspring conduct symptoms. Additionally there may be other unmeasured

confounders that might be important here, for example learning disability and autism spectrum disorder amongst parents of children with ADHD.

As mentioned previously, this sample consisted of many single parent families most of whom were mother-child dyads. Therefore there was not as much data available on fathers and this limits the power of the study to examine the influence of paternal psychopathology on the presentation and course of ADHD in offspring. It may be that single-parent families are more likely to have fathers with ADHD. The high number of single parent families might also explain the somewhat surprising low rates of assortative mating and families where both parents had ADHD; we can speculate that such families may be less likely to stay together. A survey of how partners respond to their spouses with ADHD reported that 60% of non-ADHD men left their female partners who had ADHD whereas only 10% of non-ADHD women left their male partners with ADHD (Minde *et al.*, 2003) . It can be argued however that including data from single parent families is more representative of clinic families of children with ADHD. Children in single parent families are reported to have a higher frequency of combined type ADHD, comorbid CD and significantly higher ADHD and CD symptom scores than those with intact families (West *et al.*, 2002). In this thesis, sensitivity analyses in chapters 3, 4 and 5 which looked at just complete families found similar results and associations as those found on the whole sample. If information could be obtained from fathers who are not involved in the rearing of the affected child, this would make an interesting study as association with fathers who are not involved in their child's upbringing may indicate the presence of genetic risk rather of shared environment risks.

As the child, self and family assessments were mostly completed by mothers in this sample, shared rater bias may have been present. There are concerns that parents with mental health difficulties especially depression may be biased when reporting on their child's behaviour (Fergusson, Lynskey and Horwood, 1993; Chilcoat and Breslau, 1997). There has been evidence to show that mothers who are depressed or anxious overestimate problems in their children and parents with ADHD may under report symptoms due to being desensitised to child's behaviour (Faraone, Monuteaux, *et al.*, 2003). However, other studies have also demonstrated that parents with mental health difficulties can reliably report on their child's symptoms (Rice *et al.*, 2007; Lewis *et al.*, 2012). Teacher reports on child symptoms were obtained but as 79% of children were on medication for ADHD, it was decided that this measure should not be used, as this may affect the display of ADHD symptoms during school hours. In this sample, children who were on medication had significantly lower symptom severity scores reported by teachers compared to those who were not on medication for ADHD.

6.6 Future directions

Based on findings and limitations addressed in this thesis, there are several suggestions for future studies that could further our understanding of the links between parental psychopathology and the presentation and course of offspring ADHD. Firstly given the general lack of research in this area and inconsistent findings, more studies are needed to further assess these links to build a more robust body of evidence. Even though this study highlights the importance of parent ADHD and

depression, more are needed to replicate these findings. More prospective longitudinal studies are needed to test the association between parent ADHD and severity of ADHD in children over time. This study also suggests that maternal depression is a predictor of worsening conduct symptoms in children with ADHD. Further work is needed to understand the processes that contribute to this link including intervention studies. Several treatment studies of maternal depression have shown that remission of maternal depression is associated with reduction in offspring psychiatric symptoms (Pilowsky *et al.*, 2008; Wickramaratne *et al.*, 2011; Weissman *et al.*, 2015).

Future longitudinal studies are needed in order to address the effect of the duration of parent mental health problems and outcome in children. Measuring parental psychopathology at multiple time points would be helpful here. Unfortunately parental psychopathology in this study was only measured at Time 1 not at Time 2. It would have been interesting to have a parent measure of ADHD at Time 2 to find out if there were parents who desisted in some of their ADHD symptoms. A recently published study on 230 children with and without ADHD (recruited both from schools and child services) who were followed prospectively over 6 years in 2 waves, found that variation in parental ADHD symptoms was a predictor of worsening youth ADHD and ODD symptoms (adjusting for parent depression) and this was mediated by negative parenting (Moroney *et al.*, 2017). The study by Moroney and colleagues (2017) was based on mostly mothers and did not specifically investigate the role of parent depression, however, the findings further highlight the importance of considering

parental ADHD symptoms and family factors when assessing children with ADHD (Moroney *et al.*, 2017). Additionally, measuring parental psychopathology before and after the manifestation of their child's ADHD symptoms may be useful to understand more about the direction of effects. In order to address the issue of shared rater bias and retrospective recall bias, perhaps obtaining information from more informants could be implemented in future research. In this thesis, I was able to examine neurocognitive functioning that would be free of such biases. It would be interesting to incorporate this into a longitudinal study.

Future research should consider investigating the potential differences between the effect of parental psychopathology on boys and girls. There are some studies which have documented gender differences in exposure to parental psychopathology; for example girls may be more sensitive or vulnerable to effect of maternal depression compared to boys (Cortes *et al.*, 2006; Lewis *et al.*, 2011). Given that there may be differences in the effects of maternal and paternal psychopathology, it might be interesting to investigate the gender effects in transmission between parent and child psychopathology within an ADHD sample. Furthermore, as ADHD is also highly comorbid with anxiety and depression, it would be worth investigating how parental psychopathology contributes to the development of these other comorbidities in offspring as well. Additionally, it might be important to examine how parental psychopathology may contribute to functioning in other children within the family (e.g. siblings), in order to increase understanding of the effect of parental psychopathology in a broader family perspective.

6.7 Conclusions

Overall, these findings extend the understanding of the link between parental psychopathology and phenotype variation in children with ADHD. They indicate that children with more severe clinical presentations and greater pre-frontal cognitive impairments are more likely to have a parent with mental health difficulties, specifically ADHD or depression. Further work is needed to understand the processes that contribute to this association, given the global impairment in functioning associated with ADHD. Understanding the influence of parental psychopathology has important clinical relevance; if having a parent with ADHD / depression indexes a more severe child clinical presentation, regardless of whether these links are inherited and / or environmental, then it may be important to assess parental psychopathology during clinical assessment. This will have significant implications when considering treatment and intervention strategies and planning the intensity of child follow-up.

References

- Abikoff, H. B. *et al.* (2002) 'Observed classroom behavior of children with ADHD: relationship to gender and comorbidity.', *Journal of Abnormal Child Psychology*, 30(4), pp. 349–59.
- Adler, L., Spencer, T. J. and Wilens, T. E. (2015) *Attention-Deficit Hyperactivity Disorder in Adults and Children*.
- Agha, S. S. *et al.* (2013) 'Are parental ADHD problems associated with a more severe clinical presentation and greater family adversity in children with ADHD?', *European Child & Adolescent Psychiatry*, 22(6), pp. 369–377. doi: 10.1007/s00787-013-0378-x.
- Agha, S. S. *et al.* (2016) 'Maternal psychopathology and offspring clinical outcome: a four-year follow-up of boys with ADHD', *European Child and Adolescent Psychiatry*, pp. 1–10. doi: 10.1007/s00787-016-0873-y.
- Agnew-Blais, J. C. *et al.* (2016) 'Evaluation of the Persistence, Remission, and Emergence of Attention-Deficit/Hyperactivity Disorder in Young Adulthood.', *JAMA Psychiatry*, 73(7), pp. 713–20. doi: 10.1001/jamapsychiatry.2016.0465.
- Allison, P. D. (1990) 'Change scores as dependent variables in regression analysis.', in *In C. C. Clogg (Ed.), Sociological Methodology (Pp. 93-114)*. Oxford, UK: Basil Blackwell.
- Almeida Montes, L. G., Hernandez Garcia, A. O. and Ricardo-Garcell, J. (2007) 'ADHD Prevalence in Adult Outpatients With Nonpsychotic Psychiatric Illnesses', *Journal of Attention Disorders*. Sage PublicationsSage CA: Los Angeles, CA, 11(2), pp. 150–156. doi: 10.1177/1087054707304428.
- American Psychiatric Association (2000) *Diagnostic and Statistical Manual of Mental Disorders*. Washington, DC: American Psychiatric Association.
- American Psychiatric Association (2013) *Diagnostic and Statistical Manual of Mental Disorders: DSM-5TM (5th Ed.)*, *Diagnostic and Statistical Manual of Mental Disorders: DSM-5TM (5th Ed.)*.
- Anastopoulos, A. D. *et al.* (1992) 'Parenting stress among families of children with attention deficit hyperactivity disorder.', *Journal of Abnormal Child Psychology*, 20(5), pp. 503–20.
- Angold, A. *et al.* (1995) 'The Child and Adolescent Psychiatric Assessment (CAPA)', *Psychological Medicine*, 25(4), pp. 739–753.
- Angold, A. *et al.* (2012) 'Psychiatric diagnostic interviews for children and adolescents: a comparative study.', *Journal of the American Academy of Child and Adolescent Psychiatry*, 51(5),

pp. 506–17. doi: 10.1016/j.jaac.2012.02.020.

Angold, A. and Costello, E. J. (1995) 'A test-retest reliability study of child-reported psychiatric symptoms and diagnoses using the Child and Adolescent Psychiatric Assessment (CAPA-C)', *Psychological Medicine*, 25(4), pp. 755–762.

Angold, A. and Costello, E. J. (2000) 'The Child and Adolescent Psychiatric Assessment (CAPA)', *Journal of the American Academy of Child and Adolescent Psychiatry*, 39(1), pp. 39–48.

Angold, A., Psych, M. R. C. and Costello, E. J. (1993) 'Depressive Comorbidity in Children and Adolescents: Empirical, Theoretical, and Methodological Issues', *American Journal of Psychiatry*, 50(2).

Arnold, L. E. and DiSilvestro, R. A. (2005) 'Zinc in Attention-Deficit/Hyperactivity Disorder', *Journal of Child and Adolescent Psychopharmacology*. Mary Ann Liebert, Inc. 2 Madison Avenue Larchmont, NY 10538 USA , 15(4), pp. 619–627. doi: 10.1089/cap.2005.15.619.

Asarnow, R. F. *et al.* (2002) 'Neurocognitive functioning and schizophrenia spectrum disorders can be independent expressions of familial liability for schizophrenia in community control children: The UCLA family study', in *Schizophrenia Research*, pp. 111–120. doi: 10.1016/S0920-9964(01)00358-9.

Asherson, P. *et al.* (2007) 'Adult attention-deficit hyperactivity disorder: recognition and treatment in general adult psychiatry', *British Journal of Psychiatry*. 2007/01/02, 190, pp. 4–5. doi: 190/1/4 [pii]10.1192/bjp.bp.106.026484.

Asherson, P. *et al.* (2016) 'Adult attention-deficit hyperactivity disorder: key conceptual issues', *The Lancet Psychiatry*, 3(6), pp. 568–578. doi: 10.1016/S2215-0366(16)30032-3.

August, G. J. and Garfinkel, B. D. (1990) 'Comorbidity of ADHD and reading disability among clinic-referred children.', *Journal of Abnormal Child Psychology*, 18(1), pp. 29–45.

Babinski, D. E. *et al.* (2016) 'Maternal ADHD, Parenting, and Psychopathology Among Mothers of Adolescents With ADHD', *Journal of Attention Disorders*. SAGE PublicationsSage CA: Los Angeles, CA, 20(5), pp. 458–468. doi: 10.1177/1087054712461688.

Babinski, D. E., Waxmonsky, J. G. and Pelham, W. E. (2014) 'Treating Parents with Attention-Deficit/Hyperactivity Disorder: The Effects of Behavioral Parent Training and Acute Stimulant Medication Treatment on Parent–Child Interactions', *Journal of Abnormal Child Psychology*. Springer US, 42(7), pp. 1129–1140. doi: 10.1007/s10802-014-9864-y.

Baddeley, A. (2003) 'Working memory: looking back and looking forward', *Nature Reviews Neuroscience*. Nature Publishing Group, 4(10), pp. 829–839. doi: 10.1038/nrn1201.

Banks, T. *et al.* (2008) 'Parenting behavior and cognitions in a community sample of mothers with and without symptoms of attention-deficit/hyperactivity disorder', *Journal of Child and Family Studies*, 17(1), pp. 28–43.

Barkley, R. *et al.* (2006) 'Young adult outcome of hyperactive children: adaptive functioning in major life events', *Journal of the American Academy of Child & Adolescent Psychiatry*, 45(2), pp. 167–179.

Barkley, R. A. *et al.* (1991) 'The adolescent outcome of hyperactive children diagnosed by research criteria--III. Mother-child interactions, family conflicts and maternal psychopathology', *J Child Psychol Psychiatry*, 32(2), pp. 233–255.

Barkley, R. A. (1997) 'Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD', *Psychological Bulletin*, 121(1), pp. 65–94.

Barkley, R. A. *et al.* (2002) 'The persistence of attention-deficit/hyperactivity disorder into young adulthood as a function of reporting source and definition of disorder', *Journal of Abnormal Psychology*, 111(2), pp. 279–289.

Barkley, R. A. (2012) 'Distinguishing sluggish cognitive tempo from attention-deficit/hyperactivity disorder in adults.', *Journal of Abnormal Psychology*. American Psychological Association, 121(4), pp. 978–990. doi: 10.1037/a0023961.

Barkley, R. A. and Murphy, K. R. (1998) *Attention-Deficit Hyperactivity Disorder: A Handbook for Diagnosis and Treatment*. 2nd edn. New York: The Guildford Press.

Beardslee, W. R. *et al.* (1993) 'The impact of parental affective disorder on depression in offspring: a longitudinal follow-up in a nonreferred sample', *Journal of the American Academy of Child & Adolescent Psychiatry*, 32(4), pp. 723–730.

