

Investigating the link between attention deficit/hyperactivity disorder and depression

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Thesis summary

There is increasing evidence of an association between attention deficit/hyperactivity disorder (ADHD) and depression, but potential mechanisms explaining this are unclear. The overall aim of this thesis was to expand the current literature by investigating different factors that might contribute to the association between ADHD and depression, and to examine the impact of ADHD on the clinical presentation of depression.

First, the prospective association between childhood ADHD and adolescent depression was investigated and academic attainment and friendship difficulties were tested as mediators of this association. In a general population sample, ADHD at age 7 was associated with depression 10 years later. Part of this association was mediated by academic attainment and friendship difficulties.

Second, friendships were examined in more detail by testing different features of friendship (presence of friends, quality of friendships and the characteristics of the friendship group) as mediators of the association between ADHD and depression. In addition, I tested whether parent-child relationship quality could mitigate against friendship difficulties. In a sample of secondary school pupils, friendship quality mediated part of the association between ADHD and depression 7 months later, and mother-child relationship warmth appeared to slightly mitigate against this mediation effect.

Third, the genetic overlap of ADHD and major depressive disorder (MDD) was examined by identifying specific regions of the genome that might contribute to the genetic overlap. In a genome-wide association (GWA) study meta-analysis of ADHD and MDD, 14 shared genomic regions were identified, nine of which were not highlighted previously in individual ADHD or MDD GWA studies.

Finally, the impact of ADHD on depression clinical presentation was investigated. In a prospective cohort of recurrently depressed adults, ADHD was associated with features of depression presentation, including an earlier age at onset and greater impairment, recurrence, odds of self-harm or suicide attempt and taking non-standard depression medication.

Statements and Declarations

Statement 1

This thesis is being submitted in partial fulfilment of the requirements for the degree of PhD.

Statement 2

This work has not been submitted in substance for any other degree or award at this or any other university or place of learning, nor is it being submitted concurrently for any other degree or award (outside of any formal collaboration agreement between the University and a partner organisation).

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This thesis is the result of my own independent work, except where otherwise stated, and the views expressed are my own. Other sources are acknowledged by explicit references. The thesis has not been edited by a third party beyond what is permitted by Cardiff University's Use of Third Party Editors by Research Degree Students Procedure.

Signed:

A handwritten signature in black ink, appearing to read 'Russell', with a long horizontal flourish underneath.

(candidate)

Date: 17/12/20

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Related publications to which I have contributed

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Contents

Chapter 1: General Introduction.....	1
1.1. Overview	1
1.2. Definitions and Diagnoses.....	2
1.3. Prevalence and Lifetime Trends.....	7
1.4. The Association of ADHD and Depression and Potential Contributing Factors .	8
1.4.1. School Attainment and Friendships.....	10
1.4.2. Parent-Child Relationships	12
1.4.3. Genetic Overlap	13
1.4.4. The Effect of ADHD on the Clinical Presentation of Depression	17
1.5. Limitations of the Existing Literature.....	19
1.6. Thesis Aims and Hypotheses.....	20
Chapter 2: A longitudinal study of the role of peer relationships and academic attainment in the prospective association between childhood ADHD and adolescent depression.....	22
2.1. Introduction	23
2.1.1. Peer Relationships and Academic Attainment as Mediators	23
2.1.2. The Current Study.....	25
2.2. Methods	26
2.2.1. Sample	26
2.2.2. Measures.....	26
2.2.3. Data Analysis	28
2.2.4. Sensitivity Analyses.....	30
2.2.5. Missing Data.....	31
2.3. Results	32
2.3.1. Descriptive Statistics.....	32
2.3.2. Association between Childhood ADHD and Adolescent Depression	34
2.3.3. The Role of Peer Relationships and Academic Attainment in the Association between ADHD and Depression	36
2.3.4. Inverse Probability Weighting (IPW).....	38
2.4. Discussion.....	38
2.4.1. Mediation of the Association of ADHD and Depression via Peer Relationships	39

2.4.2. Mediation of the Association of ADHD and Depression via Academic Attainment	40
2.4.3. Limitations.....	41
2.4.4. Strengths	43
2.4.5. Implications.....	43
2.4.6. Conclusions	44
Chapter 3: A longitudinal study of the role of different features of friendships and the parent-child relationship in the association between ADHD and depression.....	45
3.1. Introduction	46
3.1.1. Friendships	46
3.1.2. The Context of School.....	47
3.1.3. Parent-Child Relationships	47
3.1.4. The Current Study.....	48
3.2. Methods	48
3.2.1. Sample	48
3.2.2. Measures.....	49
3.2.3. Data Analysis	52
3.2.4. Missing Data.....	53
3.3. Results	54
3.3.1. Descriptive Statistics.....	54
3.3.2. Associations of ADHD, Features of Friendship and Depression	56
3.3.3. Indirect Effects via Friendship in the Association between ADHD and Depression.....	58
3.3.4. Moderation of Indirect Effects by Parent-Child Relationships.....	61
3.4. Discussion.....	65
3.4.1. Mediation of the Association of ADHD and Depression via Friendship Quality.....	65
3.4.2. Moderation by Parent-Child Relationship Quality of Mediated Effects via Friendship Quality	66
3.4.3. Limitations.....	68
3.4.4. Strengths	69
3.4.5. Implications.....	69
3.4.6. Conclusion.....	69
Chapter 4: A genome-wide association study meta-analysis investigating regions of shared genetic association in ADHD and MDD	71

4.1. Introduction	73
4.1.1. The Genetic Overlap of ADHD and MDD	73
4.1.2. The Current Study.....	74
4.2. Methods	75
4.2.1. Samples and Measures.....	75
4.2.2. Analysis.....	76
4.3. Results	79
4.3.1. SNP Heritability and Genetic Correlation	79
4.3.2. Identification of Regions Showing Evidence of Common Association	80
4.4. Discussion.....	90
4.4.1. Key Findings	90
4.4.2. Associations with Additional Genome Wide Association Study Phenotypes	92
4.4.3. Limitations.....	93
4.4.4. Strengths	95
4.4.5. Future Research Directions and Implications	95
4.4.6. Conclusions	96
Chapter 5: A study of ADHD in adults with recurrent depression and impact on clinical presentation of depression.....	97
5.1. Introduction	98
5.1.1. ADHD and Depression Presentation	98
5.1.2. Neurodevelopmental Contribution to Depression	99
5.1.3. The Current Study.....	99
5.2. Method.....	100
5.2.1. Sample	100
5.2.2. Overview of Assessment Procedure	102
5.2.3. Measures.....	103
5.2.4. Analysis.....	106
5.2.5. Sensitivity Analysis.....	106
5.2.6. Missing Data.....	106
5.3. Results	107
5.3.1. Descriptive Statistics.....	107
5.3.2. Association between ADHD and Clinical Features of Depression	109
5.3.3. Sensitivity Analysis and Inverse Probability Weighting.....	112

5.4. Discussion.....	112
5.4.1. Key Findings	112
5.4.2. Limitations.....	114
5.4.3. Strengths	116
5.4.4. Implications.....	116
5.4.5. Conclusions	116
Chapter 6: General Discussion	117
6.1. Overview	117
6.2. Summary and Interpretation of Findings	118
6.2.1. Academic Attainment and Peer Relationships.....	118
6.2.2. Features of Friendship and The Parent-Child Relationship.....	120
6.2.3. Genetic Overlap	123
6.2.4. The Impact of ADHD on Depression Clinical Phenotype	126
6.3. Limitations.....	128
6.4. Strengths	133
6.5. Implications.....	133
6.6. Future Directions	135
6.7. Conclusions	136
References	137
Appendices.....	171

Index of Tables

Table 2.1.	Correlation matrix of analysis variables: ADHD symptoms, peer problems, GCSE results and depressive symptoms	33
Table 2.2.	Association between childhood ADHD and late adolescent depression	35
Table 2.3.	Mediation of the association between childhood ADHD and adolescent depression by academic attainment and peer relationship problems	37
Table 3.1.	Descriptive statistics for ADHD, depression and features of friendship	55
Table 3.2.	Associations of ADHD symptoms, friendship variables and depressive symptoms	57
Table 3.3.	Indirect effects via friendship quality in the association of ADHD and depressive symptoms in a multiple mediator model	59
Table 3.4.	Moderation by gender of indirect effects via friendship quality	60
Table 3.5.	Moderation by parental warmth and hostility of indirect effects via friendship quality	62
Table 4.1.	Summary of genome-wide significant associations for SNPs identified as contributing to both ADHD and MDD	81
Table 5.1.	Descriptive statistics for ADHD symptoms and features of depression presentation and management	108
Table 5.2.	Association of adult ADHD symptoms (continuous and dichotomised) and clinical features of depression	110
Table 5.3.	Categories of psychiatric medications reported at assessment wave 4 of the EPAD study	111

Index of Figures

Figure 1.1.	Diagnostic criteria for DSM-5 combined attention deficit/hyperactivity disorder (ADHD)	5
Figure 1.2.	Diagnostic criteria for DSM-5 major depressive disorder (MDD)	6
Figure 2.1.	Hypothesised mediation model for the role of academic attainment and peer relationship problems in the link between ADHD and depression	25
Figure 3.1.	Moderation by parent-child relationship quality of mediation by friendship quality	63
Figure 3.2.	Moderated mediation model depicting the role of parent-child relationship quality and friendship quality in the link between ADHD and depression	64
Figure 4.1.	Miami plot showing the association of SNP rs12658032 with ADHD compared to MDD	83
Figure 4.2.	Forest plot showing additional associations of rs12658032	84
Figure 4.3.	Miami plot showing the association of SNP rs8084351 with ADHD compared to MDD	87
Figure 4.4.	Forest plot showing additional associations of rs8084351	88
Figure 4.5.	Locus plot showing the association of SNP rs8084351 with the meta-analysis	89
Figure 5.1.	Study design and participation rates across assessment waves of the EPAD study	101

Chapter 1: General Introduction

1.1. Overview

Attention deficit/hyperactivity disorder (ADHD) is a DSM-5 (American Psychiatric Association, 2013) defined neurodevelopmental disorder that typically onsets in childhood, characterised by symptoms of hyperactivity, impulsivity and inattention (Thapar & Cooper, 2016). Depression is a leading cause of disability worldwide (Vos et al., 2017) that is generally characterised by symptoms such as low mood, a loss of interest or pleasure (anhedonia) and decreased energy or fatigue (American Psychiatric Association, 2013). The rate of depression typically increases in adolescence and peaks in early adulthood (Avenevoli, Swendsen, He, Burstein, & Merikangas, 2015; Kessler, Berglund, et al., 2005; Merikangas et al., 2010). There is growing evidence that ADHD is associated with depression, particularly from cross-sectional studies, though the prospective association and the mechanisms explaining this link are unclear (Angold, Costello, & Erkanli, 1999; Meinzer, Pettit, & Viswesvaran, 2014). Identifying factors that might contribute to the association of ADHD and depression is important as it could highlight new ways of reducing the risk of depression in those with ADHD and potentially identify new targets for intervention.