Beardslee, W. R. *et al.* (1996) 'Prediction of Adolescent Affective Disorder: Effects of Prior Parental Affective Disorders and Child Psychopathology', *Journal of the American Academy of Child & Adolescent Psychiatry*, 35(3), pp. 279–288. doi: 10.1097/00004583-199603000-00008.

Bhutta, A. T. *et al.* (2002) 'Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis', *Journal of the American Medical Association*, 288(6), pp. 728–737.

Biederman, J. *et al.* (1987) 'High rate of affective disorders in probands with attention deficit disorder and in their relatives: A controlled family study', *American Journal of Psychiatry*, 144(3), pp. 330–333.

Biederman, J. *et al.* (1991) 'Evidence of familial association between attention deficit disorder

and major affective disorders', *Archives of General Psychiatry*, 48(7), pp. 633–642.

Biederman, J. *et al.* (1992) 'Further evidence for family-genetic risk factors in attention deficit hyperactivity disorder. Patterns of comorbidity in probands and relatives psychiatrically and pediatrically referred samples.', *Archives of General Psychiatry*, 49(9), pp. 728–738. doi: 10.1001/archpsyc.1992.01820090056010.

Biederman, J., Milberger, S., *et al.* (1995) 'Family-environment risk factors for attention-deficit hyperactivity disorder. A test of Rutter's indicators of adversity', *Archives of General Psychiatry*, 52(6), pp. 464–470.

Biederman, J., Faraone, S. V, *et al.* (1995) 'High risk for attention deficit hyperactivity disorder among children of parents with childhood onset of the disorder: a pilot study', *American Journal of Psychiatry*, 152(3), pp. 431–435. doi: 10.1176/ajp.152.3.431.

Biederman, J. *et al.* (1996) 'Predictors of persistence and remission of ADHD into adolescence: results from a four-year prospective follow-up study.', *Journal of the American Academy of Child and Adolescent Psychiatry*, 35(3), pp. 343–51. doi: 10.1097/00004583-199603000-00016.

Biederman, J. *et al.* (2002) 'Influence of Gender on Attention Deficit Hyperactivity Disorder in Children Referred to a Psychiatric Clinic', *American Journal of Psychiatry*. American Psychiatric Publishing, 159(1), pp. 36–42. doi: 10.1176/appi.ajp.159.1.36.

Biederman, J. *et al.* (2004) 'Impact of Executive Function Deficits and Attention-Deficit/Hyperactivity Disorder (ADHD) on Academic Outcomes in Children.', *Journal of Consulting and Clinical Psychology*, 72(5), pp. 757–766. doi: 10.1037/0022-006X.72.5.757.

Biederman, J., Petty, C. R., *et al.* (2008) 'Educational and occupational underattainment in adults with attention-deficit/hyperactivity disorder: a controlled study.', *The Journal of Clinical Psychiatry*, 69(8), pp. 1217–22.

Biederman, J., Ball, S. W., *et al.* (2008) 'New insights into the comorbidity between ADHD and major depression in adolescent and young adult females.', *Journal of the American Academy of Child and Adolescent Psychiatry*, 47(4), pp. 426–34. doi: 10.1097/CHI.0b013e31816429d3.

Biederman, J. *et al.* (2010) 'How persistent is ADHD? A controlled 10-year follow-up study of boys with ADHD', *Psychiatry Research*, 177(3), pp. 299–304. doi: 10.1016/j.psychres.2009.12.010.

Biederman, J. *et al.* (2011) 'Predictors of persistent ADHD: an 11-year follow-up study.', *Journal of Psychiatric Research*, 45(2), pp. 150–5. doi: 10.1016/j.jpsychires.2010.06.009.

Biederman, J., Faraone, S. V. and Monuteaux, M. C. (2002) 'Differential Effect of Environmental

Adversity by Gender: Rutter's Index of Adversity in a Group of Boys and Girls With and Without ADHD', *American Journal of Psychiatry*. American Psychiatric Publishing, 159(9), pp. 1556–1562. doi: 10.1176/appi.ajp.159.9.1556.

Biederman, J., Faraone, S. V and Monuteaux, M. C. (2002) 'Impact of exposure to parental attention-deficit hyperactivity disorder on clinical features and dysfunction in the offspring', *Psychological Medicine*. 2002/08/13, 32(5), pp. 817–827.

Bjelland, I. *et al.* (2002) 'The validity of the Hospital Anxiety and Depression Scale. An updated literature review', *Journal of Psychosomatic Research*, 52(2), pp. 69–77.

Blackman, G. L., Ostrander, R. and Herman, K. C. (2005) 'Children with ADHD and depression: a multisource, multimethod assessment of clinical, social, and academic functioning.', *Journal of Attention Disorders*, 8(4), pp. 195–207. doi: 10.1177/1087054705278777.

Bornoalova, M. A. *et al.* (2010) 'Familial transmission and heritability of childhood disruptive disorders.', *The American Journal of Psychiatry*, 167(9), pp. 1066–74. doi: 10.1176/appi.ajp.2010.09091272.

Bouchard, M. F. *et al.* (2010) 'Attention-deficit/hyperactivity disorder and urinary metabolites of organophosphate pesticides.', *Pediatrics*. NIH Public Access, 125(6), pp. e1270-7. doi: 10.1542/peds.2009-3058.

Breaux, R. P., Brown, H. R. and Harvey, E. A. (2017) 'Mediators and Moderators of the Relation between Parental ADHD Symptomatology and the Early Development of Child ADHD and ODD Symptoms', *Journal of Abnormal Child Psychology*, 45(3), pp. 443–456. doi: 10.1007/s10802-016-0213-1.

Brown, R. T. and Pacini, J. N. (1989) 'Perceived Family Functioning, Marital Status, and Depression in Parents of Boys with Attention Deficit Disorder', *Journal of Learning Disabilities*, 22(9), pp. 581–587. doi: 10.1177/002221948902200911.

Burt, S. A. *et al.* (2003) 'Parent-child conflict and the comorbidity among childhood externalizing disorders', *Archives of General Psychiatry*, 60(5), pp. 505–513.

Button, K. S. *et al.* (2013) 'Power failure: why small sample size undermines the reliability of neuroscience', *Nature Reviews Neuroscience*. Nature Publishing Group, 14(5), pp. 365–376. doi: 10.1038/nrn3475.

Cambridge Cognition (1996) 'Cambridge neuropsychological test automated battery (CANTAB). CeNeS Limited, Cambridge'.

Cartwright, K. L. *et al.* (2011) 'Disentangling child and family influences on maternal expressed

emotion toward children with attention-deficit/hyperactivity disorder', *Journal of the American Academy of Child & Adolescent Psychiatry*, 50(10), pp. 1042–1053. doi: 10.1016/j.jaac.2011.07.006.

Caye, A. *et al.* (2016) 'Attention-Deficit/Hyperactivity Disorder Trajectories From Childhood to Young Adulthood', *JAMA Psychiatry*, 73(7), p. 705. doi: 10.1001/jamapsychiatry.2016.0383.

Chacko, A., Kofler, M. and Jarrett, M. (2014) 'Improving outcomes for youth with ADHD: a conceptual framework for combined neurocognitive and skill-based treatment approaches.', *Clinical Child and Family Psychology Review*. NIH Public Access, 17(4), pp. 368–84. doi: 10.1007/s10567-014-0171-5.

Chazan, R. *et al.* (2011) 'Do Phenotypic Characteristics, Parental Psychopathology, Family Functioning, and Environmental Stressors Have a Role in the Response to Methylphenidate in Children With Attention-Deficit/Hyperactivity Disorder?', *Journal of Clinical Psychopharmacology*, 31(3), pp. 309–317. doi: 10.1097/JCP.0b013e318217b4df.

Chilcoat, H. D. and Breslau, N. (1997) 'Does Psychiatric History Bias Mothers' Reports? An Application of a New Analytic Approach', *Journal of the American Academy of Child & Adolescent Psychiatry*, 36(7), pp. 971–979. doi: 10.1097/00004583-199707000-00020.

Chorozoglou, M. *et al.* (2015) 'Preschool hyperactivity is associated with long-term economic burden: Evidence from a longitudinal health economic analysis of costs incurred across childhood, adolescence and young adulthood', *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 56(9), pp. 966–975. doi: 10.1111/jcpp.12437.

Chronis-Tuscano, A. *et al.* (2011) 'The relation between maternal ADHD symptoms & improvement in child behavior following brief behavioral parent training is mediated by change in negative parenting', *Journal of Abnormal Child Psychology*, 39(7), pp. 1047–1057. doi: 10.1007/s10802-011-9518-2.

Chronis-Tuscano, A. *et al.* (2013) 'Development and preliminary evaluation of an integrated treatment targeting parenting and depressive symptoms in mothers of children with attention-deficit/hyperactivity disorder', *Journal of Consulting and Clinical Psychology*, 81(5), pp. 918–925. doi: 10.1037/a0032112.

Chronis, A. M. *et al.* (2003) 'Psychopathology and substance abuse in parents of young children with attention-deficit/hyperactivity disorder', *Journal of the American Academy of Child and Adolescent Psychiatry*. 2003/11/25, 42(12), pp. 1424–1432. doi: 10.1097/00004583-200312000-00009S0890-8567(09)62125-0 [pii].

Chronis, A. M. *et al.* (2007) 'Maternal depression and early positive parenting predict future conduct problems in young children with attention-deficit/hyperactivity disorder', *Developmental Psychology*, 43(1), pp. 70–82. doi: 10.1037/0012-1649.43.1.70.

Clark, D. B. *et al.* (2004) 'Psychopathology risk transmission in children of parents with substance use disorders.', *The American Journal of Psychiatry*, 161(4), pp. 685–91.

Cloninger, C. R. *et al.* (1978) 'Implications of sex differences in the prevalences of antisocial personality, alcoholism, and criminality for familial transmission', *Archives of General Psychiatry*. 1978/08/01, 35(8), pp. 941–951.

Coghill, D. and Seth, S. (2011) 'Do the diagnostic criteria for ADHD need to change? Comments on the preliminary proposals of the DSM-5 ADHD and Disruptive Behavior Disorders Committee', *European Child & Adolescent Psychiatry*, 20(2), pp. 75–81. doi: 10.1007/s00787-010-0142-4.

Cogill, S. R. *et al.* (1986) 'Impact of maternal postnatal depression on cognitive development of young children.', *British Medical Journal (Clinical Research Ed.)*, 292(6529), pp. 1165–7. doi: <http://dx.doi.org/10.1136/bmj.292.6529.1165>.

Collishaw, S. (2015) 'Annual Research Review: Secular trends in child and adolescent mental health', *Journal of Child Psychology and Psychiatry*, 56(3), pp. 370–393. doi: 10.1111/jcpp.12372.

Connell, A. M. and Goodman, S. H. (2002) 'The association between psychopathology in fathers versus mothers and children's internalizing and externalizing behavior problems: a meta-analysis', *Psychological Bulletin*. 2002/09/11, 128(5), pp. 746–773.

Conners, C. K. *et al.* (1998) 'Revision and restandardization of the Conners Teacher Rating Scale (CTRS-R): factor structure, reliability, and criterion validity', *Journal of Abnormal Child Psychology*, 26(4), pp. 279–291.

Cortes, R. C. *et al.* (2006) 'Gender Differences in the Association between Maternal Depressed Mood and Child Depressive Phenomena from Grade 3 through Grade 10', *Journal of Youth and Adolescence*, 35(5), pp. 810–821. doi: 10.1007/s10964-006-9083-0.

Cortese, S. *et al.* (2015) 'Cognitive Training for Attention-Deficit/Hyperactivity Disorder: Meta-Analysis of Clinical and Neuropsychological Outcomes From Randomized Controlled Trials', *Journal of the American Academy of Child & Adolescent Psychiatry*, 54(3), pp. 164–174. doi: 10.1016/j.jaac.2014.12.010.

Crosbie, J. and Schachar, R. (2001) 'Deficient Inhibition as a Marker for Familial ADHD', *American Journal of Psychiatry*, 158(11), pp. 1884–1890. doi: 10.1176/appi.ajp.158.11.1884.

Cross-Disorder Group of the Psychiatric Genomics Consortium (2013) 'Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis.', *Lancet*, 381(9875), pp. 1371–9. doi: 10.1016/S0140-6736(12)62129-1.

- Curko Kera, E. a *et al.* (2004) 'Self-report and objective measures of ADHD-related behaviors in parents of preschool children at risk for ADHD.', *CNS Spectrums*, 9(9), pp. 639–47.
- D'Amico, F. *et al.* (2014) 'Use of services and associated costs for young adults with childhood hyperactivity/conduct problems: 20-year follow-up.', *The British Journal of Psychiatry : The Journal of Mental Science*, 204(6), pp. 441–7. doi: 10.1192/bjp.bp.113.131367.
- Dalsgaard, S. (2013) 'Attention-deficit/hyperactivity disorder (ADHD)', *European Child & Adolescent Psychiatry*, 22(S1), pp. 43–48. doi: 10.1007/s00787-012-0360-z.
- Dalsgaard, S. *et al.* (2015) 'Mortality in children, adolescents, and adults with attention deficit hyperactivity disorder: a nationwide cohort study', *The Lancet*, 385(9983), pp. 2190–2196. doi: 10.1016/S0140-6736(14)61684-6.
- Danforth, J. S. *et al.* (1991) 'Observations of parent-child interactions with hyperactive children: Research and clinical implications', *Clinical Psychology Review*, 11(6), pp. 703–727. doi: 10.1016/0272-7358(91)90127-G.
- Deault, L. C. (2010) 'A systematic review of parenting in relation to the development of comorbidities and functional impairments in children with attention-deficit/hyperactivity disorder (ADHD).', *Child Psychiatry and Human Development*, 41(2), pp. 168–92. doi: 10.1007/s10578-009-0159-4.
- DeVito, E. E. *et al.* (2008) 'The Effects of Methylphenidate on Decision Making in Attention-Deficit/Hyperactivity Disorder', *Biological Psychiatry*, 64(7), pp. 636–639. doi: 10.1016/j.biopsych.2008.04.017.
- Diamond, A. (2013) 'Executive functions.', *Annual Review of Psychology*, 64, pp. 135–68. doi: 10.1146/annurev-psych-113011-143750.
- Downes, J. J. *et al.* (1989) 'Impaired extra-dimensional shift performance in medicated and unmedicated Parkinson's disease: evidence for a specific attentional dysfunction.', *Neuropsychologia*, 27(11–12), pp. 1329–43.
- Downey, G. and Coyne, J. C. (1990) 'Children of depressed parents: an integrative review', *Psychological Bulletin*, 108(1), pp. 50–76.
- Doyle, A. E., Willcutt, E. G., *et al.* (2005) 'Attention-deficit/hyperactivity disorder endophenotypes', *Biological Psychiatry*, 57(11), pp. 1324–1335.
- Doyle, A. E., Biederman, J., *et al.* (2005) 'Neuropsychological functioning in relatives of girls with and without ADHD.', *Psychological Medicine*, 35(8), pp. 1121–32.

- Doyle, A. E. (2006) 'Executive functions in attention-deficit/hyperactivity disorder', *The Journal of Clinical Psychiatry*, 67 Suppl 8, pp. 21–26.
- DuPaul, G. (1981) 'Parent and teacher ratings of ADHD symptoms: Psychometric properties in a community based sample', *Journal of Clinical Child Psychology*, 20, pp. 245–253.
- DuPaul, G. J., McGoey, K. E., *et al.* (2001) 'Preschool children with attention-deficit/hyperactivity disorder: impairments in behavioral, social, and school functioning.', *Journal of the American Academy of Child and Adolescent Psychiatry*. Sopris West, Longmont, CO, 40(5), pp. 508–15. doi: 10.1097/00004583-200105000-00009.
- DuPaul, G. J., Schaughency, E. A., *et al.* (2001) 'Self-Report of ADHD Symptoms in University Students: Cross-Gender and Cross-National Prevalence', *Journal of Learning Disabilities*, 34(4), pp. 370–379. doi: 10.1177/002221940103400412.
- DuPaul, G. and Stoner, G. (2014) *ADHD in the Schools: Assessment and Intervention Strategies*.
- Edelbrock, C. *et al.* (1985) 'Age differences in the reliability of the psychiatric interview of the child.', *Child Development*, 56(1), pp. 265–75.
- Epstein, J. N. *et al.* (2000) 'Familial aggregation of ADHD characteristics.', *Journal of Abnormal Child Psychology*, 28(6), pp. 585–94.
- Epstein, J. N. and Loren, R. E. (2013) 'Changes in the definition of ADHD in DSM-5: subtle but important', *Neuropsychiatry*, 3(5), pp. 455–458. doi: 10.2217/npj.13.59.
- Eubig, P. A., Aguiar, A. and Schantz, S. L. (2010) 'Lead and PCBs as Risk Factors for Attention Deficit/Hyperactivity Disorder', *Environmental Health Perspectives*, 118(12), pp. 1654–1667. doi: 10.1289/ehp.0901852.
- Eyre, O. *et al.* (2017) 'Irritability in ADHD: Associations with depression liability', *Journal of Affective Disorders*, 215, pp. 281–287. doi: 10.1016/j.jad.2017.03.050.
- Faraone, S. V *et al.* (1995) 'Genetic heterogeneity in attention-deficit hyperactivity disorder (ADHD): gender, psychiatric comorbidity, and maternal ADHD', *Journal of Abnormal Psychology*. 1995/05/01, 104(2), pp. 334–345.
- Faraone, S. V *et al.* (1997) 'Attention deficit disorder and conduct disorder: longitudinal evidence for a familial subtype', *Psychological Medicine*. 1997/03/01, 27(2), pp. 291–300.
- Faraone, S. V, Monuteaux, M. C., *et al.* (2003) 'Does parental ADHD bias maternal reports of ADHD symptoms in children?', *Journal of Consulting and Clinical Psychology*, 71(1), pp. 168–75.

Faraone, S. V, Sergeant, J., *et al.* (2003) 'The worldwide prevalence of ADHD: is it an American condition?', *World Psychiatry*, 2(2), pp. 104–113.

Faraone, S. V *et al.* (2005) 'Molecular genetics of attention-deficit/hyperactivity disorder', *Biological Psychiatry*, 57(11), pp. 1313–1323.

Faraone, S. V. *et al.* (2016) 'Can Attention-Deficit/Hyperactivity Disorder Onset Occur in Adulthood?', *JAMA Psychiatry*. American Medical Association, 73(7), p. 655. doi: 10.1001/jamapsychiatry.2016.0400.

Faraone, S. V and Biederman, J. (1997) 'Do attention deficit hyperactivity disorder and major depression share familial risk factors?', *The Journal of Nervous and Mental Disease*. 1997/10/06, 185(9), pp. 533–541.

Faraone, S. V and Biederman, J. (2005) 'What is the prevalence of adult ADHD? Results of a population screen of 966 adults.', *Journal of Attention Disorders*, 9(2), pp. 384–91. doi: 10.1177/1087054705281478.

Faraone, S. V, Biederman, J. and Monuteaux, M. C. (2000a) 'Attention-deficit disorder and conduct disorder in girls: evidence for a familial subtype', *Biological Psychiatry*, 48(1), pp. 21–29.

Faraone, S. V, Biederman, J. and Monuteaux, M. C. (2000b) 'Toward guidelines for pedigree selection in genetic studies of attention deficit hyperactivity disorder', *Genetic Epidemiology*, 18(1), pp. 1–16.

Fayyad, J. *et al.* (2007) 'Cross-national prevalence and correlates of adult attention-deficit hyperactivity disorder', *The British Journal of Psychiatry*, 190(5).

Fedele, D. A. *et al.* (2012) 'Sex Differences in the Manifestation of ADHD in Emerging Adults', *Special Section: Gender Issues in ADHD Journal of Attention Disorders*. *J. of Att. Dis*, 16(162), pp. 109–117. doi: 10.1177/1087054710374596.

Fergusson, D. M., Lynskey, M. T. and Horwood, L. J. (1993) 'The effect of maternal depression on maternal ratings of child behavior', *Journal of Abnormal Child Psychology*. Kluwer Academic Publishers-Plenum Publishers, 21(3), pp. 245–269. doi: 10.1007/BF00917534.

Ford, T. *et al.* (2008) 'Five Years On: Public Sector Service Use Related to Mental Health in Young People with ADHD or Hyperkinetic Disorder Five Years After Diagnosis', *Child and Adolescent Mental Health*, 13(3), pp. 122–129.

Ford, T., Goodman, R. and Meltzer, H. (2003) 'The British Child and Adolescent Mental Health Survey 1999: the prevalence of DSM-IV disorders.', *Journal of the American Academy of Child &*

Adolescent Psychiatry, 42(10), pp. 1203–1211.

Franke, B. *et al.* (2012) 'The genetics of attention deficit/hyperactivity disorder in adults, a review', *Molecular Psychiatry*, 17(10), pp. 960–987. doi: 10.1038/mp.2011.138.

Franke, B., Neale, B. M. and Faraone, S. V (2009) 'Genome-wide association studies in ADHD', *Human Genetics*, 126(1), pp. 13–50.

Gadeyne, E., Ghesquière, P. and Onghena, P. (2004) 'Longitudinal relations between parenting and child adjustment in young children', *Journal of Clinical Child & Adolescent Psychology*, 33(2), pp. 347–358.

Gamble, S. A. *et al.* (2013) 'Self-Esteem Reactivity Among Mothers of Children with Attention-Deficit/Hyperactivity Disorder: The Moderating Role of Depression History.', *Cognitive Therapy and Research*, 37(6), pp. 1233–1242. doi: 10.1007/s10608-013-9562-z.

Garon, N., Moore, C. and Waschbusch, D. a (2006) 'Decision making in children with ADHD only, ADHD-anxious/depressed, and control children using a child version of the Iowa Gambling Task.', *Journal of Attention Disorders*, 9(4), pp. 607–619. doi: 10.1177/1087054705284501.

Gau, S. S. F. and Shang, C. Y. (2010) 'Executive functions as endophenotypes in ADHD: Evidence from the Cambridge Neuropsychological Test Battery (CANTAB)', *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 51(7), pp. 838–849. doi: 10.1111/j.1469-7610.2010.02215.x.

Gaub, M. and Carlson, C. L. (1997) 'Gender differences in ADHD: a meta-analysis and critical review', *Journal of the American Academy of Child & Adolescent Psychiatry*. 1997/08/01, 36(8), pp. 1036–1045. doi: S0890-8567(09)62612-5 [pii] 10.1097/00004583-199708000-00011.

Gerdes, A. C. *et al.* (2007) 'Maternal Depressive Symptomatology and Parenting Behavior: Exploration of Possible Mediators', *Journal of Abnormal Child Psychology*. Springer US, 35(5), pp. 705–714. doi: 10.1007/s10802-007-9134-3.

Gershon, J. (2002) 'A Meta-Analytic Review of Gender Differences in ADHD', *Journal of Attention Disorder*, 5(3), pp. 143–154.

Getahun, D. *et al.* (2013) 'Recent Trends in Childhood Attention-Deficit/Hyperactivity Disorder', *JAMA Pediatrics*. American Medical Association, 167(3), p. 282. doi: 10.1001/2013.jamapediatrics.401.

Gillberg, C. *et al.* (2004) 'Co-existing disorders in ADHD -- implications for diagnosis and intervention', *European Child & Adolescent Psychiatry*. 2004/08/24, 13 Suppl 1, pp. 180-92. doi: 10.1007/s00787-004-1008-4.

Glover, V. (2011) 'Annual Research Review: Prenatal stress and the origins of psychopathology: an evolutionary perspective', *Journal of Child Psychology and Psychiatry*, 52(4), pp. 356–367. doi: 10.1111/j.1469-7610.2011.02371.x.

Goldstein, S. and Schwebach, A. J. (2004) 'The comorbidity of Pervasive Developmental Disorder and Attention Deficit Hyperactivity Disorder: results of a retrospective chart review', *Journal of Autism and Developmental Disorders*, 34(3), pp. 329–339.

Goodman, R. *et al.* (2000) 'The Development and Well-Being Assessment: description and initial validation of an integrated assessment of child and adolescent psychopathology', *J Child Psychol Psychiatry*, 41(5), pp. 645–655.

Goodman, S. H. *et al.* (2011) 'Maternal Depression and Child Psychopathology: A Meta-Analytic Review', *Clinical Child and Family Psychology Review*, pp. 1–27. doi: 10.1007/s10567-010-0080-1.

Goodman, S. H. and Gotlib, I. H. (1999) 'Risk for psychopathology in the children of depressed mothers: a developmental model for understanding mechanisms of transmission', *Psychological Review*, 106(3), pp. 458–490.

Goos, L. M. *et al.* (2009) 'Validation and Extension of the Endophenotype Model in ADHD Patterns of Inheritance in a Family Study of Inhibitory Control', *American Journal of Psychiatry*, 166(6), pp. 711–717. doi: 10.1176/appi.ajp.2009.08040621.

Goos, L. M., Ezzatian, P. and Schachar, R. (2007) 'Parent-of-origin effects in attention-deficit hyperactivity disorder', *Psychiatry Research*. 2006/11/30, 149(1–3), pp. 1–9. doi: S0165-1781(06)00222-8 [pii]10.1016/j.psychres.2006.08.006.

van Goozen, S. H. M. *et al.* (2016) 'Identifying mechanisms that underlie links between COMT genotype and aggression in male adolescents with ADHD', *Journal of Child Psychology and Psychiatry*, 57(4), pp. 472–480. doi: 10.1111/jcpp.12464.

Gordon, M. *et al.* (2006) 'Symptoms Versus Impairment: The Case for Respecting DSM-IV's Criterion D', *Journal of Attention Disorders*, 9(3), pp. 465–475. doi: 10.1177/1087054705283881.

Gottesman II and Gould, T. D. (2003) 'The endophenotype concept in psychiatry: etymology and strategic intentions', *American Journal of Psychiatry*, 160(4), pp. 636–645.

Griggs, M. S. and Mikami, A. Y. (2011) 'The Role of Maternal and Child ADHD Symptoms in Shaping Interpersonal Relationships', *Journal of Abnormal Child Psychology*, 39(3), pp. 437–449. doi: 10.1007/s10802-010-9464-4.

Grimbos, T. and Wiener, J. (2016) 'Testing the Similarity Fit/Misfit Hypothesis in Adolescents and Parents With ADHD', *Journal of Attention Disorders*. SAGE PublicationsSage CA: Los Angeles, CA. doi: 10.1177/1087054715622014.

Groen-Blokhuis, M. M. *et al.* (2011) 'Evidence for a Causal Association of Low Birth Weight and Attention Problems', *Journal of the American Academy of Child & Adolescent Psychiatry*, 50(12), p. 1247–1254.e2. doi: 10.1016/j.jaac.2011.09.007.