The broad aims of this thesis were to: 1) Investigate the prospective association of ADHD and depression in childhood and adolescence from the perspective of both shared environmental and genetic risk. 2) Assess how ADHD might affect the clinical presentation of depression in adults. In this introductory chapter, I first discuss the definitions and epidemiology of ADHD and of depression, before discussing the link between ADHD and depression and possible factors underlying this. I then provide a detailed review of possible mediating factors underlying the link, the genetic overlap of ADHD and depression, and the evidence suggesting that ADHD may influence the clinical presentation of depression. The potential contributing factors to the association between ADHD and depression focussed upon in this thesis are academic attainment, peer relationships and friendships, parent-child relationship quality, shared genetic risk and the potential

effect of ADHD on depression presentation. Finally, the gaps in the current literature are outlined and I specify the aims and hypotheses of this thesis.

1.2. Definitions and Diagnoses

ADHD is a DSM-5 defined neurodevelopmental disorder (American Psychiatric Association, 2013). Like other neurodevelopmental disorders, ADHD generally onsets early in life, has a course that is stable over time rather than remitting and relapsing, and is often associated with early cognitive difficulties (Thapar, Cooper, & Rutter, 2017). For a DSM-5 diagnosis of ADHD, symptoms that are not consistent with the developmental level of the child across three central domains – hyperactivity, impulsivity and inattention – must be reported as having onset before the age of 12 and having an effect on functioning in multiple contexts, for example, at school and home (Figure 1.1). Examples of these symptoms include difficulty sitting still (a hyperactivity symptom), interrupting others without prior thought (an impulsivity symptom) and difficulty focussing on tasks until completion (an inattention symptom). As with many disorders, ADHD varies in its symptom presentation, degree of associated impairment and functional outcomes (Sonuga-Barke & Taylor, 2015). The DSM-5 describes different subtypes of ADHD diagnosis dependent on symptom presentation. If a child demonstrates symptoms across three domains of hyperactivity, impulsivity and inattention, they may be diagnosed with combined ADHD. Inattentive ADHD may be diagnosed if symptoms affect attention only. The hyperactive/impulsive ADHD subtype may be diagnosed if symptoms are only within the other domains. Very similar criteria are required for an ICD-11 ADHD diagnosis (World Health Organization, 2018), although in previous ICD editions the diagnosis has been named hyperkinetic disorder (e.g. ICD-10; World Health Organization, 1992). The ICD-10 hyperkinetic disorder diagnosis captures a more severely impaired group of individuals, as indicated by studies that indicate a lower prevalence of ICD-10 hyperkinetic disorder compared to DSM-IV ADHD within the same population (Thapar & Cooper, 2016).

Depression is a leading cause of disability worldwide (Vos et al., 2017). The term ‘depression’ in this thesis is used to refer to Major Depressive Disorder (MDD) as well as depressive symptoms. I first describe the clinical diagnosis of MDD and

then justify taking a dimensional approach to depression. The DSM-5 (American Psychiatric Association, 2013) defines two core symptoms of MDD; depressed mood and anhedonia – a diminished interest or pleasure in previously enjoyable activities. In order for a diagnosis of MDD to be made, one of these two core symptoms must be met and a total of at least 5 of the specified depressive symptoms, which occur most of the day nearly every day for at least a two-week period (Figure 1.2). Other depressive symptoms include a loss of energy, a change in appetite or weight, psychomotor agitation or retardation, sleep problems, difficulty concentrating, excessive feelings of worthlessness or guilt and suicidality. Very similar criteria are required for an ICD-11 depressive episode diagnosis although ICD considers decreased energy as an additional core depressive symptom (World Health Organization, 2018). One additional difference is that in the MDD DSM-5 criteria, depressed mood can present as irritable mood in children and adolescents (American Psychiatric Association, 2013). Studies have found substantial variation between individuals in the presentation of depression, including the age of onset, recurrence, chronicity and severity or associated functional impairment (Colman, Ploubidis, Wadsworth, Jones, & Croudace, 2007; Jaffee et al., 2002; Rice et al., 2019; Weissman et al., 1986).

In addition to disorder diagnoses, ADHD and depression have both been evidenced to act as continuous traits in the general population. Indeed, individuals with subthreshold ADHD whose symptoms do not meet diagnosis criteria are still at increased risk of adverse outcomes (Bussing, Mason, Bell, Porter, & Garvan, 2010). The same phenomenon has been observed for depression (Fergusson, Horwood, Ridder, & Beautrais, 2005). For instance, the number of depressive symptoms is associated with elevated risk for later “full-blown” depressive episodes that meet diagnostic criteria (Pickles et al., 2001). Subthreshold symptoms of various psychiatric disorders including ADHD and depression are also associated with functional impairment (Angold, Costello, Farmer, Burns, & Erkanli, 1999). This highlights the importance of investigating both ADHD and depression as continuous traits in population samples, in addition to studies of those with diagnoses in clinical samples, which capture more severely affected individuals.

It is important to note the overlap of symptoms in the diagnosis of depression and ADHD which could affect the observed association of these two disorders. Namely, difficulty concentrating and psychomotor agitation can be symptoms of both disorders, although for depression, the symptom of difficulties concentrating represents a change from usual functioning. However, ADHD and major depression comorbidity has been observed in a study of clinically referred children, clinically referred adults and non-referred adults even when accounting for these two overlapping symptoms, indicating that the comorbidity of ADHD and depression is not simply an artefact of sharing similar symptoms (Milberger, Biederman, Faraone, Murphy, & Tsuang, 1995).

Diagnostic criteria for DSM-5 combined Attention Deficit/Hyperactivity Disorder (ADHD)

6 of the 9 inattention symptoms plus 6 of the 9 hyperactivity/impulsivity symptoms¹ present for 6 months or more with some symptoms present before the age of 12. Symptoms cause impairment in social/academic/occupational/important areas of functioning. Symptoms are present in at least 2 settings (e.g. at home and at school) and are inconsistent with developmental level of child:

Symptoms of inattention:

- Lack of attention to detail or makes careless mistakes
- Difficulty sustaining attention in tasks or play
- Does not listen when spoken to
- Does not follow through on instructions
- Difficulty organising activities
- Avoids sustained mental effort
- Often loses things
- Easily distracted
- Forgetful in daily activities

Symptoms of hyperactivity/impulsivity:

- Fidgets or finds it difficult to sit still
- Often leaves seat
- Often restless or running around
- Excessively noisy
- Always on the go
- Talks excessively
- Blurts out answers
- Difficulty waiting their turn
- Often acts without thinking

1. For adults, 5 of 9 inattention symptoms and 5 of 9 hyperactivity/impulsivity symptoms are needed

Figure 1.1. Diagnostic criteria for DSM-5 combined attention deficit/hyperactivity disorder (ADHD)

Diagnostic criteria for DSM-5 Major Depressive Disorder (MDD)

5 or more of the following 9 symptoms¹ present over a 2-week period representing change from previous functioning. Symptoms cause distress or impairment in social/occupational/important areas of functioning. Symptoms are not due to another disorder or the effects of a drug:

- Depressed mood most of the day, nearly every day²
- Loss of interest or pleasure in all or most of activities most of the day, nearly every day
- Marked change in weight or appetite nearly every day³
- Insomnia or hypersomnia nearly every day
- Psychomotor agitation or retardation nearly every day (observed by others)
- Fatigue or loss of energy nearly every day
- Feelings of worthlessness or excessive/inappropriate guilt nearly every day
- Diminished ability to think/concentrate or indecisiveness nearly every day
- Recurrent thoughts of death, suicide ideation without specific plan, or suicide attempt or specific plan

1. At least one symptom must be depressed mood or loss of interest/enjoyment
2. Depressed mood can be irritable mood in children or adolescents
3. In children, appetite or weight change can be failing to make expected weight gain

Figure 1.2. Diagnostic criteria for DSM-5 major depressive disorder (MDD)

1.3. Prevalence and Lifetime Trends

As a diagnosis of DSM-5 ADHD requires an onset of symptoms before the age of 12, ADHD is typically considered as a childhood disorder, although there is increasing evidence of persistence of ADHD into adulthood, in addition to adult-onset cases of ADHD (Agnew-Blais et al., 2016; Kessler et al., 2010). In the general population of children worldwide, an estimated 3.4% have a diagnosis ADHD (Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015). Estimates for hyperkinetic disorder are lower, with a prevalence of 1.5% in the general population of UK children (Green, McGinnity, Meltzer, Ford, & Goodman, 2005). The adult ADHD prevalence estimate in population studies is generally around 2.5% (Simon, Czobor, Bálint, Mészáros, & Bitter, 2009), though studies often use differing approaches to defining an ADHD diagnosis which affects estimates. An excess of males cases compared to female cases of ADHD is a consistent finding in both epidemiological (male:female ratio of 3-4:1) and clinical samples (male:female ratio of 7-8:1) (Thapar & Cooper, 2016).