Groen, Y. *et al.* (2013) 'Risky Behavior in Gambling Tasks in Individuals with ADHD - A Systematic Literature Review', *PLoS ONE*, 8(9). doi: 10.1371/journal.pone.0074909.

Gualtieri, C. T. and Johnson, L. G. (2005) 'ADHD: Is Objective Diagnosis Possible?', *Psychiatry (Edgmont (Pa. : Township))*. Matrix Medical Communications, 2(11), pp. 44–53.

Halperin, J. M. *et al.* (2013) 'Training executive, attention, and motor skills: a proof-of-concept study in preschool children With ADHD.', *Journal of Attention Disorders*, 17(8), pp. 711–21. doi: 10.1177/1087054711435681.

Hamshere, M. L. *et al.* (2013) 'High loading of polygenic risk for ADHD in children with comorbid aggression.', *The American Journal of Psychiatry*, 170(8), pp. 909–16. doi: 10.1176/appi.ajp.2013.12081129.

Harold, G. T. *et al.* (2013) 'Biological and rearing mother influences on child ADHD symptoms: revisiting the developmental interface between nature and nurture.', *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, 54(10), pp. 1038–46. doi: 10.1111/jcpp.12100.

Harpin, V. A. (2005) 'The effect of ADHD on the life of an individual, their family, and community from preschool to adult life.', *Archives of Disease in Childhood*, 90 Suppl 1, pp. i2-7. doi: 10.1136/adc.2004.059006.

Harvey, E. *et al.* (2003) 'Parenting of children with attention-defecit/hyperactivity disorder (ADHD): the role of parental ADHD symptomatology', *Journal of Attention Disorders*. 2004/01/24, 7(1), pp. 31–42.

Harvey, E., Stoessel, B. and Herbert, S. (2011) 'Psychopathology and Parenting Practices of Parents of Preschool Children With Behavior Problems', *Parenting*. Taylor & Francis Group , 11(4), pp. 239–263. doi: 10.1080/15295192.2011.613722.

Hechtman, L. *et al.* (2016) 'Functional Adult Outcomes 16 Years After Childhood Diagnosis of Attention-Deficit/Hyperactivity Disorder: MTA Results', *Journal of the American Academy of Child & Adolescent Psychiatry*, 55(11), p. 945–952.e2. doi: 10.1016/j.jaac.2016.07.774.

Hill, E. L. (2004) 'Evaluating the theory of executive dysfunction in autism', *Developmental*

Review, 24(2), pp. 189–233. doi: 10.1016/j.dr.2004.01.001.

Hill, J. and Schoener, E. (1996) 'Age-dependent decline of attention deficit hyperactivity disorder', *The American Journal of Psychiatry*.

Hinney, A. *et al.* (2011) 'Genome-wide association study in German patients with attention deficit/hyperactivity disorder', *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 156(8), pp. 888–897. doi: 10.1002/ajmg.b.31246.

Holden, S. E. *et al.* (2013) 'The prevalence and incidence, resource use and financial costs of treating people with attention deficit/hyperactivity disorder (ADHD) in the United Kingdom (1998 to 2010).', *Child and Adolescent Psychiatry and Mental Health*. BioMed Central, 7(1), p. 34. doi: 10.1186/1753-2000-7-34.

Holmes, J. *et al.* (2004) 'The Child Attention-Deficit Hyperactivity Disorder Teacher Telephone Interview (CHATTI): reliability and validity', *British Journal of Psychiatry*, 184, pp. 74–78.

Hong, S.-B. *et al.* (2014) 'Subthreshold attention-deficit/hyperactivity disorder is associated with functional impairments across domains: a comprehensive analysis in a large-scale community study', *European Child & Adolescent Psychiatry*, 23(8), pp. 627–636. doi: 10.1007/s00787-013-0501-z.

Hughes, C. *et al.* (2013) 'Does maternal depression predict young children's executive function? - A 4-year longitudinal study', *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 54(2), pp. 169–177. doi: 10.1111/jcpp.12014.

Humphreys, K. L., Mehta, N. and Lee, S. S. (2012) 'Association of parental ADHD and depression with externalizing and internalizing dimensions of child psychopathology.', *Journal of Attention Disorders*, 16(4), pp. 267–75. doi: 10.1177/1087054710387264.

Jans, T. *et al.* (2015) 'Does intensive multimodal treatment for maternal ADHD improve the efficacy of parent training for children with ADHD? A randomized controlled multicenter trial', *Journal of Child Psychology and Psychiatry*, 12, p. n/a-n/a. doi: 10.1111/jcpp.12443.

Jarrett, M. A. and Ollendick, T. H. (2008) 'A conceptual review of the comorbidity of attention-deficit/hyperactivity disorder and anxiety: Implications for future research and practice', *Clinical Psychology Review*, 28(7), pp. 1266–1280. doi: 10.1016/j.cpr.2008.05.004.

Jensen, C. M. and Steinhausen, H.-C. (2015) 'Comorbid mental disorders in children and adolescents with attention-deficit/hyperactivity disorder in a large nationwide study', *ADHD Attention Deficit and Hyperactivity Disorders*. Springer Vienna, 7(1), pp. 27–38. doi: 10.1007/s12402-014-0142-1.

Jensen, P. S. *et al.* (2001) 'ADHD comorbidity findings from the MTA study: comparing comorbid subgroups.', *Journal of the American Academy of Child and Adolescent Psychiatry*, 40(2), pp. 147–58. doi: 10.1097/00004583-200102000-00009.

Jensen, P. S., Martin, D. and Cantwell, D. P. (1997) 'Comorbidities in ADHD: Implications for research, practice and DSM-IV', *Journal of the American Academy of Child & Adolescent Psychiatry*, 36, pp. 1065–1079.

Johnston, C. *et al.* (2002) 'Responsiveness in interactions of mothers and sons with ADHD: relations to maternal and child characteristics.', *Journal of Abnormal Child Psychology*, 30(1), pp. 77–88.

Johnston, C. *et al.* (2012) 'Parenting in adults with attention-deficit/hyperactivity disorder (ADHD)', *Clinical Psychology Review*. 2012/03/31, 32(4), pp. 215–228. doi: S0272-7358(12)00025-6 [pii] 10.1016/j.cpr.2012.01.007.

Johnston, C. and Lee-Flynn, S. (2011) 'Parents' attribution for child behavior: Relations to parent and child ADHD symptoms.', in *In: Coles EK (Chair), Gender Differences in the Clinical Presentation, Treatment and Outcome of Children with ADHD. Association for Behavioral and Cognitive Therapies*. Toronto.

Johnston, C. and Mash, E. J. (2001) 'Families of children with attention-deficit/hyperactivity disorder: review and recommendations for future research', *Clinical Child and Family Psychology Review*, 4(3), pp. 183–207.

Kadesjo, B. and Gillberg, C. (2001) 'The Comorbidity of ADHD in the General Population of Swedish School-age Children', *Journal of Child Psychology and Psychiatry*. Blackwell Publishers Ltd., 42(4), pp. 487–492. doi: 10.1111/1469-7610.00742.

Kar, S. K. and Jain, M. (2016) 'Current understandings about cognition and the neurobiological correlates in schizophrenia.', *Journal of Neurosciences in Rural Practice*. Medknow Publications, 7(3), pp. 412–8. doi: 10.4103/0976-3147.176185.

Kazdin, A. E. and Wassell, G. (1999) 'Barriers to Treatment Participation and Therapeutic Change Among Children Referred for Conduct Disorder', *Journal of Clinical Child Psychology*, 28(2), pp. 160–172. doi: 10.1207/s15374424jccp2802_4.

Kempton, S. *et al.* (1999) 'Executive function and attention deficit hyperactivity disorder: Stimulant medication and better executive function performance in children.', *Psychological Medicine*, 29(3), pp. 527–38. doi: 10.1017/S0033291799008338.

Kendler, K. S. *et al.* (1987) 'Symptoms of anxiety and symptoms of depression. Same genes, different environments?', *Archives of General Psychiatry*, 44(5), pp. 451–7.

Kessler, R. C. *et al.* (2005) 'Patterns and predictors of attention-deficit/hyperactivity disorder persistence into adulthood: results from the national comorbidity survey replication.', *Biological Psychiatry*. NIH Public Access, 57(11), pp. 1442–51. doi: 10.1016/j.biopsych.2005.04.001.

Kessler, R. C. *et al.* (2006) 'The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication', *American Journal of Psychiatry*. 2006/04/06, 163(4), pp. 716–723. doi: 163/4/716 [pii] 10.1176/appi.ajp.163.4.716.

Kessler, R. C. *et al.* (2010) 'Structure and Diagnosis of Adult Attention-Deficit/Hyperactivity Disorder', *Archives of General Psychiatry*, 67, pp. 1168–1178. doi: 10.1001/archgenpsychiatry.2010.146.

Kim-Cohen, J. *et al.* (2005) 'Maternal depression and children's antisocial behavior: nature and nurture effects', *Archives of General Psychiatry*, 62(2), pp. 173–181. doi: 10.1001/archpsyc.62.2.173.

Klein, R. G., Mannuzza, S., Ramos Olazagasti, M. A., *et al.* (2012) 'Clinical and Functional Outcome of Childhood ADHD 33 Years Later', *Arch Gen Psychiatry*, 69(12), pp. 1295–1303. doi: 10.1001/archgenpsychiatry.2012.271.Clinical.

Klein, R. G., Mannuzza, S., Olazagasti, M. A. R., *et al.* (2012) 'Clinical and functional outcome of childhood attention-deficit/hyperactivity disorder 33 years later.', *Archives of General Psychiatry*. NIH Public Access, 69(12), pp. 1295–303. doi: 10.1001/archgenpsychiatry.2012.271.

Klimes-Dougan, B. *et al.* (2006) 'Neuropsychological Functioning in Adolescent Children of Mothers with a History of Bipolar or Major Depressive Disorders', *Biological Psychiatry*, 60(9), pp. 957–965. doi: 10.1016/j.biopsych.2006.03.031.

Kozielec, T. and Starobrat-Hermelin, B. (1997) 'Assessment of magnesium levels in children with attention deficit hyperactivity disorder (ADHD).', *Magnesium Research*, 10(2), pp. 143–8.

Lahey, B. B. *et al.* (1988) 'Psychopathology in the Parents of Children with Conduct Disorder and Hyperactivity', *Journal of the American Academy of Child & Adolescent Psychiatry*, 27(2), pp. 163–170. doi: 10.1097/00004583-198803000-00005.

Lahey, B. B. *et al.* (2005) 'Instability of the DSM-IV Subtypes of ADHD From Preschool Through Elementary School', *Archives of General Psychiatry*. American Medical Association, 62(8), p. 896. doi: 10.1001/archpsyc.62.8.896.

Langley, K. *et al.* (2005) 'Maternal smoking during pregnancy as an environmental risk factor for attention deficit hyperactivity disorder behaviour. A review', *Minerva Pediatrica*, 57(6), pp. 359–371.

- Langley, K. *et al.* (2010) 'Adverse clinical outcomes for young people with diagnosed Attention Deficit Hyperactivity Disorder', *British Journal of Psychiatry*, 196(3), pp. 235–240.
- Langley, K. and Thapar, A. (no date) 'Genetics of ADHD', in Geddes, J., Andreasen, N., and Goodwin, G. (eds) *New Oxford Textbook of Psychiatry*. Third Edit. Oxford University Press.
- Lara, C. *et al.* (2009) 'Childhood Predictors of Adult Attention-Deficit/Hyperactivity Disorder: Results from the World Health Organization World Mental Health Survey Initiative', *Biological Psychiatry*, 65(1), pp. 46–54. doi: 10.1016/j.biopsych.2008.10.005.
- Larson, K. *et al.* (2011) 'Patterns of Comorbidity, Functioning, and Service Use for US Children With ADHD, 2007', *Pediatrics*, 127(3), pp. 462–470. doi: 10.1542/peds.2010-0165.
- Larsson, H. *et al.* (2011) 'Developmental trajectories of DSM-IV symptoms of attention-deficit/hyperactivity disorder: genetic effects, family risk and associated psychopathology', *Journal of Child Psychology and Psychiatry*, 52(9), pp. 954–963. doi: 10.1111/j.1469-7610.2011.02379.x.
- Lee, P. *et al.* (2013) 'Parent-child interaction of mothers with depression and their children with ADHD.', *Research in Developmental Disabilities*, 34(1), pp. 656–68. doi: 10.1016/j.ridd.2012.09.009.
- Lesch, K.-P. *et al.* (2008) 'Molecular genetics of adult ADHD: converging evidence from genome-wide association and extended pedigree linkage studies.', *Journal of Neural Transmission (Vienna, Austria : 1996)*, 115(11), pp. 1573–85. doi: 10.1007/s00702-008-0119-3.
- Lesesne, C. *et al.* (2000) *Attention Deficit/ Hyperactivity Disorder: A Public Health Research Agenda*. Atlanta, GA.
- Lewis, G. *et al.* (2011) 'Investigating environmental links between parent depression and child depressive/anxiety symptoms using an assisted conception design.', *Journal of the American Academy of Child and Adolescent Psychiatry*, 50(5), p. 451–459.e1. doi: 10.1016/j.jaac.2011.01.015.
- Lewis, K. J. S. *et al.* (2012) 'Do parents know best? Parent-reported vs. child-reported depression symptoms as predictors of future child mood disorder in a high-risk sample.', *Journal of Affective Disorders*, 141(2–3), pp. 233–6. doi: 10.1016/j.jad.2012.03.008.
- van Lieshout, M. *et al.* (2016) 'Neurocognitive Predictors of ADHD Outcome: a 6-Year Follow-up Study', *Journal of Abnormal Child Psychology*, pp. 1–12. doi: 10.1007/s10802-016-0175-3.
- Lifford, K. J., Harold, G. T. and Thapar, A. (2008) 'Parent-child relationships and ADHD symptoms: a longitudinal analysis', *Journal of Abnormal Child Psychology*, 36(2), pp. 285–296.