Depression on the other hand is not as common in childhood, with a prevalence estimate of approximately 0.9% in the general population of UK children (Green et al., 2005). However, rates of depression typically rise in adolescence (Avenevoli et al., 2015; Merikangas et al., 2010) and peak in early adulthood (Kessler, Berglund, et al., 2005; Thapar, Collishaw, Pine, & Thapar, 2012). The lifetime prevalence of MDD is estimated to be between 15 and 18% (Bromet et al., 2011; Kessler et al., 2003; Kessler, Berglund, et al., 2005). Similar to ADHD, there is a clear gender difference in depression prevalence. Almost twice as many females are affected than males (Malhi & Mann, 2018), which is first observed during adolescence (Thapar et al., 2012). The course of major depression across the lifetime varies greatly between individuals with some individuals recovering, others experiencing multiple episodes over time, and some experiencing more chronic than episodic depression (Malhi & Mann, 2018). However, the course and prognosis of depression may vary according to the age at which it onsets, with evidence that early or adolescent onset depression may be particularly persistent over time compared to adult onset depression (Klein et al., 1999).

1.4. The Association of ADHD and Depression and Potential Contributing Factors

There is growing evidence to suggest that ADHD is associated with increased risk of subsequent depression. ADHD and depression demonstrate high levels of comorbidity or contemporaneous association in community samples of children (Angold, Costello, & Erkanli, 1999) and the prospective association of ADHD and subsequent depression has been observed in both clinical (Biederman et al., 2008; Chronis-Tuscano et al., 2010; Gundel, Pedersen, Munk-Olsen, & Dalsgaard, 2018) and population samples (Eyre et al., 2019; Fergusson, Boden, & Horwood, 2010). In addition, there is some evidence to suggest that young people with ADHD are at an increased risk of depression with an earlier age of onset, increased chronicity and a higher risk of suicide compared to those with depression alone (Biederman et al., 2008). A meta-analysis of studies investigating the association of ADHD and depression found that the two disorders are positively related (Meinzer et al., 2014). However, the meta-analysis found that the majority of studies used clinical samples, with reliable evidence of an association coming from cross-sectional but not longitudinal designs (Meinzer et al., 2014). This highlights the need for further testing of the prospective association of ADHD and depression, particularly in population samples. As ADHD and depression have different risk periods, it is also important to test their association using longitudinal follow up that includes the risk periods of childhood and adolescence/young adulthood. The use of population samples is important in producing findings more representative of the general population, as it includes individuals across the spectrum of depression symptom severity and not just those at the severe end, thus avoiding the selection bias that can affect clinical studies. The meta-analysis also highlighted that the potential mechanisms explaining the association of ADHD and depression are unclear (Meinzer et al., 2014). In order to investigate risk factors that might contribute to the pathway from ADHD to subsequent depression, it is important to use prospective follow-up, allowing for investigation of how one disorder may lead to another over time.

The prospective association of ADHD and depression is an example of heterotypic continuity, whereby one disorder earlier in life subsequently leads to increased risk of a different disorder (Rutter, Kim-Cohen, & Maughan, 2006). Possible

explanations underlying such associations include a direct effect of ADHD on depression risk in addition to a combination of shared environmental and genetic risks (Caron & Rutter, 1991). Indeed, ADHD and depression have been evidenced to be genetically correlated (Demontis et al., 2019; P. H. Lee et al., 2019; Wray et al., 2018). There are also several areas of life and functioning that may be impacted by ADHD and thus increase risk of subsequent depression. These include performance at school and friendship problems which have been shown to be associated with ADHD and depression in separate studies (Birchwood & Daley, 2012; Blachman & Hinshaw, 2002; Goodyer, Wright, & Altham, 1989; Marton, Wiener, Rogers, & Moore, 2015; Riglin, Petrides, Frederickson, & Rice, 2014). The parent-child relationship might also impact on children's friendships, as parents have been found to influence friendships in children with ADHD (Mikami, Jack, Emeh, & Stephens, 2010) and to compensate for the negative impact of a lack of friends on emotional adjustment in school children (Stocker, 1994). The observed genetic overlap of ADHD and depression is also likely to play an important role (e.g. Demontis et al., 2019; Wray et al., 2018), but how genetic overlap might contribute to the association of ADHD and depression is still unclear (Faraone & Larsson, 2019), including which regions of the genome and associated mechanisms might be important. In addition to potential explanatory factors, it is also important to consider the potential effect of ADHD on the phenotype of later depression, as there is some evidence to suggest that children with ADHD are more likely to experience an earlier-onset and more chronic depression with an increased risk of suicide than those without ADHD (e.g. Biederman et al., 2008).

In this thesis, I aim to address the need for further investigation of the mechanisms explaining the association of ADHD and depression. In this thesis, I consider difficulties in achieving at school and with friendships as potential mediators of the association of ADHD and depression. I consider the quality of parent-child relationships as a potential moderator of any mediation via friendship difficulties. In addition, I investigate the genetic overlap of ADHD and depression. Finally, I consider the effect of ADHD on the clinical presentation of depression. In

the following sections of this chapter (1.4.1 – 1.4.4), I show the reasons for this by next reviewing the relevant literature in detail.

1.4.1. School Attainment and Friendships

A range of evidence suggests that school factors may be important to consider in the link between ADHD and depression. School life as well as school transitions may be particularly challenging for those with ADHD (Ford, 2020; Richardson et al., 2015). A systematic review of non-pharmacological interventions for ADHD in school settings found that performing well academically and interacting positively with peers were areas that were negatively impacted by the expectations of the classroom context not being a good “fit” for those with ADHD (Richardson et al., 2015). Indeed, educational performance has been shown to be reduced in those with ADHD (Birchwood & Daley, 2012; Kessler et al., 2014) and children with ADHD are likely to have fewer stable friendships (Blachman & Hinshaw, 2002; Marton et al., 2015). There is strong evidence that educational performance is associated with depression (Cole, 1990; Rahman et al., 2018), including in a meta-analysis (Riglin et al., 2014). Poor quality friendships may also increase the risk of depression in school-aged children (Goodyer et al., 1989).

School is an important context where young people’s academic performance is monitored and where they make most of their friends (Ng-Knight et al., 2019). The quality of school and children’s sense of school belonging can influence children’s psychological development and wellbeing (Pittman & Richmond, 2007; Ramberg, Brodin Låftman, Åkerstedt, & Modin, 2019; Rutter & Maughan, 2002; Shochet, Dadds, Ham, & Montague, 2006). The quality of the transition from primary to secondary school is also associated with emotional and behavioural outcomes (Rice, Frederickson, & Seymour, 2011; West, Sweeting, & Young, 2010). Many changes in the child’s life take place during the transition from primary to secondary school, including disruption of established friendships and the need to find new friends (Chung, Elias, & Schneider, 1998).

The psychological challenges of school life can be more successfully navigated when one has good friends (Hamm & Faircloth, 2005). Having good friendships

during school transitions can also protect against poor mental health (Ng-Knight et al., 2019). Friendships are an important source of social support, particularly in adolescence when individuals spend increasing amounts of time with their friends (Larson & Richards, 1991). Good social support can help to increase one's sense of self-esteem and act as a buffer against life stresses (H. Y. Lee et al., 2019; Rueger, Malecki, Pyun, Aycock, & Coyle, 2016). Friendships capture peer relationships on an individual level and can be considered to have 3 dimensions; presence of friends, characteristics of these friends and the quality of these friendships (Bukowski, Newcombe, & Hartup, 1996).

Difficulties in academic attainment and friendships may explain part of the link between ADHD and depression. Competency-based theories of depression in young people describe difficulties in these areas of school life as risk factors for depression (Cole, Martin, Powers, & Truglio, 1996; Patterson & Stoolmiller, 1991). One study tested this theory as an explanation of the association of conduct disorder and depression, finding that school competency contributed to the association between behavioural problems and later depressive symptoms (Capaldi, 1992). Similarly, the "stress generation" theory of depression (Hammen, 2006) describes at-risk individuals as being at increased risk of being exposed to stressful situations, in part due to the individual's own characteristics and the way in which this affects their environment and interpersonal interactions, which may increase vulnerability to later mental health problems. For instance, this might apply to children with ADHD being at increased risk of being exposed to stressful situations in various areas of life, including education and social interactions (Harpin, 2005). Rutter et al., (1997) described the two-way interaction between an individual and their environment as person-environment correlation, where individuals react to their environment and shape the experiences they are exposed to according to their traits and behaviour. However, there is minimal literature on academic attainment and friendship difficulties as potential mediators of the association between ADHD and depression (Meinzer et al., 2014). Studies conducted in samples of children with ADHD have highlighted the potential importance of social skills, school related functioning and peer rejection in predicting subsequent emotional problems or depressive symptoms

in this group (Eadeh et al., 2017; Mrug et al., 2012). I am aware of only two extant longitudinal studies testing mediation with time lags between exposure, mediator and outcome (Humphreys et al., 2013; Roy, Hartman, Veenstra, & Oldehinkel, 2015) – an important part of testing mediation (Selig & Preacher, 2009). The first study of 472 participants in a sample selected to over-represent the children of depressed mothers found that a latent variable capturing social functioning and peer acceptance mediated the association between attention problems at age 5 and depressive symptoms 15 years later, though general school functioning as measured by “academic stress” was not a mediator in their multiple mediator model (Humphreys et al., 2013). The second study was conducted in a longitudinal population sample of 728 participants aged approximately 13 at baseline, which found that children’s peer-nominations of who they disliked (i.e. peer rejection) and who they bullied mediated the association of attention problems and depression approximately 5 years later (Roy et al., 2015). While these aforementioned measures of peer acceptance and rejection can capture how popular or liked or disliked an individual is on a group level (e.g. in their class or school), measures that capture children’s friendships may be more predictive of later depression than measures of peer acceptance (Narr, Allen, Tan, & Loeb, 2019), and therefore are also important to examine in the relationship of ADHD and depression.

1.4.2. Parent-Child Relationships

In addition to friendships, a key source of social support for young people is their parents (Larson & Richards, 1991). It is possible that the quality of parent-child relationships could act as a moderator of any indirect effects via friendship in the association of ADHD and depression. The parent-child relationship has been found to protect against negative outcomes including depression in the presence of psychosocial adversity (Collishaw et al., 2016, 2007) and may be able to compensate for the adverse impact of a lack of good friendships on emotional functioning in school children (Stocker, 1994). In addition, the quality of the parent-child relationship may affect the quality of the child’s friendships (Deković & Meeus, 1997). This influence of parents on friendships might be particularly important in children with ADHD (Mikami et al., 2010), though there is limited research on the

role of the parent in studies of ADHD and friendship (Mikami, 2010). In addition, the majority of studies of the parent-child relationship focus on mothers, and thus less is known about the father-child relationship (Cabrera, Volling, & Barr, 2018). It is important that both mother and father-child relationships are investigated however, as mothers and fathers may influence their children's friendships in different ways. For instance, a previous study found that while mother's supportive and hostile behaviours were associated with their child's interaction style with peers, for fathers, it was their hostile behaviour and problem-solving behaviour that influenced the child's peer interactions (Flynn, Felmlee, Shu, & Conger, 2018). The parent-child relationship might be particularly important for children with ADHD as they are more likely to have more hostile parent-child relationships (Lifford, Harold, & Thapar, 2008).

The quality of parent-child relationships is also important to consider from the perspective of clinical intervention. Though the impact of friendships in ADHD and depression might be important and requires investigation, it might be the case that interventions with more focus on the parent-child relationship might be more successful than intervening on friendships alone. For instance, existing peer-focussed interventions focussed on peer acceptance and social skills have had limited success in children with ADHD so far (Mikami, 2010), but interventions focussed on the parent-child relationship or on friendships but with a parental component may be more promising for children with ADHD according to initial evidence (Abikoff et al., 2015; Gardner, Gerdes, & Weinberger, 2019). Improved parent-child relationships might have direct effects in reducing depression risk (Humphreys et al., 2013; Morgan, Brugha, Fryers, & Stewart-Brown, 2012), in addition to potentially compensating for friendship difficulties in the association between ADHD and depression as investigated in this thesis.

1.4.3. Genetic Overlap

It is also important to consider the genetic overlap of ADHD and depression. It would be incomplete not to investigate the genetic overlap given that both ADHD and depression have been evidenced to be heritable and familial (Flint & Kendler, 2014; Thapar, 2018), ADHD and depression are genetically correlated (Demontis et

al., 2019; Wray et al., 2018), and that person-environment correlation is likely to be involved in mediated pathways via school and friendships which may involve indirect genetic effects (Rutter et al., 1997). Evidence of the heritable and familial nature of ADHD and depression and evidence of their genetic overlap comes from several study designs – namely, family studies, genetically-informed designs (twin and adoption studies) and genome-wide association (GWA) studies. The findings of these studies are discussed below.

Meta-analyses of the family studies show that first degree relatives of those with MDD are at an elevated risk of having MDD themselves compared to first degree relatives of individuals without MDD (Rice, Harold, & Thapar, 2002; Sullivan, Neale, & Kendler, 2000). For instance, the offspring of depressed parents have been found to be at an increased risk of depression compared to the offspring of unaffected parents in “top-down” studies, and the parents of depressed children are at an increased risk of depression compared to parents of unaffected children in “bottom-up” studies (Rice et al., 2002). Additional studies since this meta-analysis have also found that offspring of parents with depression are more likely to have depression (Brennan, Hammen, Katz, & Le Brocque, 2002; Mars et al., 2012; Weissman et al., 2006). ADHD also runs in families (Thapar, 2018). Family studies show that the risk of ADHD in first degree relatives of children with ADHD is increased by between two and eight-fold compared to first degree relatives of unaffected individuals (Faraone et al., 2005). Several family studies have also provided evidence that ADHD and depression share common familial risk, whereby the first-degree relatives of those with ADHD are at increased risk of depression compared to relatives of controls (Biederman, Faraone, Keenan, & Tsuang, 1991; Biederman et al., 1987, 1986). More recently, intergenerational family studies have found that offspring of those with ADHD symptoms are at an increased risk of psychopathology including internalising problems (Agha, Zammit, Thapar, & Langley, 2013; Humphreys, Mehta, & Lee, 2012).

Genetically-informed designs such as twin or adoption studies are able to estimate the genetic and environmental contributions to a disorder. Twin studies show that MDD is a disorder of genetic and environmental origin, with a heritability

of around 37% (Kendler, Gardner, & Prescott, 2006; Sullivan et al., 2000). However, estimates depend upon the age group studied, with twin studies suggesting that depression is not heritable in childhood, but that genetic factors become important in adolescence, when heritability estimates are similar to adulthood (Rice, Harold, & Thapar, 2002a; Scourfield et al., 2003; Thapar & McGuffin, 1994). Potential explanations of this include gene-environment correlations becoming more important as children grow into adolescents and have more influence in shaping their own environment (Rice, Harold, & Thapar, 2003). Twin studies are conducted on siblings of the same generation, ruling out heterogeneity effects caused by differing generations. As a result, the twin design does not investigate the transmission of genetics from parent to offspring. For this, extended children of twins, adoption, or IVF studies are useful. However, until recently there were few high quality adoption studies of depression available, most of which found negligible genetic contributions to the intergenerational transmission of depression, as discussed in two review papers (Rice, 2010; Sullivan et al., 2000). Similarly, transmission of depression from parent to offspring has been found to remain even when accounting for shared genetics in children-of-twin studies (McAdams et al., 2015; Silberg, Maes, & Eaves, 2010; Singh et al., 2011) and in IVF studies (Harold et al., 2011; Lewis, Rice, Harold, Collishaw, & Thapar, 2011). More recently however, a national register-based adoption study of over 2.2 million offspring and their parents found that transmission of MDD from parent to offspring arose from genetics factors and the child rearing environment to an almost equal degree, with the two acting additively on risk of MDD in offspring (Kendler, Ohlsson, Sundquist, & Sundquist, 2018). Genetically-informed studies also support a genetic and environmental contribution to ADHD. Twin studies support a heritability of ADHD of around 76% (Chen et al., 2017; Faraone et al., 2005). Adoption studies show that biological relatives of those with ADHD are more likely to have ADHD than adoptive relatives (Faraone et al., 2005; Sprich, Biederman, Crawford, Mundy, & Faraone, 2000). Genetically-informed studies also support the genetic overlap of ADHD and depression. Twin studies report a co-heritability of 0.23 to 0.77 between ADHD and depression depending on sex and age (T. J. Chen et al., 2016; Cole, Ball, Martin,

Scourfield, & McGuffin, 2009; Lahey, Van Hulle, Singh, Waldman, & Rathouz, 2011; Rydell, Taylor, & Larsson, 2017; Schmitz & Mrazek, 2001)

For psychiatric disorders, molecular genetic findings of the last decade come largely from GWA studies – the result of rapid development of genotyping technology in recent years. GWA studies examine common genetic variants across the whole genome in a hypothesis-free approach and allele frequencies in affected and non-affected individuals are compared (Visscher et al., 2017). The genetic variants reported by GWA studies are referred to as Single Nucleotide Polymorphisms (SNPs) – genetic variants that affect a single base and are common in the population (have a minor allele frequency > 1%). The most recent GWA study of MDD found that 44 independent SNPs were associated with MDD at a genome-wide significant level ($p < 5 \times 10^{-8}$) (Wray et al., 2018). MDD SNP heritability (the heritability of a disorder that is attributable to SNPs) on the liability scale was estimated at 0.087 (SE = 0.004). The most recent GWA study of ADHD found that 12 independent SNPs were associated with ADHD at a genome-wide significant level (Demontis et al., 2019). The estimated SNP heritability on the liability scale was 0.216 (SE=0.014). These are the most recent and thus well-powered estimates, but as GWA studies rapidly develop and increase in sample size, more SNPs are likely to be discovered (Visscher et al., 2017). Both of these GWA studies have identified a genetic correlation of $r_g=0.42$ between ADHD and depression (Demontis et al., 2019; Wray et al., 2018). Studies have found that polygenic scores derived from the ADHD GWA study positively predict depression symptoms in a twin sample of children (Brikell et al., 2018), depression symptoms in an adolescent population sample (Rice et al., 2019) and depression diagnosis in an adult population sample (Du Rietz et al., 2018). In line with these findings, the most recent genome wide meta-analysis across 8 psychiatric disorders by the Cross Disorder Group of the Psychiatric Genomics Consortium (PGC) (P. H. Lee et al., 2019) reported a similar genetic correlation between ADHD and MDD ($r_g=0.44$). Though the literature supports a genetic overlap of ADHD and depression, there has been minimal insight thus far into the genes or variants that might contribute to this overlap. GWA study meta-analysis focussed on ADHD and depression only, rather than multiple disorders (e.g. Lee et al., 2019), is

one approach that may advance understanding of this, whereby the results of the ADHD and MDD GWA studies are compared and thus variants potentially contributing to both disorders are detected. The investigation of multiple disorders in Lee et al., (2019) requires evidence across multiple GWA studies and therefore might not detect regions impacting ADHD and MDD only.

It is important to note that genetic overlap has been observed across multiple psychiatric disorders in addition to ADHD and depression (e.g. Lee et al., 2019) in a phenomenon referred to as pleiotropy, which can be vertical or horizontal (van Rheenen, Peyrot, Schork, Lee, & Wray, 2019). Horizontal pleiotropy describes a scenario in which two or more different disorders or phenotypes are the result of the same genetic variants. Vertical pleiotropy on the other hand, is when genetic variants lead to one phenotype which in turn leads to another phenotype in a causal cascade. It is likely that the genetic origins of some psychiatric disorders transcend diagnostic boundaries.