Lifford, K. J., Harold, G. T. and Thapar, A. (2009) 'Parent-child hostility and child ADHD symptoms: a genetically sensitive and longitudinal analysis', *Journal of Child Psychology & Psychiatry*, Epub ahead.

Lisspers, J., Nygren, A. and Söderman, E. (1997) 'Hospital Anxiety and Depression Scale (HAD): some psychometric data for a Swedish sample', *Acta Psychiatrica Scandinavica*. Blackwell Publishing Ltd, 96(4), pp. 281–286. doi: 10.1111/j.1600-0447.1997.tb10164.x.

Lovejoy, M. C. *et al.* (2000) 'Maternal depression and parenting behavior: a meta-analytic review', *Clinical Psychology Review*, 20(5), pp. 561–592.

Luciana, M. and Nelson, C. A. (2002) 'Assessment of neuropsychological function through use of the Cambridge Neuropsychological Testing Automated Battery: Performance in 4- to 12-year-old children', *Developmental Neuropsychology*, 22, pp. 595–624. doi: 10.1207/S15326942DN2203_3.

Magnusson, P. *et al.* (2006) 'Validity of Self-Report and Informant Rating Scales of Adult ADHD Symptoms in Comparison With a Semistructured Diagnostic Interview', *Journal of Attention Disorders*. Sage PublicationsSage CA: Thousand Oaks, CA, 9(3), pp. 494–503. doi: 10.1177/1087054705283650.

Mannuzza, S. and Klein, R. G. (2000) 'Long-term prognosis in attention-deficit/hyperactivity disorder.', *Child and Adolescent Psychiatric Clinics of North America*, 9(3), pp. 711–726.

Manolio, T. A. *et al.* (2009) 'Finding the missing heritability of complex diseases.', *Nature*, 461(7265), pp. 747–53. doi: 10.1038/nature08494.

Marcus, S. M. and Heringhausen, J. E. (2009) 'Depression in childbearing women: when depression complicates pregnancy.', *Primary Care*. NIH Public Access, 36(1), p. 151–65, ix. doi: 10.1016/j.pop.2008.10.011.

Margari, F. *et al.* (2013) 'Parents psychopathology of children with Attention Deficit Hyperactivity Disorder.', *Research in Developmental Disabilities*, 34(3), pp. 1036–43. doi: 10.1016/j.ridd.2012.12.001.

Martin, J. *et al.* (2015) 'Neurocognitive abilities in the general population and composite genetic risk scores for attention-deficit hyperactivity disorder.', *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, 56(6), pp. 648–56. doi: 10.1111/jcpp.12336.

Martinussen, R. *et al.* (2005) 'A meta-analysis of working memory impairments in children with attention-deficit/hyperactivity disorder.', *Journal of the American Academy of Child and Adolescent Psychiatry*, 44(4), pp. 377–84. doi: 10.1097/01.chi.0000153228.72591.73.

- Mash, E. J. and Johnston, C. (1982) 'A Comparison of the Mother-Child Interactions of Younger and Older Hyperactive and Normal Children', *Child Development*, 53(5), p. 1371. doi: 10.2307/1129028.
- Mathew, A. R. *et al.* (2011) 'Co-morbidity between major depressive disorder and anxiety disorders: shared etiology or direct causation?', *Psychological Medicine*, 41(10), pp. 2023–2034. doi: 10.1017/S0033291711000407.
- Mayfield, A. R. *et al.* (2016) 'Equivalence of mother and father ratings of ADHD in children', *Child Neuropsychology*. Routledge, pp. 1–18. doi: 10.1080/09297049.2016.1236186.
- McCarthy, S. *et al.* (2012) 'The epidemiology of pharmacologically treated attention deficit hyperactivity disorder (ADHD) in children, adolescents and adults in UK primary care', *BMC Pediatrics*, 12(1), p. 654. doi: 10.1186/1471-2431-12-78.
- McGough, J. J. and Barkley, R. A. (2004) 'Diagnostic controversies in adult attention deficit hyperactivity disorder', *American Journal of Psychiatry*, 161(11), pp. 1948–1956.
- McLaughlin, K. A. *et al.* (2012) 'Parent psychopathology and offspring mental disorders: results from the WHO World Mental Health Surveys', *British Journal of Psychiatry*, 200(4), pp. 290–299. doi: 10.1192/bjp.bp.111.101253.
- Mehta, M. A., Goodyer, I. M. and Sahakian, B. J. (2004) 'Methylphenidate improves working memory and set-shifting in AD/HD: Relationships to baseline memory capacity', *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 45(2), pp. 293–305. doi: 10.1111/j.1469-7610.2004.00221.x.
- Melby, J. *et al.* (1993) *The Iowa Family Interaction Scales*. Iowa State University Centre for Family Research in Rural Mental Health.
- Melchior, M. and van der Waerden, J. (2016) 'Parental influences on children's mental health: the bad and the good sides of it', *European Child & Adolescent Psychiatry*, 25(8), pp. 805–807. doi: 10.1007/s00787-016-0891-9.
- Micco, J. A. *et al.* (2009) 'Executive functioning in offspring at risk for depression and anxiety', *Depression and Anxiety*. Wiley Subscription Services, Inc., A Wiley Company, 26(9), pp. 780–790. doi: 10.1002/da.20573.
- Mick, E. *et al.* (2002) 'Case-control study of attention-deficit hyperactivity disorder and maternal smoking, alcohol use, and drug use during pregnancy', *Journal of the American Academy of Child & Adolescent Psychiatry*, 41(4), pp. 378–385.
- Middeldorp, C. M. *et al.* (2016a) 'Parents of children with psychopathology: psychiatric

problems and the association with their child's problems', *European Child & Adolescent Psychiatry*, 25(8), pp. 919–927. doi: 10.1007/s00787-015-0813-2.

Middeldorp, C. M. *et al.* (2016b) 'Parents of children with psychopathology: psychiatric problems and the association with their child's problems', *European Child & Adolescent Psychiatry*. Springer Berlin Heidelberg, 25(8), pp. 919–927. doi: 10.1007/s00787-015-0813-2.

Mikami, A. Y. *et al.* (2010) 'Parental influence on children with attention-deficit/hyperactivity disorder: II. Results of a pilot intervention training parents as friendship coaches for children.', *Journal of Abnormal Child Psychology*. NIH Public Access, 38(6), pp. 737–49. doi: 10.1007/s10802-010-9403-4.

Miller, C. J., Newcorn, J. H. and Halperin, J. M. (2010) 'Fading memories: retrospective recall inaccuracies in ADHD.', *Journal of Attention Disorders*, 14(1), pp. 7–14. doi: 10.1177/1087054709347189.

Minde, K. *et al.* (2003) 'The psychosocial functioning of children and spouses of adults with ADHD', *Journal of Child Psychology and Psychiatry*. 2003/05/20, 44(4), pp. 637–646.

Moffitt, T. E. (1990) 'Juvenile Delinquency and Attention Deficit Disorder: Boys' Developmental Trajectories from Age 3 to Age 15', *Child Development*. Blackwell Publishing Ltd, 61(3), pp. 893–910. doi: 10.1111/j.1467-8624.1990.tb02830.x.

Moffitt, T. E. *et al.* (2015) 'Is adult ADHD a childhood-onset neurodevelopmental disorder? Evidence from a four-decade longitudinal cohort study', *American Journal of Psychiatry*, 172(10), pp. 967–977. doi: 10.1176/appi.ajp.2015.14101266.

Moffitt, T. E. *et al.* (2015) 'Is Adult ADHD a Childhood-Onset Neurodevelopmental Disorder? Evidence From a Four-Decade Longitudinal Cohort Study', *American Journal of Psychiatry*, 172(10), pp. 967–977. doi: 10.1176/appi.ajp.2015.14101266.

Moffitt, T. E. and Melchior, M. (2007) 'Why Does the Worldwide Prevalence of Childhood Attention Deficit Hyperactivity Disorder Matter?', *American Journal of Psychiatry*, 164(6), pp. 856–858. doi: 10.1176/ajp.2007.164.6.856.

Moos, R. H. and Moos, B. S. (1974) 'Manual for the Family Environment Scale. Palo Alto', *Consulting Psychologists Press*.

Moos, R. and Moos, B. (1981) *Family Environment Scale Manual*. Palo Alto CA : Consulting Psychologists Press.

Moroney, E. *et al.* (2017) 'Externalizing Outcomes of Youth with and without ADHD: Time-Varying Prediction by Parental ADHD and Mediated Effects.', *Journal of Abnormal Child*

Psychology, 45(3), pp. 457–470. doi: 10.1007/s10802-016-0215-z.

Mrug, S. *et al.* (2012) 'Peer Rejection and Friendships in Children with Attention-Deficit/Hyperactivity Disorder: Contributions to Long-Term Outcomes', *Journal of Abnormal Child Psychology*. Springer US, 40(6), pp. 1013–1026. doi: 10.1007/s10802-012-9610-2.

Mrug, S., Hoza, B. and Gerdes, A. C. (2001) 'Children with Attention-Deficit/Hyperactivity Disorder: Peer Relationships and Peer-Oriented Interventions', *New Directions for Child and Adolescent Development*. Jossey-Bass, A Wiley Company, 2001(91), p. 51. doi: 10.1002/cd.5.

Murphy, K. R. and Barkley, R. A. (1996) 'Parents of children with attention-deficit/hyperactivity disorder: psychological and attentional impairment', *American Journal of Orthopsychiatry*. 1996/01/01, 66(1), pp. 93–102.

Murphy, P. and Schachar, R. (2000) 'Use of self-ratings in the assessment of symptoms of attention deficit hyperactivity disorder in adults', *American Journal of Psychiatry*. 2000/06/30, 157(7), pp. 1156–1159.

Murray, C. and Johnston, C. (2006) 'Parenting in mothers with and without attention-deficit/hyperactivity disorder', *Journal of Abnormal Psychology*. 2006/02/24, 115(1), pp. 52–61. doi: 10.1037/0021-843X.115.1.52.

Najman, J. M. *et al.* (2001) 'Bias Influencing Maternal Reports of Child Behaviour and Emotional State', *Social Psychiatry and Psychiatric Epidemiology*, 36(4), pp. 186–194. doi: 10.1007/s001270170062.

Neale, B. M. *et al.* (2008) 'Genome-wide association scan of attention deficit hyperactivity disorder', *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 147B(8), pp. 1337–1344. doi: 10.1002/ajmg.b.30866.

Neale, B. M., Medland, S., *et al.* (2010) 'Case-Control Genome-Wide Association Study of Attention-Deficit/Hyperactivity Disorder', *Journal of the American Academy of Child & Adolescent Psychiatry*, 49(9), pp. 906–920. doi: 10.1016/j.jaac.2010.06.007.

Neale, B. M., Medland, S. E., *et al.* (2010) 'Meta-Analysis of Genome-Wide Association Studies of Attention-Deficit/Hyperactivity Disorder', *Journal of the American Academy of Child & Adolescent Psychiatry*, 49(9), pp. 884–897. doi: 10.1016/j.jaac.2010.06.008.

NICE (2008) *Attention Deficit Hyperactivity Disorder (ADHD): The NICE Guideline on Diagnosis and Management of ADHD in Children, Young People and Adults*. www.nice.org.uk.

Nigg, J. T. *et al.* (2004) 'Evaluating the endophenotype model of ADHD neuropsychological deficit: results for parents and siblings of children with ADHD combined and inattentive

subtypes.', *Journal of Abnormal Psychology*, 113(4), pp. 614–25. doi: 10.1037/0021-843X.113.4.614.

Nigg, J. T. *et al.* (2005) 'Causal heterogeneity in attention-deficit/hyperactivity disorder: do we need neuropsychologically impaired subtypes?', *Biological Psychiatry*, 57(11), pp. 1224–30. doi: 10.1016/j.biopsych.2004.08.025.

Nigg, J. T. (2008) 'ADHD, lead exposure and prevention: how much lead or how much evidence is needed?', *Expert Review of Neurotherapeutics*, 8(4), pp. 519–521. doi: 10.1586/14737175.8.4.519.

Nigg, J. T. *et al.* (2012) 'Meta-analysis of attention-deficit/hyperactivity disorder or attention-deficit/hyperactivity disorder symptoms, restriction diet, and synthetic food color additives.', *Journal of the American Academy of Child and Adolescent Psychiatry*. NIH Public Access, 51(1), p. 86–97.e8. doi: 10.1016/j.jaac.2011.10.015.

Nigg, J. T., Swanson, J. M. and Hinshaw, S. P. (1997) 'Covert visual spatial attention in boys with attention deficit hyperactivity disorder: lateral effects, methylphenidate response and results for parents.', *Neuropsychologia*, 35(2), pp. 165–76.

O'Connor, T. G. *et al.* (1998) 'Co-occurrence of depressive symptoms and antisocial behavior in adolescence: a common genetic liability', *Journal of Abnormal Psychology*, 107(1), pp. 27–37.

Owens, E. B. *et al.* (2003) 'Which treatment for whom for ADHD? Moderators of treatment response in the MTA', *Journal of Consulting and Clinical Psychology*, 71(3), pp. 540–552.