Findings on genetic aetiology may vary depending on the clinical presentation of ADHD and depression, or by how the phenotypes are defined. For example, Chen et al., (2017) found that persistence of ADHD into adulthood was associated with greater familial aggregation of ADHD. Depression that onsets earlier and is more persistent may be more associated with higher genetic risk of psychiatric disorders with a neurodevelopmental component (ADHD and schizophrenia) compared with depression that onsets later in life (Rice et al., 2019). More strictly defined clinical depression may also have a different genetic aetiology to a more broadly defined depressive phenotype (Howard et al., 2018).

1.4.4. The Effect of ADHD on the Clinical Presentation of Depression

In addition to investigating factors that might explain the association of ADHD and depression, it is important to consider how having ADHD might affect the clinical presentation of depression. Depression is highly heterogeneous in its clinical presentation (Fried & Nesse, 2015; Kendler et al., 1996; Weissman et al., 1986). Comorbid ADHD symptoms may be one explanation of this observed phenotypic heterogeneity, though the evidence supporting this is not conclusive. There is some

evidence from a follow-up of a US clinical cohort that children with ADHD are at an increased risk of more severe depression-related outcomes, including earlier-onset and more chronic depression, hospitalisation and suicide, compared to those with depression alone (Biederman et al., 2008). A study in a longitudinal population sample also found that ADHD in childhood is associated with an increased risk of recurrent depression in young adulthood (Riglin et al., 2020). There is strong evidence that ADHD is associated with increased risk of self-harm and suicidal behaviours as shown in a meta-analysis (Septier, Stordeur, Zhang, Delorme, & Cortese, 2019), and this association appears to remain even when adjusting for comorbid mental health disorders including MDD (Ljung, Chen, Lichtenstein, & Larsson, 2014). This apparent increased risk of poor depression-related outcomes in those with ADHD may be driven by ADHD negatively affecting successful depression treatment response, as suggested by preliminary evidence of increased antidepressant resistance in those with ADHD and depression compared to those with depression alone (M.H. Chen et al., 2016). Alternatively, these observations may be driven by an effect of ADHD on the clinical phenotype and thus heterogeneity of depression. It is also important to note that children with ADHD have been found to under-report their depressive symptoms relative to parent reports, which is the opposite to what is observed in the general population of young people, suggesting that young people with ADHD may have less insight into their depressive symptoms (Fraser et al., 2018).

There is a possibility that some cases of depression fall into a more neurodevelopmental subgroup. For instance, longitudinal studies of young people have found an earlier onset, more chronic class of depression which is associated with increased neurodevelopmental traits (Jaffee et al., 2002; Rice et al., 2019; van Os, Jones, Lewis, Wadsworth, & Murray, 1997), including ADHD symptoms and genetic risk (Rice et al., 2019), compared to later onset depression. One study of adults found that the risk of probable ADHD was higher when participants reported an earlier age at onset of depression and had longer depressive episodes in a 4-year follow-up of a case-control sample (Bron et al., 2016). There is emerging evidence that suggests underlying neurodevelopmental disorders such as ADHD may be

masked by depression in recurrently depressed adults and thus missed in clinical practice (McIntosh et al., 2009). However, the effect of ADHD on different clinical features of depression, particularly in middle adulthood, is not clear.

1.5. Limitations of the Existing Literature

In summary, there is a growing body of research supporting the association of ADHD and depression, largely in clinical samples and/or cross-sectional studies. However, the prospective association of ADHD and depression in important vulnerability periods for ADHD and depression (childhood and adolescence, respectively) and the mechanisms explaining this are unclear (Meinzer et al., 2014). It seems likely that this association involves a combination of environmental and genetic factors (T. J. Chen et al., 2016; Cole et al., 2009; Rydell, Taylor, & Larsson, 2017; Schmitz & Mrazek, 2001). Such factors may include academic attainment and friendships, which are associated with both ADHD and with depression separately (Birchwood & Daley, 2012; Blachman & Hinshaw, 2002; D. A. Cole, 1990; D. A. Cole et al., 1996; Goodyer et al., 1989; Kessler et al., 2014; Patterson & Stoolmiller, 1991; Rahman et al., 2018; Riglin et al., 2014). Although social functioning and peer acceptance at school and bullying have been found to mediate the longitudinal association of ADHD and depression symptoms (Humphreys et al., 2013; Roy et al., 2015), the wider contribution of relationships with friends and peers is not clear. Nor is the role of the different features of friendship including having friends, the quality of these friendships and the characteristic of the friendship group (Bukowski et al., 1996; Mikami, 2010). The quality of relationships at home, namely the parent-child relationship, in addition to school is also important to consider as it might moderate the effects of friendship difficulties. However, the interaction of friendships and the parent-child relationship is often not considered in studies of ADHD and friendship, particularly with fathers (Cabrera et al., 2018; Mikami, 2010). The genetic overlap of ADHD and depression also requires more detailed molecular investigation because the regions of the genome that might be responsible for the genetic correlation of ADHD and depression and the way in which the genetic variants might operate biologically is not clear. Finally, as well as investigating factors that might mediate the association of ADHD and depression, it is important to investigate how the clinical

presentation of depression may be affected by ADHD. Though there is some evidence in children and young people that ADHD is associated with an earlier onset and more chronic depression (Biederman et al., 2008; Rice et al., 2019; Riglin et al., 2020), the way in which ADHD affects various clinical features of depression, particularly in adulthood, is not known.

1.6. Thesis Aims and Hypotheses

The overall aim of this thesis was to investigate the relationship between ADHD and depression, to investigate the role of different potentially contributing factors that might account for part of this relationship, and to examine how the clinical phenotype of depression is affected by ADHD. These aims are addressed in four empirical study chapters.

The aim of the first study was to investigate whether ADHD is prospectively associated with depression over a 10-year period that captures important risk periods for ADHD and depression (childhood and adolescence, respectively) in a population sample. The secondary aim was to investigate whether school attainment and peer relationships explain part of this prospective association between ADHD at age 7 and depression symptoms 10 years later. This was conducted in the Avon Longitudinal Study of Parents and Children (ALSPAC; Boyd et al., 2013) – a prospective, longitudinal UK population sample.

The aim of the second study was to investigate peer relationships in more detail by testing which components of friendship may be important in the association of ADHD and depression symptoms. Whether the parent-child relationship moderated any observed indirect effects via friendship was also tested. This was conducted in the School Transition Adjustment Research Study (STARS; Ng-Knight et al., 2016) – a sample of young people recruited from schools in the UK.

The aim of the third study was to investigate the genetic correlation of ADHD and depression by identifying the specific regions of the genome that might contribute to the genetic overlap. This was done by conducting an adapted GWA study meta-analysis of the most recent and thus well-powered GWA studies of ADHD

and MDD (Demontis et al., 2019; Wray et al., 2018), followed by annotation methods to investigate the biological functions of any shared variants identified.

The aim of the fourth study was to investigate the rate of ADHD symptoms in recurrently depressed adults and to investigate the impact of ADHD symptoms on the clinical presentation of depression. This was investigated in the Early Prediction of Adolescent Depression study (EPAD; Mars et al., 2012) –a prospective, longitudinal study of recurrently depressed adults based in the UK.

The hypotheses were:

- 1) Academic attainment and peer relationship difficulties will mediate the prospective association between ADHD and depression, whereby ADHD symptoms are associated with reduced academic attainment and increased peer problems, which in turn is associated with increased depression risk.
- 2) Specific aspects of friendship including having less stable, lower quality friendships and friendships with more deviant peers will mediate part of the association between ADHD and depression, but a good parent-child relationship will be able to buffer to an extent against this mediated effect.
- 3) GWA study meta-analysis will reveal specific regions of genomic overlap between ADHD and depression. These regions might have relevant biological roles through affecting gene expression or demonstrate associations with relevant traits that could act as shared risk factors for ADHD and depression, for example.
- 4) In adults with recurrent depression, increased ADHD symptoms will be observed, which will be associated with specific clinical features of depression that have been associated with neurodevelopmental phenotypes and genetic risk in previous studies, such as early age of onset, increased recurrence and increased impairment.

Chapter 2: A longitudinal study of the role of peer relationships and academic attainment in the prospective association between childhood ADHD and adolescent depression

This chapter is an amended version of a published paper:

Powell, V., Riglin, L., Hammerton, G., Eyre, O., Martin, J., Anney, R., Thapar, A., & Rice, F. (2020) What explains the link between childhood ADHD and adolescent depression? Investigating the role of peer relationships and academic attainment.

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There is growing evidence of an association between ADHD and depression, but the prospective relationship and mechanisms underlying this are not clear. The aim of this study was to investigate the prospective association between ADHD and depression and to test academic attainment and peer relationship difficulties as potential mediators of this association. Analyses were conducted in 2161 individuals from a longitudinal UK-based population cohort who had data on parent-reported ADHD symptoms in childhood (7.5 years), parent-reported peer problems (16 years), academic attainment (16 years) and self-reported depressive symptoms in late adolescence (17.5 years). Childhood ADHD symptoms were positively associated with depressive symptoms. Mediation analysis found that this association was mediated in part by peer relationship problems and academic attainment.

2.1. Introduction

As discussed in chapter 1, there is increasing evidence that ADHD is associated with an increased risk of subsequent depression. The majority of reliable evidence of the association between ADHD and depression comes from clinical samples or cross-sectional study designs (Meinzer et al., 2014), highlighting the need to test the longitudinal association of ADHD and depression in population samples. Population-based studies are useful for investigating the longitudinal association between ADHD and depression as there is good evidence that both ADHD and depression behave as continuously distributed risks in the population, in addition to being viewed as diagnostic categories (Bussing et al., 2010; Fergusson et al., 2005). One such population study found that 50% of those meeting clinical criteria for ADHD in adolescence (age 14 to 16) had major depression *or* an anxiety disorder by the age of 18 to 25, compared to 35% in those without ADHD (Fergusson et al., 2010). As ADHD typically onsets in childhood (Thapar et al., 2017) and the incidence of depression rises markedly in adolescence (Kessler et al., 2005; Thapar et al., 2012), it is also important to test the association of ADHD and depression in longitudinal studies that cover these time periods. In addition, while there is growing evidence of a prospective relationship between ADHD and depression, the underlying mechanisms explaining this association are unclear. Further studies are needed to understand *how* childhood ADHD increases depression risk to help inform interventions to support young people with ADHD. Thus, the study presented in the current chapter sought to build on the existing literature by testing whether peer relationships and academic attainment mediated the association of childhood ADHD and adolescent depression in a longitudinal population sample. The existing literature relating to the role of peer relationships and academic attainment in the association between ADHD and depression is outlined below, before detailing the current study aims.

2.1.1. Peer Relationships and Academic Attainment as Mediators

Two factors that might contribute to the link between ADHD and depression are difficulties in peer relationships and academic attainment, as discussed in

chapter 1. Children with ADHD are more likely to have difficulties with peers (Finsaas et al., 2018; Mikami, 2010), and peer relationship difficulties have been found to increase depression risk in separate studies (Cole, 1990; Goodyer et al., 1989; Vaananen, Marttunen, Helminen, & Kaltiala-Heino, 2014). Studies have also shown that ADHD is associated with difficulties in academic attainment and other aspects of educational performance including general cognitive ability and the ability to behave in a way that fits the expectations of a typical classroom setting (Birchwood & Daley, 2012; Kessler et al., 2014; Richardson et al., 2015). Academic difficulties are also associated with depression in separate studies (Cole, 1990; Glaser et al., 2011; Rahman et al., 2018; Riglin et al., 2015, 2014). Previous studies have shown that a child's sense of competency or failure with peers and in academic domains may be important in conferring later depression risk (Capaldi, 1992; Cole, Martin, & Powers, 1997; Patterson & Stoolmiller, 1991). Therefore, difficulties with peer relationships and academic attainment could act as mediators of the link between ADHD and depression, as demonstrated in Figure 2.1. A meta-analysis of studies of the association between ADHD and depression found that there are few mechanistic studies (Meinzer et al., 2014). Two studies to date have tested mediation using longitudinal data with time lags between exposure, mediator and outcome (Humphreys et al., 2013; Roy et al., 2015), which is an important part of testing mediation (Selig & Preacher, 2009). One found that a latent variable capturing social functioning and popularity mediated the association between attention problems at age 5 and depressive symptoms 15 years later in a sample selected to over-represent children of depressed mothers (n=472) (Humphreys et al., 2013). In the same study, child perceptions of general school functioning measured as 'academic stress' did not act as a mediator in the multiple mediator model, though it was correlated with both attention problems and depressive symptoms. The second study examined peer victimization and asked children who they disliked and who they bullied in their class, finding that this mediated 7% of the relationship between attention problems at approximately 13 years old and depression approximately 5 years later in a longitudinal population sample (n=728) (Roy et al., 2015). Therefore, these two longitudinal mediation studies highlight the need for studies examining additional aspects of peer relationships and the role of objective academic attainment in the

prospective association of ADHD and depression. More generally, studies spanning childhood and adolescence that investigate the potential underlying mechanisms in the association between ADHD and depression are needed.

2.1.2. The Current Study

In the present study, peer relationships and academic attainment were tested as mediators of the association between childhood ADHD and adolescent depressive symptoms in a large prospective population study spanning 10 years (Fig. 1). The hypotheses were that childhood ADHD would be positively associated with adolescent depression, and that part of this association would be mediated by difficulties with peer relationships and academic attainment.

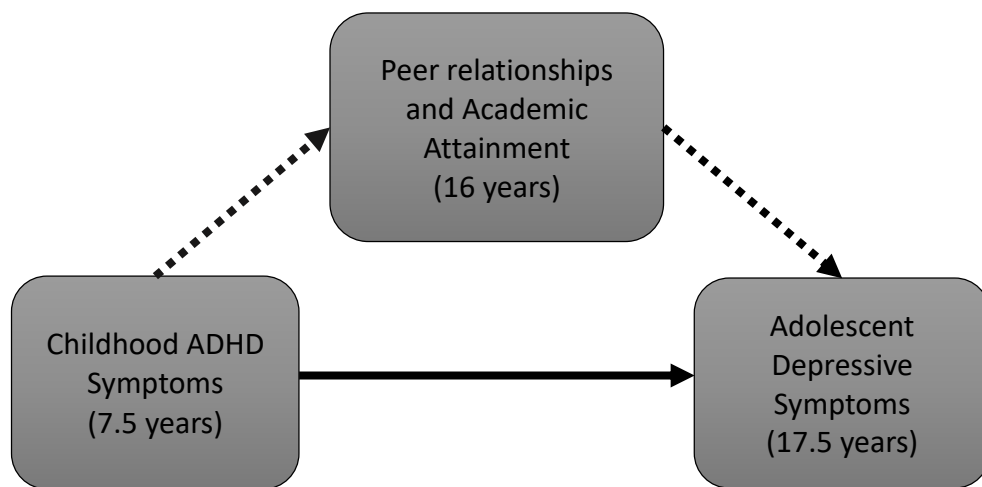


Figure 2.1. Hypothesised mediation model for the role of academic attainment and peer relationship problems in the link between ADHD and depression. The hypothesized mediation model was that part of the association between childhood ADHD and adolescent depression would be explained by peer relationships and academic attainment. *ADHD* attention deficit/hyperactivity disorder

2.2. Methods

2.2.1. Sample

The sample was derived from the Avon Longitudinal Study of Parents and Children (ALSPAC) (<http://www.alspac.bris.ac.uk>) – a large prospective birth-cohort in South-West England. Pregnant women in Bristol with a due date between April 1991 and December 1992 were approached to participate. This resulted in 14,541 pregnancies enrolled in the study and 13,988 children alive at 1 year. The children's development has been followed regularly since birth largely via questionnaires and face-to-face assessments. The methodology and sample are described elsewhere, but the population is generally representative of UK children (Boyd et al., 2013; Fraser et al., 2013). Please note the ALSPAC website contains details of all available data through a searchable data dictionary (<http://www.bristol.ac.uk/alspac/researchers/our-data/>). This study is based on a primary sample of 2950 participants for whom data were available on childhood ADHD symptoms at age 7.5 years, depression symptoms in late adolescence at age 17.5 years and covariates (socioeconomic status, maternal age at birth, sex and childhood emotional problems). Mediation analyses included 2161 participants where data were additionally available on peer problems and academic attainment at 16 years. Ethical approval was obtained from ALSPAC Law and Ethics Committee and Local Research Ethics Committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of ALSPAC Ethics and Law Committee at the time.

2.2.2. Measures

Childhood ADHD Symptoms

Childhood ADHD symptoms were measured using mother-rated DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) (American Psychiatric Association, 1994) ADHD symptoms at 7 years and 7 months measured with the Development and Well-Being Assessment (DAWBA) (Goodman, Ford, Richards, Gatward, & Meltzer, 2000). This was the main exposure variable in the study. The DAWBA is a well validated, reliable tool which can be used to derive DSM-

IV diagnoses in children and adolescents via computer algorithms and clinical raters. Symptoms of ADHD include inattention, for example “often forgetful in daily activities”, hyperactivity such as “often fidgets with hands or feet” and impulsivity such as “often interrupts or intrudes on others” that are inconsistent with developmental level and have been present for 6 months or more, with some symptoms causing impairment in multiple domains before age 7. Symptoms were classed as present if mothers reported them occurring in their child “a little” or “a lot” more than in other children to create a count of ADHD symptoms ranging from 0 to 18. DSM-IV (American Psychiatric Association, 1994) diagnosis of ADHD derived from the DAWBA was used in a sensitivity analysis.

Late Adolescent Depression

Continuous and binary depression variables were used as the outcome in this study to give an indication of the impact of ADHD on continuous depression symptoms and on the odds of reaching a clinical cut-point for depression. For the continuous outcome, ‘depressive symptom score’ was indicated by the self-rated Short Moods and Feelings Questionnaire (SMFQ) at 17 years and 6 months. The SMFQ is a 13-item questionnaire designed to cover core depressive symptomology with a 3-point response scale for each question of ‘not true’ (0), ‘somewhat true’ (1) or ‘true’ (2) summed to generate a maximum score of 26 (Angold et al., 1995). For the binary outcome, those scoring ≥ 12 on the SMFQ were classed as having ‘clinically significant depressive symptoms’ as recommended previously (Thabrew, Stasiak, Bavin, Frampton, & Merry, 2018). The SMFQ is a reliable, valid measure of adolescent depression (Thabrew et al., 2018), with high sensitivity and specificity for detecting DSM-IV (American Psychiatric Association, 1987) and ICD-10 (World Health Organization, 1992) MDD diagnoses (Thapar & McGuffin, 1998; Turner, Joinson, Peters, Wiles, & Lewis, 2014).

Mediator Variables

Mediator variables were measured at age 16 years to ensure a time lag between exposure (age 7.5), mediator (age 16) and outcome (age 17.5) as recommended for mediation analysis (Selig & Preacher, 2009).

Peer relationships. The 5-item Peer Problems subscale of the mother-completed Strengths and Difficulties Questionnaire (SDQ) at 16 years was used (Goodman, 1997). Items such as ‘Teenager has at least one good friend’ and ‘Teenager is generally liked by others’ were rated with responses of ‘Not true’ (2), ‘Sometimes true’ (1) and ‘Certainly true’ (0), with higher scores indicating more peer problems. Items were summed to generate a total score (maximum=10). The SDQ is a well validated, reliable screening tool for a range of mental health difficulties in young people (Goodman, 1997).

Academic attainment. Academic attainment was assessed by performance in formal examinations at the end of secondary school at 16 years (General Certificate of Secondary Education; GCSE examinations). GCSEs are graded from A* (highest grade achievable) to U (lowest grade achievable). A total GCSE and equivalents point score was calculated by summing individual point scores for each GCSE and equivalent qualification grade achieved (A* being equivalent to 58 points, A to 52, B to 46 etc.) (Department of Education, 2010).