Park, S. *et al.* (2014) 'Neuropsychological and behavioral profiles in attention-deficit hyperactivity disorder children of parents with a history of mood disorders: a pilot study.', *Psychiatry Investigation*, 11(1), pp. 65–75. doi: 10.4306/pi.2014.11.1.65.

Patterson, G. R. (1982) *Coercive Family Process*. Eugene, OR: Castalia.

Pennington, B. F. and Ozonoff, S. (1996) 'Executive functions and developmental psychopathology.', *Journal of Child Psychology and Psychiatry*, 37(1), pp. 51–87. doi: 10.1111/j.1469-7610.1996.tb01380.x.

Perneger, T. V (1998) 'What's wrong with Bonferroni adjustments.', *British Medical Journal (Clinical Research Ed.)*, 316(7139), pp. 1236–1238. doi: 10.1136/bmj.316.7139.1236.

Pilowsky, D. J. *et al.* (2008) 'Children of depressed mothers 1 year after the initiation of maternal treatment: findings from the STAR*D-Child Study', *American Journal of Psychiatry*. 2008/06/19, 165(9), pp. 1136–1147. doi: appi.ajp.2008.07081286 [pii]10.1176/appi.ajp.2008.07081286.

Pingault, J.-B. *et al.* (2015) 'Genetic and Environmental Influences on the Developmental Course of Attention-Deficit/Hyperactivity Disorder Symptoms From Childhood to Adolescence', *JAMA Psychiatry*, 72(7), p. 651. doi: 10.1001/jamapsychiatry.2015.0469.

Pliszka, S. R. (2000) 'Patterns of psychiatric comorbidity with attention-deficit/hyperactivity disorder.', *Child and Adolescent Psychiatric Clinics of North America*, 9(3), p. 525–40, vii.

Polanczyk, G. *et al.* (2007) 'The Worldwide Prevalence of ADHD: A Systematic Review and Metaregression Analysis', *American Journal of Psychiatry*, 164(6), pp. 942–948. doi: 10.1176/ajp.2007.164.6.942.

Polanczyk, G. *et al.* (2010) 'Implications of Extending the ADHD Age-of-Onset Criterion to Age 12: Results from a Prospectively Studied Birth Cohort', *Journal of the American Academy of Child & Adolescent Psychiatry*, 49(3), pp. 210–216. doi: 10.1016/j.jaac.2009.12.014.

Polanczyk, G. V. *et al.* (2014) 'ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis', *International Journal of Epidemiology*. Oxford University Press, 43(2), pp. 434–442. doi: 10.1093/ije/dyt261.

Polanczyk, G. V. *et al.* (2015) 'Annual Research Review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents', *Journal of Child Psychology and Psychiatry*, 56(3), pp. 345–365. doi: 10.1111/jcpp.12381.

Polanczyk, G. V. and Moffitt, T. E. (2014) 'How Evidence on the Developmental Nature of Attention-Deficit/Hyperactivity Disorder Can Increase the Validity and Utility of Diagnostic Criteria', *Journal of the American Academy of Child & Adolescent Psychiatry*, 53(7), pp. 723–725. doi: 10.1016/j.jaac.2014.04.012.

Pressman, L. J. *et al.* (2006) 'Relationship of family environment and parental psychiatric diagnosis to impairment in ADHD', *Journal of the American Academy of Child and Adolescent Psychiatry*. 2006/03/17, 45(3), pp. 346–354. doi: 10.1097/01.chi.0000192248.61271.c8S0890-8567(09)62026-8 [pii].

Psychogiou, L. *et al.* (2007) 'Mothers' expressed emotion toward their school-aged sons', *European Child & Adolescent Psychiatry*, 16(7), pp. 458–464. doi: 10.1007/s00787-007-0619-y.

Psychogiou, L. *et al.* (2008) 'Do maternal attention-deficit/hyperactivity disorder symptoms exacerbate or ameliorate the negative effect of child attention-deficit/hyperactivity disorder symptoms on parenting?', *Development and Psychopathology*. 2008/01/24, 20(1), pp. 121–137. doi: S0954579408000060 [pii]10.1017/S0954579408000060.

Psychogiou, L. and Parry, E. (2014) 'Why do depressed individuals have difficulties in their parenting role?', *Psychological Medicine*, 44(7), pp. 1345–7. doi: 10.1017/S0033291713001931.

Quinn, P. O. and Madhoo, M. (2014) 'A review of attention-deficit/hyperactivity disorder in women and girls: uncovering this hidden diagnosis.', *The Primary Care Companion for CNS Disorders*. Physicians Postgraduate Press, Inc., 16(3). doi: 10.4088/PCC.13r01596.

Rajendran, K. *et al.* (2013) 'Association between variation in neuropsychological development and trajectory of ADHD severity in early childhood.', *The American Journal of Psychiatry*. NIH Public Access, 170(10), pp. 1205–11. doi: 10.1176/appi.ajp.2012.12101360.

Reyno, S. M. and McGrath, P. J. (2006) 'Predictors of parent training efficacy for child externalizing behavior problems - a meta-analytic review', *Journal of Child Psychology and Psychiatry*, 47(1), pp. 99–111. doi: 10.1111/j.1469-7610.2005.01544.x.

Rhee, S. H. *et al.* (1999) 'Sex differences in genetic and environmental influences on DSM-III-R attention-deficit/hyperactivity disorder', *Journal of Abnormal Psychology*. 1999/03/06, 108(1), pp. 24–41.

Rhee, S. H. and Waldman, I. D. (2004) 'Etiology of sex differences in the prevalence of ADHD: An examination of inattention and hyperactivity-impulsivity', *American Journal of Medical Genetics*. Wiley Subscription Services, Inc., A Wiley Company, 127B(1), pp. 60–64. doi: 10.1002/ajmg.b.20131.

Rice, F. *et al.* (2007) 'Mental health and functional outcomes of maternal and adolescent reports of adolescent depressive symptoms.', *Journal of the American Academy of Child and Adolescent Psychiatry*, 46(9), pp. 1162–1170. doi: 10.1097/chi.0b013e3180cc255f.

Richters, J. and Pellegrini, D. (1989) 'Depressed mothers' judgments about their children: An examination of the depression-distortion hypothesis', *Child Development*, 60(5), pp. 1068–1075. doi: 10.1111/j.1467-8624.1989.tb03537.x.

Riglin, L. *et al.* (2016) 'Association of Genetic Risk Variants With Attention-Deficit/Hyperactivity Disorder Trajectories in the General Population', *JAMA Psychiatry*. American Medical Association, 73(12), p. 1285. doi: 10.1001/jamapsychiatry.2016.2817.

Robinson, S. *et al.* (2009) 'Executive functions in children with Autism Spectrum Disorders'.

Rogers, R. D. *et al.* (1999) 'Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteers: evidence for monoaminergic mechanisms', *Neuropsychopharmacology*, 20(4), pp. 322–339. doi: 10.1016/S0893-133X(98)00091-8.

Rommelse, N. N. J. *et al.* (2010) 'Shared heritability of attention-deficit/hyperactivity disorder and autism spectrum disorder', *European Child & Adolescent Psychiatry*, 19(3), pp. 281–295. doi: 10.1007/s00787-010-0092-x.

- Roy, A. *et al.* (2016) 'Childhood Factors Affecting Persistence and Desistence of Attention-Deficit/Hyperactivity Disorder Symptoms in Adulthood: Results From the MTA', *Journal of the American Academy of Child & Adolescent Psychiatry*, 55(11), p. 937–944.e4. doi: 10.1016/j.jaac.2016.05.027.
- Rucklidge, J. J. and Tannock, R. (2002) 'Neuropsychological profiles of adolescents with ADHD: effects of reading difficulties and gender', *Journal of Child Psychology and Psychiatry*, 43(8), pp. 988–1003. doi: 10.1111/1469-7610.00227.
- Russell, A. E., Ford, T. and Russell, G. (2015) 'Socioeconomic Associations with ADHD: Findings from a Mediation Analysis.', *PLoS One*. Public Library of Science, 10(6), p. e0128248. doi: 10.1371/journal.pone.0128248.
- Rutter, M. *et al.* (2007) 'Effects of profound early institutional deprivation: An overview of findings from a UK longitudinal study of Romanian adoptees', *European Journal of Developmental Psychology*. Psychology Press, 4(3), pp. 332–350. doi: 10.1080/17405620701401846.
- Rutter, M., Giller, H. and Hagell, A. (1998) *Antisocial Behavior by Young People*. New York & London: Cambridge University Press.
- Rutter, M. and Sroufe, L. A. (2000) 'Developmental psychopathology: concepts and challenges', *Dev Psychopathol*, 12(3), pp. 265–296.
- Salmon, G. and Kemp, A. (2002) 'ADHD: A Survey of Psychiatric and Paediatric Practice', *Child and Adolescent Mental Health*. Blackwell Publishers, 7(2), pp. 73–78. doi: 10.1111/1475-3588.00014.
- Sameroff, A. J. and Seifer, R. (1983) 'Familial Risk and Child Competence', *Child Development*, 54(5), p. 1254. doi: 10.2307/1129680.
- Satterfield, J. H. *et al.* (2007) 'A 30-year prospective follow-up study of hyperactive boys with conduct problems: adult criminality.', *Journal of the American Academy of Child & Adolescent Psychiatry*, 46(5), pp. 601–610.
- Sayal, K., Taylor, E. and Beecham, J. (2003) 'Parental perception of problems and mental health service use for hyperactivity', *Journal of the American Academy of Child & Adolescent Psychiatry*, 42(12), pp. 1410–1414.
- Scahill, L. *et al.* (1999) 'Psychosocial and clinical correlates of ADHD in a community sample of school-age children.', *Journal of the American Academy of Child and Adolescent Psychiatry*, 38(8), pp. 976–84. doi: 10.1097/00004583-199908000-00013.

- Schachar, R. *et al.* (1987) 'Changes in family function and relationships in children who respond to methylphenidate', *Journal of the American Academy of Child & Adolescent Psychiatry*. 1987/09/01, 26(5), pp. 728–732. doi: S0890-8567(09)65029-2 [pii] 10.1097/00004583-198709000-00019.
- Schachar, R. and Wachsmuth, R. (1990) 'Hyperactivity and Parental Psychopathology', *Journal of Child Psychology and Psychiatry*, 31(3), pp. 381–392. doi: 10.1111/j.1469-7610.1990.tb01576.x.
- Segenreich, D. *et al.* (2014) 'Multilevel analysis of ADHD, anxiety and depression symptoms aggregation in families.', *European Child & Adolescent Psychiatry*, 24(5), pp. 525–36. doi: 10.1007/s00787-014-0604-1.
- Seidman, L. J. *et al.* (1995) 'Effects of family history and comorbidity on the neuropsychological performance of children with ADHD: Preliminary findings.', *Journal of the American Academy of Child & Adolescent Psychiatry*, pp. 1015–1024. doi: <http://dx.doi.org/10.1097/00004583-199508000-00011>.
- Seidman, L. J. *et al.* (1997) 'Toward defining a neuropsychology of attention deficit-hyperactivity disorder: performance of children and adolescents from a large clinically referred sample.', *Journal of Consulting and Clinical Psychology*, 65(1), pp. 150–160. doi: 10.1037/0022-006X.65.1.150.
- Seidman, L. J. (2006) 'Neuropsychological functioning in people with ADHD across the lifespan', *Clinical Psychology Review*, 26(4), pp. 466–485. doi: 10.1016/j.cpr.2006.01.004.
- Sellers, R. *et al.* (2015) 'Trends in parent- and teacher-rated emotional, conduct and ADHD problems and their impact in prepubertal children in Great Britain: 1999-2008', *Journal of Child Psychology and Psychiatry*, 56(1), pp. 49–57. doi: 10.1111/jcpp.12273.
- Sellers, R. *et al.* (2016) 'Examining whether offspring psychopathology influences illness course in mothers with recurrent depression using a high-risk longitudinal sample.', *Journal of Abnormal Psychology*. American Psychological Association, 125(2), pp. 256–66. doi: 10.1037/abn0000080.
- Sibley, M. H. *et al.* (2011) 'The Delinquency Outcomes of Boys with ADHD with and Without Comorbidity', *Journal of Abnormal Child Psychology*, 39(1), pp. 21–32. doi: 10.1007/s10802-010-9443-9.
- Sibley, M. H. *et al.* (2012) 'When diagnosing ADHD in young adults emphasize informant reports, DSM items, and impairment.', *Journal of Consulting and Clinical Psychology*, 80(6), pp. 1052–1061. doi: 10.1037/a0029098.
- Sibley, M. H. *et al.* (2016) 'Defining ADHD symptom persistence in adulthood: optimizing sensitivity and specificity', *Journal of Child Psychology and Psychiatry*. doi: 10.1111/jcpp.12620.

Sibley, M. H., Mitchell, J. T. and Becker, S. P. (2016) 'Method of adult diagnosis influences estimated persistence of childhood ADHD: a systematic review of longitudinal studies', *The Lancet Psychiatry*, 3(12), pp. 1157–1165. doi: 10.1016/S2215-0366(16)30190-0.

Silberg, J. *et al.* (1996) 'Genetic and environmental influences on the covariation between hyperactivity and conduct disturbance in juvenile twins', *Journal of Child Psychology & Psychiatry*, 37(7), pp. 803–816.

Silberg, J. and Eaves, L. (2004) 'Analysing the contributions of genes and parent-child interaction to childhood behavioural and emotional problems: a model for the children of twins', *Psychological Medicine*, 34(2), pp. 347–356.