Confounding Variables

Analyses were adjusted for mother’s socioeconomic status according to occupation and maternal age at birth to account for sociodemographic factors associated with ADHD (Galéra et al., 2012) and depression (Gilman, Kawachi, Fitzmaurice, & Buka, 2002). These were available from mother-reported questionnaires completed during pregnancy or the early years of the study child’s life. Analyses were additionally adjusted for the child’s sex. Sex and sociodemographic variables could potentially confound all three paths between variables tested in the mediation analyses (Figure 2.1). Thus, all analyses presented are adjusted for both.

2.2.3. Data Analysis

The Association between ADHD and Depression

Childhood ADHD symptoms were standardised so that a unit increase was equivalent to a standard deviation unit increase. Linear regression was used to

examine the association between standardized childhood ADHD symptoms and continuous depression symptom score at 17.5 years. Logistic regression was used to examine the association between standardised childhood ADHD symptoms and depression assessed using the binary SMFQ clinical cut-point at 17.5 years. To examine whether sex influenced the association between ADHD symptoms and depression, an interaction term of ADHD symptoms and sex was regressed against depressive symptoms. The Wald test was then used to test whether the model with the interaction term was significantly different to the model without the interaction term. Regressions were also repeated using an exposure variable of ADHD diagnosis.

Mediation by Peer relationships and Academic Attainment

Peer problems and GCSE result scores at 16 years were tested as mediators of the association between childhood ADHD symptoms and adolescent depression symptoms in two single mediator models. A 'potential outcomes' causal mediation framework was used with STATA commands 'medeff' and 'medsens' (Hicks & Tingley, 2011; Imai, Keele, & Tingley, 2010). Medeff conducts mediation analyses using Monte Carlo simulation whilst allowing for interaction of exposure and mediator on the outcome. Medsens considers mediation models' sensitivity to potential confounding by unobserved confounders of the mediator-outcome relationship. This mediation method was selected because traditional mediation methods can be subject to biases resulting from not considering potential exposure-mediator interaction or unobserved confounding of the mediator-outcome association (Richiardi, Bellocco, & Zugna, 2013). Confidence intervals for indirect effects were estimated using a non-parametric bootstrapping approach with 10,000 replications (Montoya & Hayes, 2017). Reported statistics are Pure Natural Direct Effect (PNDE), Total Natural Indirect Effect (TNIE), and percentage of the total effect that was mediated. PNDE is the direct (unmediated) effect of the exposure on the outcome when the mediator takes the value it would take in the absence of the exposure. TNIE captures the mediated effect of the exposure on the outcome that operates by changing the mediator (Vanderweele, 2014). In addition, the effect of simultaneously estimating mediation by peer relationships and academic attainment was tested in a multiple mediator model using Structural Equation Modelling (SEM) (Gunzler, Chen,

Wu, & Zhang, 2013). SEM uses a conceptual model and a series of regression-like equations to capture complex relationships within a network of variables, which is expressed as a path diagram. SEM does not have the ‘potential outcomes’ advantages of considering exposure-mediator interaction or mediator-outcome confounding, but is suited to testing more complex mediation models where the effect of multiple mediators is estimated simultaneously in the same model.

2.2.4. Sensitivity Analyses

As previous work has found victimization to mediate the association between ADHD symptoms and subsequent depression (Roy et al., 2015), an additional test of whether observations of mediation effects by peer problems were driven by victimisation was conducted. To do this, the peer problems mediation analysis was repeated with the item “young person is picked on or bullied by other young people” removed from the Peer Problems score of the SDQ (Goodman, 1997).

As noted in the introduction (section 2.1), educational performance involves several components. Therefore, cognitive ability as measured by IQ was tested as a mediator of the association between ADHD and depression and this result was compared to the result observed for academic attainment measured by GCSE results. For this, total IQ score derived from the Wechsler Abbreviated Scale of Intelligence (WASI) – a reliable measure of cognitive intelligence (Wechsler, 1999) – at 15.5 years was used.

Three sensitivity tests were conducted to check for the effect of timing of variables. Use of mediator data collected at an earlier time point than depression data does not ensure that these mediators actually preceded depression symptoms. Thus, mediation analyses were repeated adjusting for depression symptoms at 14 years – prior to the measurement of mediators – to account for depression occurring earlier in adolescence (Appendix 2.1). Furthermore, although academic attainment data was not available at an earlier age than 16 years, the peer relationships mediation analysis was repeated using peer problem and depression data collected at earlier time points. SDQ peer problems data collected at 9.5 years (prior to the typical age of onset of depression; Thapar et al., 2012) and SMFQ depressive symptoms at age 13 years were used (Appendix 2.2). In addition, a check of whether

observed associations between ADHD and adolescent depression were due to 'pre-existing' childhood emotional problems occurring approximately contemporaneously with ADHD was conducted. This could confound the direct association between ADHD and depressive symptoms. Therefore, emotional problems as indicated by the SDQ emotional problems subscale at 8 years (with a score of ≥ 5 classed as 'abnormal') (Goodman, 1997) was adjusted for in an additional regression. However, it is possible that childhood emotional problems may be on the causal pathway between ADHD and depression. Therefore, it was not included as a covariate in the fully adjusted regressions.

2.2.5. Missing Data

To address the possibility of bias due to non-random missing data, all analyses were repeated with Inverse Probability Weighting (IPW) applied, as conducted previously in ALSPAC (e.g. Anderson et al., 2018). IPW is a reliable technique for handling missing data, particularly in longitudinal studies where participants can have missing values on multiple variables (Seaman & White, 2013). This is often the case in ALSPAC where missingness from a group of variables occurs due to non-participation in a clinic assessment, for example. IPW involves weighting the analysis sample by the inverse probability of being missing. Based on the attrition analyses documented in Appendix 2.3, in those with data available on ADHD at 7 years, variables measured at early time points in the ALSPAC cohort predicting missingness from depression data at 17.5 years and mediator data at 16 years (e.g. socioeconomic status) were examined and formed two missingness models – one predicting missingness from the outcome and another predicting missingness from both the outcome and mediators – from which two weights were created. Minimal missing data on these predictors were singly imputed as the modal value (all predictors had <14% of values missing). The Hosmer-Lemeshow test showed no indication of poor fit for the outcome missingness model (Hosmer-Lemeshow $\chi^2(8)=4.11$, $p=0.85$) or for the outcome and mediators missingness model (Hosmer-Lemeshow $\chi^2(8)=11.93$, $p=0.15$). Weights ranged from 1.36 to 23.45. Regressions and mediation analyses were re-run with the respective IPW weights applied to address potential bias caused by missing data.

2.3. Results

2.3.1. Descriptive Statistics

In the 2950 participants (1298 males and 1652 females) with complete data, 0.47% (n=14) met the criteria for DSM-IV ADHD diagnosis at 7.5 years. DSM-IV ADHD symptoms (mean=3.58, standard deviation=4.55) was used to define the primary ADHD exposure variable. 17.32% (n=511) met the clinical cut-point for depression at 17.5 years (mean symptom score=6.45, standard deviation=5.18). As expected, the majority of those with ADHD were male (85.71%) and the majority of those reaching the binary cut-point for clinically significant depressive symptoms were female (66.73%). Table 2.1 shows the correlations of analysis variables.

Table 2.1. Correlation matrix of analysis variables: ADHD symptoms, peer problems, GCSE results and depressive symptoms

Variable	ADHD symptoms	Peer problems	GCSE results	Depressive symptoms
ADHD symptoms	1			
Peer problems	.21*	1		
GCSE results			1	
Depressive symptoms				1

Pearson correlations of mediation analysis variables were conducted on complete cases for exposure, mediators, outcome and confounders (n=2161). *ADHD* attention deficit/hyperactivity disorder, *GCSE* general certificate of secondary education. *correlation significant at p<0.001

2.3.2. Association between Childhood ADHD and Adolescent Depression

Standardised childhood ADHD symptoms predicted the continuous outcome of adolescent depression symptom score ($b=0.49$, $SE=0.11$, $p<0.001$). There was no significant interaction between ADHD symptoms and sex in predicting depression symptom score (Wald test: $F=0.99$, $d.f.=(1, 2946)$, $p=0.32$), though the relationship was slightly stronger in females ($b=0.59$, $SE=0.17$, $p<0.001$) than males ($b=0.40$, $SE=0.13$, $p=0.002$).

Childhood ADHD symptoms predicted the binary outcome of clinically significant depressive symptoms at age 17.5 years ($OR=1.27$, $95\% CI=1.15-1.41$, $p<0.001$). This remained the case when adjusting for socioeconomic factors, sex and childhood emotional problems (Table 2.2). When examining sex differences, there was no significant interaction between ADHD symptoms and sex in predicting clinically significant depression symptoms (Wald test: $X^2=2.02$, $d.f.=(1)$, $p=0.16$), though the association was slightly stronger in females ($OR=1.36$, $95\% CI=1.18-1.56$, $p<0.001$) than males ($OR=1.18$, $95\% CI=1.01-1.37$, $p=0.04$). Clinical diagnosis of ADHD ($n=14$: 12 males and 2 females) was also associated with increased odds of clinically significant depression symptoms at 17.5 years ($OR=4.49$, $95\% CI=1.53-13.19$, $p=0.006$).