Silberg, J. L., Maes, H. and Eaves, L. J. (2010) 'Genetic and environmental influences on the transmission of parental depression to children's depression and conduct disturbance: an extended Children of Twins study', *Journal of Child Psychology and Psychiatry*, 51(6), pp. 734–744. doi: 10.1111/j.1469-7610.2010.02205.x.

Silberg, J. L., Maes, H. and Eaves, L. J. (2012) 'Unraveling the effect of genes and environment in the transmission of parental antisocial behavior to children's conduct disturbance, depression and hyperactivity', *Journal of Child Psychology and Psychiatry*. 2011/12/07, 53(6), pp. 668–677. doi: 10.1111/j.1469-7610.2011.02494.x.

Silva, D. *et al.* (2015) 'Comorbidities of Attention Deficit Hyperactivity Disorder: Pregnancy Risk Factors and Parent Mental Health', *Community Mental Health Journal*, 51(6), pp. 738–745. doi: 10.1007/s10597-014-9773-0.

Simon, V. *et al.* (2009) 'Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis', *British Journal of Psychiatry*. 2009/03/03, 194(3), pp. 204–211. doi: 10.1192/bjp.bp.107.048827.

Simon, V., Czobor, P. and Bitter, I. (2013) 'Is ADHD severity in adults associated with the lifetime prevalence of comorbid depressive episodes and anxiety disorders?', *European Psychiatry*, 28(5), pp. 308–314. doi: 10.1016/j.eurpsy.2012.05.002.

Simonoff, E. *et al.* (2007) 'ADHD symptoms in children with mild intellectual disability', *Journal of the American Academy of Child & Adolescent Psychiatry*.

Smalley, S. L. *et al.* (2000) 'Familial clustering of symptoms and disruptive behaviors in multiplex families with attention-deficit/hyperactivity disorder', *Journal of the American Academy of Child and Adolescent Psychiatry*, 39(9), pp. 1135–1143.

Smith, E. *et al.* (2015) 'Overcoming barriers to effective early parenting interventions for attention-deficit hyperactivity disorder (ADHD): parent and practitioner views', *Child: Care, Health and Development*, 41(1), pp. 93–102. doi: 10.1111/cch.12146.

Snaith, R. P. (2003) 'The Hospital Anxiety And Depression Scale', *Health Quality Life Outcomes*, 1, p. 29. doi: 10.1186/1477-7525-1-29.

Sonuga-Barke, E. J., Daley, D. and Thompson, M. (2002) 'Does maternal ADHD reduce the effectiveness of parent training for preschool children's ADHD?', *Journal of the American Academy of Child and Adolescent Psychiatry*. 2002/06/07, 41(6), pp. 696–702. doi: S0890-8567(09)61024-8 [pii]10.1097/00004583-200206000-00009.

Sonuga-Barke, E. J. S. (2002) 'Psychological heterogeneity in AD/HD - A dual pathway model of behaviour and cognition', in *Behavioural Brain Research*, pp. 29–36. doi: 10.1016/S0166-4328(01)00432-6.

Sonuga-Barke, E. J. S. *et al.* (2005) 'Varieties of preschool hyperactivity: multiple pathways from risk to disorder', *Developmental Science*. Blackwell Publishing, Ltd., 8(2), pp. 141–150. doi: 10.1111/j.1467-7687.2005.00401.x.

Sonuga-Barke, E. J. S. and Taylor, E. (2015) 'ADHD and Hyperkinetic Disorder', in Thapar, A. *et al.* (eds) *Rutter's Child and Adolescent Psychiatry*. Sixth Edit. Wiley-Blackwell, p. 738.

Spencer, T. J. (2006) 'ADHD and comorbidity in childhood', *Journal of Clinical Psychiatry*, 67(SUPPL. 8), pp. 27–31.

Sprich, S. *et al.* (2000) 'Adoptive and biological families of children and adolescents with ADHD.', *Journal of the American Academy of Child and Adolescent Psychiatry*, 39(11), pp. 1432–7. doi: 10.1097/00004583-200011000-00018.

Standard Occupational Classification (2000). London: HMSO.

State, M. W. and Thapar, A. (2015) 'Genetics', in Thapar, A. *et al.* (eds) *Rutter's Child and Adolescent Psychiatry*. Sixth. John Wiley and Sons Limited UK, pp. 303–316.

Stefanatos, G. A. and Baron, I. S. (2007) 'Attention-deficit/hyperactivity disorder: A neuropsychological perspective towards DSM-V', *Neuropsychology Review*, 17(1), pp. 5–38. doi: 10.1007/s11065-007-9020-3.

Stein, A. *et al.* (2012) 'Maternal cognitions and mother–infant interaction in postnatal depression and generalized anxiety disorder.', *Journal of Abnormal Psychology*, 121(4), pp. 795–809. doi: 10.1037/a0026847.

Stein, A. and Harold, G. (2015) *Impact of Parental Psychiatric Disorder and Physical Illness in Rutter's Child and Adolescent Psychiatry*. Sixth. Edited by A. Thapar *et al.* John Wiley and Sons Limited UK.

Stergiakouli, E. *et al.* (2012) 'Investigating the contribution of common genetic variants to the risk and pathogenesis of ADHD', *American Journal of Psychiatry*, 169(2), pp. 186–194.

Stergiakouli, E. *et al.* (2015) 'Shared genetic influences between attention-deficit/hyperactivity disorder (ADHD) traits in children and clinical ADHD', *Journal of the American Academy of Child and Adolescent Psychiatry*, 54(4), pp. 322–327. doi: 10.1016/j.jaac.2015.01.010.

Swanson, J. M. *et al.* (1998) 'Attention-deficit hyperactivity disorder and hyperkinetic disorder', *The Lancet @ Bulletin*, 351.

Swensen, A. R. *et al.* (2003) 'Attention-deficit/hyperactivity disorder: increased costs for patients and their families.', *Journal of the American Academy of Child and Adolescent Psychiatry*. National Institutes of Health, Bethesda, MD, 42(12), pp. 1415–23. doi: 10.1097/00004583-200312000-00008.

Syngelaki, E. M. *et al.* (2009) 'Executive functioning and risky decision making in young male offenders', *Criminal Justice and Behavior*, 36(11), pp. 1213–1227. doi: 10.1177/0093854809343095.

Takeda, T. *et al.* (2010) 'Parental ADHD status and its association with proband ADHD subtype and severity', *Journal of Pediatrics*. 2010/07/16, 157(6), p. 995–1000 e1. doi: S0022-3476(10)00480-4 [pii]10.1016/j.jpeds.2010.05.053.

Tamm, L., Nakonezny, P. A. and Hughes, C. W. (2014) 'An Open Trial of a Metacognitive Executive Function Training for Young Children With ADHD.', *Journal of Attention Disorders*, 18(6), pp. 551–559. doi: 10.1177/1087054712445782.

Tarver, J., Daley, D. and Sayal, K. (2015) 'Beyond symptom control for attention-deficit hyperactivity disorder (ADHD): What can parents do to improve outcomes?', *Child: Care, Health and Development*, 41(1), pp. 1–14. doi: 10.1111/cch.12159.

Taylor, E. *et al.* (1996) 'Hyperactivity and conduct problems as risk factors for adolescent development', *Journal of the American Academy of Child & Adolescent Psychiatry*, 35(9), pp. 1213–1226.

Taylor, E. and Sonuga-Barke, E. J. (2008) 'Disorders of attention and activity', in Rutter, M. *et al.* (eds) *Rutter's Textbook of Child Psychiatry*. 5th edn. Oxford: Blackwell, pp. 521–542.

Telford, C. *et al.* (2013) 'Estimating the costs of ongoing care for adolescents with attention-deficit hyperactivity disorder', *Social Psychiatry and Psychiatric Epidemiology*. Springer-Verlag, 48(2), pp. 337–344. doi: 10.1007/s00127-012-0530-9.

Thapar, A. *et al.* (1999) 'Genetic basis of attention deficit and hyperactivity', *British Journal of*

Psychiatry, 174, pp. 105–111.

Thapar, A. *et al.* (2009) 'Prenatal smoking might not cause Attention-Deficity/Hyperactivity Disorder: Evidence from a novel design', *Biological Psychiatry*, 66(8), pp. 722–727.

Thapar, A. *et al.* (2012) 'What causes attention deficit hyperactivity disorder?', *Archives of Disease in Childhood*. 2011/09/10, 97(3), pp. 260–265. doi: archdischild-2011-300482 [pii] 10.1136/archdischild-2011-300482.

Thapar, A. *et al.* (2013) 'Practitioner Review: What have we learnt about the causes of ADHD?', *Journal of Child Psychology and Psychiatry*. 2012/09/12, 54(1), pp. 3–16. doi: 10.1111/j.1469-7610.2012.02611.x.

Thapar, A. and Cooper, M. (2015) 'Attention deficit hyperactivity disorder.', *The Lancet*, 6736(15). doi: 10.1016/S0140-6736(15)00238-X.

Thapar, A., Harrington, R. and McGuffin, P. (2001) 'Examining the comorbidity of ADHD-related behaviours and conduct problems using a twin study design', *British Journal of Psychiatry*, 179, pp. 224–229.

Theule, J. *et al.* (2011) 'Predicting Parenting Stress in Families of Children with ADHD: Parent and Contextual Factors', *Journal of Child and Family Studies*, 20(5), pp. 640–647.

Thissen, A. J. A. M., Rommelse, N. N. J., Hoekstra, P. J., *et al.* (2014) 'Attention deficit hyperactivity disorder (ADHD) and executive functioning in affected and unaffected adolescents and their parents: challenging the endophenotype construct.', *Psychological Medicine*, 44(4), pp. 881–92. doi: 10.1017/S0033291713001153.

Thissen, A. J. A. M., Rommelse, N. N. J., Altink, M. E., *et al.* (2014) 'Parent-of-Origin Effects in ADHD: Distinct Influences of Paternal and Maternal ADHD on Neuropsychological Functioning in Offspring', *Journal of Attention Disorders*, 18(6), pp. 521–531. doi: 10.1177/1087054712443159.

Thomas, S. R. *et al.* (2014) 'Maternal Depression History Moderates Parenting Responses to Compliant and Noncompliant Behaviors of Children with ADHD.', *Journal of Abnormal Child Psychology*. doi: 10.1007/s10802-014-9957-7.

Toh, S. (2006) 'Datapoints: Trends in ADHD and Stimulant Use Among Children, 1993-2003', *Psychiatric Services*, 57(8), pp. 1091–1091. doi: 10.1176/ps.2006.57.8.1091.

Toplak, M. E., Jain, U. and Tannock, R. (2005) 'Executive and motivational processes in adolescents with Attention-Deficit-Hyperactivity Disorder (ADHD).', *Behavioral and Brain Functions : BBF*, 1(1), p. 8. doi: 10.1186/1744-9081-1-8.

Tully, E. C., Iacono, W. G. and McGue, M. (2008) 'An adoption study of parental depression as an environmental liability for adolescent depression and childhood disruptive disorders', *American Journal of Psychiatry*, 165(9), pp. 1148–1154. doi: 10.1176/appi.ajp.2008.07091438.

Vidair, H. B. *et al.* (2011) 'Screening parents during child evaluations: Exploring parent and child psychopathology in the same clinic', *Journal of the American Academy of Child and Adolescent Psychiatry*, 50(5), pp. 441–450. doi: 10.1016/j.jaac.2011.02.002.

Vande Voort, J. L. *et al.* (2014) 'Impact of the DSM-5 attention-deficit/hyperactivity disorder age-of-onset criterion in the US adolescent population.', *Journal of the American Academy of Child and Adolescent Psychiatry*, 53(7), pp. 736–44. doi: 10.1016/j.jaac.2014.03.005.

Wang, C. H., Mazursky-Horowitz, H. and Chronis-Tuscano, A. (2014) 'Delivering evidence-based treatments for child attention-deficit/hyperactivity disorder (ADHD) in the context of parental ADHD', *Current Psychiatry Reports*. doi: 10.1007/s11920-014-0474-8.

Waxmonsky, J. G. *et al.* (2014) 'Does Pharmacological Treatment of ADHD in Adults Enhance Parenting Performance? Results of a Double-Blind Randomized Trial', *CNS Drugs*, 28(7), pp. 665–677. doi: 10.1007/s40263-014-0165-3.

Wechsler, D. (2003) *Wechsler Intelligence Scale for Children - Fourth Edition (WISC-IV) Administration and Scoring Manual*. San Antonio, Tx: The Psychological Association.

Weiss, M., Hechtman, L. and Weiss, G. (2000) 'ADHD in parents', *Journal of the American Academy of Child and Adolescent Psychiatry*. 2000/08/12, 39(8), pp. 1059–1061.

Weiss, M. and Murray, C. (2003) 'Assessment and management of attention-deficit hyperactivity disorder in adults', *Canadian Medical Association Journal*. 2003/03/19, 168(6), pp. 715–722.

Weissman, M. M. *et al.* (1997) 'Offspring of depressed parents. 10 Years later.', *Archives of General Psychiatry*, 54(10), pp. 932–40.

Weissman, M. M. *et al.* (2015) 'Treatment of maternal depression in a medication clinical trial and its effect on children.', *The American Journal of Psychiatry*. American Psychiatric Association Arlington, VA, 172(5), pp. 450–9. doi: 10.1176/appi.ajp.2014.13121679.

West, A. *et al.* (2002) 'Evidence to suggest biased phenotypes in children with Attention Deficit Hyperactivity Disorder from completely ascertained trios', *Molecular Psychiatry*. 2002/10/26, 7(9), pp. 962–966. doi: 10.1038/sj.mp.4001129.

WHO (1993) 'The ICD-10 Classification of Mental and Behavioural Disorders.', Geneva, Swi.

- Wickramaratne, P. *et al.* (2011) 'Children of Depressed Mothers 1 Year After Remission of Maternal Depression: Findings From the STAR*D-Child Study', *American Journal of Psychiatry*, 168(6), pp. 593–602. doi: 10.1176/appi.ajp.2010.10010032.
- Wietecha, L. *et al.* (2012) 'Atomoxetine Once Daily for 24 Weeks in Adults With Attention-Deficit/Hyperactivity Disorder (ADHD)', *Clinical Neuropharmacology*, 35(3), pp. 125–133. doi: 10.1097/WNF.0b013e3182560315.
- Wilens, T. E., Faraone, S. V and Biederman, J. (2004) 'Attention-deficit/hyperactivity disorder in adults', *Journal of the American Medical Association*. 2004/08/05, 292(5), pp. 619–623. doi: 10.1001/jama.292.5.619292/5/619 [pii].
- Willcutt, E. G. *et al.* (2005) 'Validity of the executive function theory of attention-deficit/hyperactivity disorder: A meta-analytic review.', *Biological Psychiatry*, 57(11), pp. 1336–46. doi: 10.1016/j.biopsych.2005.02.006.
- Willcutt, E. G. (2012) 'The Prevalence of DSM-IV Attention-Deficit/Hyperactivity Disorder: A Meta-Analytic Review', *Neurotherapeutics*, 9(3), pp. 490–499. doi: 10.1007/s13311-012-0135-8.
- Willcutt, E. G. *et al.* (2012) 'Validity of DSM-IV attention deficit/hyperactivity disorder symptom dimensions and subtypes.', *Journal of Abnormal Psychology*. NIH Public Access, 121(4), pp. 991–1010. doi: 10.1037/a0027347.
- Williams, N. M. *et al.* (2010) 'Rare chromosomal deletions and duplications in attention-deficit hyperactivity disorder: a genome-wide analysis.', *Lancet (London, England)*. Elsevier, 376(9750), pp. 1401–8. doi: 10.1016/S0140-6736(10)61109-9.
- Williams, N. M. *et al.* (2012) 'Genome-wide analysis of copy number variants in attention deficit hyperactivity disorder: the role of rare variants and duplications at 15q13.3.', *The American Journal of Psychiatry*. American Psychiatric Publishing, 169(2), pp. 195–204. doi: 10.1176/appi.ajp.2011.11060822.
- Williamson, D. and Johnston, C. (2015) 'Gender differences in adults with attention-deficit/hyperactivity disorder: A narrative review', *Clinical Psychology Review*, 40, pp. 15–27. doi: 10.1016/j.cpr.2015.05.005.
- Wray, N. R. *et al.* (2014) 'Research Review: Polygenic methods and their application to psychiatric traits', *Journal of Child Psychology and Psychiatry and Allied Disciplines*, pp. 1068–1087. doi: 10.1111/jcpp.12295.
- Zayats, T. *et al.* (2015) 'Genome-wide analysis of attention deficit hyperactivity disorder in Norway.', *PLoS One*, 10(4), p. e0122501. doi: 10.1371/journal.pone.0122501.

Zigmond, A. S. and Snaith, R. P. (1983) 'The hospital anxiety and depression scale', *Acta Psychiatrica Scandinavica*, 67(6), pp. 361–370.

Appendices

Appendix 3.1: Associations between mother ADHD (using DSM-5 criteria) and child clinical presentation

Mother ADHD DSM-5					
Child Clinical Presentation	No ADHD n=425	ADHD n=117	<i>B</i>	95% <i>CI</i>	<i>p</i>
	Mean (SD)	Mean (SD)			
ADHD Severity	15.03 (2.79)	15.64 (2.35)	0.138	0.006, 0.271	0.041
Inattention Severity	7.42 (1.72)	7.72 (1.60)	0.090	-0.012, 0.193	0.083
Hyperactive-Impulsive Severity	7.61 (1.66)	7.91 (1.47)	0.085	-0.008, 0.178	0.074
CD symptom severity	1.17 (1.65)	1.56 (1.99)	0.108	0.004, 0.212	0.041
	<i>n</i> (%)	<i>n</i> (%)	<i>OR</i>	95% <i>CI</i>	<i>P</i>
CD Diagnosis	65 (16)	28 (24)	1.780	1.077, 2.943	0.025

Appendix 3.2: Associations between father ADHD (using DSM-5 criteria) and child clinical presentation

Father ADHD DSM-5					
Child Clinical Presentation	No ADHD n=197	ADHD n=80	<i>B</i>	95% <i>CI</i>	<i>p</i>
	Mean (SD)	Mean (SD)			
ADHD Severity	14.72 (2.63)	15.03 (3.29)	0.074	-0.101, 0.249	0.404
Inattention Severity	7.41 (1.63)	7.37 (1.80)	-0.013	-0.144, 0.118	0.841
Hyperactive-Impulsive Severity	7.31 (1.71)	7.65 (2.06)	0.107	-0.025, 0.240	0.113
CD symptom severity	0.97 (1.51)	1.47 (2.04)	0.142	0.013, 0.270	0.031
	<i>n</i> (%)	<i>n</i> (%)	<i>OR</i>	95% <i>CI</i>	<i>p</i>
CD Diagnosis	27 (14)	17 (22)	1.693	0.861, 3.330	0.127

Appendix 3.3: Associations between mother ADHD (using DSM-5 criteria) and family environment

Mother ADHD DSM-5					
Family Environment	No ADHD	ADHD			
	n= 425	n= 117			
	<i>Mean(SD)</i>	<i>Mean(SD)</i>	<i>B</i>	<i>95% CI</i>	<i>p</i>
Parent report Low Warmth	10.72 (5.24)	11.77 (5.34)	0.173	0.025, 0.321	0.022
Parent report Hostility	15.28 (4.37)	16.37 (4.60)	1.111	0.198, 2.024	0.017
Child report Mother Low Warmth	11.20 (6.39)	12.89 (6.27)	0.301	0.027, 0.575	0.032
Child report Mother Hostility	18.15 (6.64)	20.27 (6.64)	2.183	-0.003, 4.370	0.050
Child report Father Low Warmth	14.79 (8.92)	17.97 (8.22)	3.159	-0.198, 6.517	0.065
Child report Father Hostility	17.62 (7.65)	19.22 (7.21)	1.559	-1.404, 4.532	0.300
Conflict	3.99 (2.35)	5.01 (2.37)	1.025	0.533, 1.517	0.000
Low Cohesion	2.14 (1.87)	2.74 (2.17)	0.612	0.207, 1.017	0.003

Appendix 3.4: Associations between mother ADHD (using DSM-5 criteria) and family environment

Father ADHD DSM-5					
Family Environment	No ADHD	ADHD			
	n= 197	n= 80			
	<i>Mean(SD)</i>	<i>Mean(SD)</i>	<i>B</i>	<i>95% CI</i>	<i>p</i>
Parent report Low Warmth	12.01 (5.98)	10.15 (4.62)	-0.219	-0.423, -0.015	0.035
Parent report Hostility	15.30 (4.41)	15.45 (4.73)	0.184	-1.037, 1.404	0.767
Child report Mother Low Warmth	13.12 (7.69)	9.22 (4.64)	-0.467	-0.874, -0.060	0.025
Child report Mother Hostility	18.32 (7.10)	15.78 (7.21)	-2.407	-5.637, 0.824	0.142
Child report Father Low Warmth	14.40 (8.96)	13.70 (7.53)	-0.083	-3.899, 3.732	0.966
Child report Father Hostility	18.44 (7.53)	17.85 (7.69)	-0.165	-3.606, 3.275	0.924
Conflict	4.12 (2.42)	4.16 (2.47)	0.052	-0.614, 0.717	0.879
Low Cohesion	2.21 (1.89)	2.25 (1.99)	0.037	-0.486, 0.559	0.891

Appendix 4.1 Baseline associations for chapter 4

	Unadjusted model			
	n	B	95%CI	p
Child ADHD symptoms at Time 1*				
Mother ADHD DSM-5	134	0.17	-0.29, 0.63	0.47
Mother Depression	135	0.42	-0.02, 0.87	0.06
Child conduct symptoms at Time 1*				
Mother ADHD DSM-5	133	-0.09	-0.54, 0.36	0.69
Mother Depression	134	0.60	0.18, 1.02	0.01

*Standardized

Appendix A: Parent questionnaire on childhood ADHD symptoms

CHILDHOOD ADHD SYMPTOMS SCALE – SELF REPORT

Instructions: Please circle the number next to each item that best describes your behaviour
WHEN YOU WERE A CHILD AGED AROUND 7-11 YEARS OLD (PRIMARY/JUNIOR SCHOOL)

		Never	Rarely	Some- times	Often
1.	Failed to give close attention to details or made careless mistakes in my work.	0	1	2	3
2.	Fidgeted with hands or feet or squirmed in seat.	0	1	2	3
3.	Difficulty sustaining my attention in tasks or fun activities.	0	1	2	3
4.	Left my seat in classroom or in other situations in which seating is expected.	0	1	2	3
5.	Didn't listen when spoken to directly.	0	1	2	3
6.	Felt restless.	0	1	2	3
7.	Didn't follow through on instructions and failed to finish work.	0	1	2	3
8.	Had difficulty engaging in leisure activities or doing fun things quietly.	0	1	2	3
9.	Had difficulty organizing tasks and activities.	0	1	2	3
10.	Felt "on the go" or "driven by a motor".	0	1	2	3
11.	Avoided, disliked, or was reluctant to engage in work that requires sustained mental effort.	0	1	2	3
12.	Talked excessively.	0	1	2	3
13.	Lost things necessary for tasks or activities.	0	1	2	3
14.	Blurted out answers before questions had been completed.	0	1	2	3
15.	Easily distracted.	0	1	2	3
16.	Had difficulty awaiting turn.	0	1	2	3
17.	Forgetful in daily activities.	0	1	2	3
18.	Interrupted or intruded on others.	0	1	2	3

Appendix B: Parent questionnaire on childhood conduct symptoms

BEHAVIOURS – SELF-REPORT

Instructions: Please circle the number next to each item that best describes your behaviour
WHEN YOU AROUND 7 -11 YEARS OLD (PRIMARY/JUNIOR SCHOOL)

		Never	Rarely	Some- times	Often
1.	Lied or broke promises to obtain goods or favours or to avoid obligations	0	1	2	3
2.	Initiated physical fights (other than with siblings)	0	1	2	3
3.	Used a weapon that could cause serious physical harm to others (eg. bat, brick, broken bottle, knife, gun)	0	1	2	3
4.	Stayed out after dark despite parental prohibition (beginning before 13 years of age)	0	1	2	3
5.	Exhibited physical cruelty to other people (e.g. tied up, cut or burnt a victim)	0	1	2	3
6.	Exhibited physical cruelty to animals	0	1	2	3
7.	Deliberately destroyed the property of others (other than by fire-setting)	0	1	2	3
8.	Deliberately set fires with a risk or intention of causing serious damage	0	1	2	3
9.	Stole objects of non-trivial value without confronting the victim, either within the home or outside (eg. shoplifting, burglary, forgery)	0	1	2	3
10.	Truanted from school (beginning before 13 years of age)	0	1	2	3
11.	Ran away from parental or parental surrogate home at least twice or ran away once for more than a single night (this does not include leaving to avoid physical or sexual abuse)	0	1	2	3
12.	Committed a crime involving confrontation with the victim (including purse-snatching, extortion, mugging)	0	1	2	3
13.	Bullied others (eg. deliberate infliction of pain or hurt, including persistent intimidation, tormenting, or molestation)	0	1	2	3
14.	Broken into someone else's house, building or car.	0	1	2	3

Appendix C: Parent questionnaire on current ADHD symptoms

CURRENT ADHD SYMPTOMS SCALE – SELF-REPORT

Instructions: Please circle the number next to each item that best describes your behaviour DURING THE PAST 6 MONTHS.

		Never	Rarely	Some- times	Often
1.	Fail to give close attention to details or make careless mistakes in my work.	0	1	2	3
2.	Fidget with hands or feet or squirm in seat.	0	1	2	3
3.	Difficulty sustaining my attention in tasks or fun activities.	0	1	2	3
4.	Leave my seat in situations in which seating is expected.	0	1	2	3
5.	Don't listen when spoken to directly.	0	1	2	3
6.	Feel restless.	0	1	2	3
7.	Don't follow through on instructions and fail to finish work.	0	1	2	3
8.	Have difficulty engaging in leisure activities or doing fun things quietly.	0	1	2	3
9.	Having difficulty organizing tasks and activities.	0	1	2	3
10.	Felt "on the go" or "driven by a motor".	0	1	2	3
11.	Avoided, dislike, or was reluctant to engage in work that requires sustained mental effort.	0	1	2	3
12.	Talk excessively.	0	1	2	3
13.	Lose things necessary for tasks or activities.	0	1	2	3
14.	Blurt out answers before questions have been completed.	0	1	2	3
15.	Easily distracted.	0	1	2	3
16.	Have difficulty awaiting turn.	0	1	2	3
17.	Forgetful in daily activities.	0	1	2	3
18.	Interrupt or intrude on others.	0	1	2	3