Table 2.2. Association between childhood ADHD and late adolescent depression

	Unadjusted	Adjusted for emotional problems at 8 years	Adjusted for sociodemographic variables	Adjusted for sex	Fully adjusted (adjusted for sociodemographic variables and sex)
	OR, 95% CI, p	OR, 95% CI, p	OR, 95% CI, p	OR, 95% CI, p	OR, 95% CI, p
Overall (n=2950)	1.21, 1.10-1.34, <0.001	1.19, 1.08-1.31, 0.001	1.20, 1.09-1.33, <0.001	1.29, 1.16-1.42, <0.001	1.27, 1.15-1.41, <0.001
Males (n=1298)	1.18, 1.01-1.38, 0.03	1.13, 0.97-1.33, 0.12	1.18, 1.01-1.37, 0.04		
Females (n=1652)	1.37, 1.20-1.57, <0.001	1.36, 1.19-1.56, <0.001	1.36, 1.18-1.56, <0.001		

ADHD attention deficit/hyperactivity disorder, OR odds ratio, CI confidence interval

2.3.3. The Role of Peer Relationships and Academic Attainment in the Association between ADHD and Depression

Peer relationships at 16 years mediated the association between childhood ADHD symptoms and late adolescent depressive symptoms, accounting for 14.68% of the total effect (Table 2.3). Peer problems remained a mediator when the item tapping victimization – “picked on or bullied by other young people” – was removed (Total Natural Indirect Effect: $b=0.07$, 95% CI= $0.01-0.14$), accounting for 12.50% of the association.

Academic attainment mediated the association between childhood ADHD symptoms and late adolescent depression symptoms, accounting for 20.13% of the total effect (Table 2.3).

A sensitivity analysis checked whether cognitive ability as measured by IQ contributed to the association of ADHD symptoms and depression symptoms to a comparable extent to academic attainment. IQ did not contribute to the association (Total Natural Indirect Effect: $b=0.01$, 95% CI= $-0.03-0.06$).

Additional sensitivity analyses checked whether mediation results were affected by the timing of variables. Mediation analysis adjusted for depressive symptoms at 14 years (prior to the measurement of peer relationships or academic attainment mediators) and mediation analysis repeated using data collected at earlier time points both produced similar results (Appendices 2.1 - 2.2).

When testing peer relationships and academic attainment simultaneously in a multiple mediator SEM model, mediated pathways between ADHD and depressive symptoms via peer relationships and academic attainment revealed a similar pattern of results (Appendix 2.4).

Table 2.3. Mediation of the association between childhood ADHD and adolescent depression by academic attainment and peer relationship problems

Mediator (Measured at 16 years)	Pure Natural Direct Effect b (95% CI)	Total Natural Indirect Effect b (95% CI)	Proportion of Total Effect Mediated % (95% CI)
Peer problems	0.45 (0.19-0.70)	0.08 (0.02-0.15)	14.68 (9.97-28.78)
GCSE results	0.41 (0.15-0.66)	0.10 (0.01-0.21)	20.13 (13.89-41.81)

The exposure levels being compared in these analyses were mean ADHD symptoms and 1 Standard Deviation above this. Significant mediators are indicated by confidence intervals of 'Total Natural Indirect Effect' not containing zero. n=2161. *ADHD* attention deficit/hyperactivity disorder, *GCSE* general certificate of secondary education, *b* unstandardized beta, *CI* bootstrapped confidence interval

One of the advantages of the potential outcomes approach to mediation is that it allowed testing of potential unobserved confounding of the mediator-depression relationship. The ‘medsens’ test indicated that the product of observed variance in mediator and outcome that would need to be explained by an unmeasured confounder for mediation effects to disappear ranged from approximately 0.005 to 0.008 (Appendix 2.5). To aid interpretation of this coefficient, it was compared with the estimate for a measured confounder – socioeconomic status of mother. The estimate for socioeconomic status of mother on mediation by academic attainment was 0.0002. The coefficient for unobserved confounding required to eliminate the observed mediated effects is therefore considerably larger than that present for the measured confounder of socioeconomic status. It therefore seems unlikely that unobserved confounding would account for the observed results.

2.3.4. Inverse Probability Weighting (IPW)

Results remained very similar when IPW was applied to analyses. Childhood ADHD symptoms remained associated with the continuous late adolescent depression symptom score ($b=0.55$, $SE=0.12$, $p<0.001$) and with the binary measure of clinically significant depressive symptoms in late adolescence ($OR=1.29$, 95% $CI=1.16-1.44$, $p<0.001$). Mediation results with IPW applied are shown in Appendix 2.6.

2.4. Discussion

This study investigated the prospective association between childhood ADHD symptoms and late adolescent depressive symptoms over a 10-year period in a population cohort and tested peer relationships and academic attainment as mediators. This study found a positive association between ADHD symptoms at 7 years and depression symptoms at 17 years. This adds to the growing body of research evidencing a prospective association between ADHD and depression (Gundel et al., 2018; Meinzer et al., 2014), by testing the association across the key developmental stages of childhood and adolescence in a population sample. Results

demonstrated that difficulties with peer relationships and academic attainment at 16 years mediated the pathway from childhood ADHD symptoms to adolescent depression symptoms as hypothesized (Figure 2.1). This is in line with previously proposed models suggesting that young people who struggle in their school performance and with their peers are more likely to experience feelings of failure and rejection, which leave them more vulnerable to depression (Capaldi, 1992; Patterson & Stoolmiller, 1991). The present study helps to reconcile previous uncertainties in the literature as to whether peer and academic-related factors contribute to the association of ADHD and depression, which stems from a lack of longitudinal studies investigating the mediation of this association (Meinzer et al., 2014).

2.4.1. Mediation of the Association of ADHD and Depression via Peer Relationships

In the current study, peer problems mediated 14.68% of the total association between ADHD and depression symptoms. A previous study found that a latent variable capturing social functioning and popularity mediated an association between attention problems (as measured by the attention problems subscale of the CBCL (Achenbach & Ruffle, 2000) and depressive symptoms in a sample selected to over-represent the children of depressed mothers (Humphreys et al., 2013). The results of the current study show that peer relationship problems more broadly may play an important part in the pathway from ADHD to depression in the general population. Results also suggest that this is not driven entirely by the effect of peer victimization, as peer problems still mediated 12.50% of the total relationship between ADHD and depression when the victimisation item of the peer problems scale was removed. This is important as peer victimization has previously been found to mediate the prospective association of ADHD and depression (Roy et al., 2015). The findings of the current study suggest that additional aspects of peer relationships including having good friendships, feeling liked by others, playing or socialising with others and getting on with people your own age may also be important protective factors for depression in those with ADHD. It is important to consider that different features of peer relationships may have different effects in children with ADHD, which might affect the most appropriate choice of target for depression

interventions. For example, good quality peer relationships have been shown to be associated with mental health resilience in young people at elevated familial risk for depression (Collishaw et al., 2016).

2.4.2. Mediation of the Association of ADHD and Depression via Academic Attainment

Academic attainment also mediated the link between ADHD and depression in the current study. GCSE results explained 20.13% of the association between childhood ADHD and adolescent depressive symptoms. This finding differs somewhat to the results of a longitudinal mediation study that found that child perceptions of academic stress did not mediate the association between attention problems and depressive symptoms (Humphreys et al., 2013). However, this discrepancy may be accounted for by differences between the two studies. In particular, the present study assessed academic attainment by performance in formal public examinations (GCSE results) as a mediator, while Humphreys and colleagues used a life stress interview to assess perceptions of stress and functioning at school. The current study focused on the two measured mediators of academic attainment and peer relationships, whereas Humphreys and colleagues tested mediation models comprising of multiple latent variables that captured functioning in various domains. Due to these study differences, it is difficult to compare the mediation results. However, it may be interesting to consider whether different aspects of life at school have distinctive effects in those with elevated ADHD symptoms. While the previous study did not find evidence to support general functioning in school as a mediator of the association between attention problems and depressive symptoms (Humphreys et al., 2013), the current study found that objectively measured academic attainment (GCSE exam results) mediated the association between ADHD and depressive symptoms. This suggests that academic attainment may be an important target within school life for depression intervention in those with ADHD. Nonetheless, comparison of results from these differing study designs should be interpreted with caution.

Children with ADHD may struggle with academic attainment for various reasons, including difficulties with formal classroom learning where sustained attention, self-control, emotion modulation and adherence to rules are frequently

required. IQ might also affect academic attainment (Finn et al., 2014), although this was not the focus of the current study. Academic attainment was focussed upon as a mediator as it could occur at a time point between ADHD and depression (a key assumption of a mediation model) and may perhaps be more amenable to intervention when compared to IQ. However, as a sensitivity analysis, IQ was tested as a mediator to check whether IQ contributed to the relationship of ADHD and depression to a comparable extent to academic attainment. Although cognitive ability has been reported to be associated with both ADHD and depression (Birchwood & Daley, 2012; Glaser et al., 2011; Riglin et al., 2015), IQ did not contribute to the association of ADHD and depression in the current study. Nevertheless, it is worth noting that this test should be interpreted with caution because it violates the assumption that a mediator occurs at a time point between the exposure and outcome variable. However, the possible implication of this finding is that children with ADHD struggling with school achievement as opposed to cognitive difficulties *per se* is what increases later depression risk. The attributes required for traditional classroom learning including self-control have been shown to predict academic attainment measured by school grades more strongly than IQ (Duckworth & Seligman, 2005). A systematic review of school-based non-pharmacological interventions for ADHD found that the expectations of the classroom were not a good “fit” for those with ADHD, which negatively affected academic performance and interactions with peers (Richardson et al., 2015). Repeated infringements of classroom expectations resulting in lowered academic attainment and less positive peer interactions may lead to feelings of failure and isolation, thus increasing risk for developing depression (Capaldi, 1992; Patterson & Stoolmiller, 1991). Overall, the findings of the current study suggest that increased difficulty in peer relationships and academic attainment may drive part of the increased risk of adolescent depression in those with childhood ADHD in the general population.

2.4.3. Limitations

Limitations include that mediators were tested independently as the potential-outcomes mediation method using the ‘medeff’ STATA command does not

allow simultaneous estimation. The potential-outcomes method was used as it overcomes limitations of traditional mediation testing methods, including consideration of exposure-mediator interaction and unobserved confounding of the mediator-outcome association (Richiardi et al., 2013). However, to check that the results did not differ when the mediators were tested simultaneously, a multiple mediator model was also tested using SEM (Gunzler et al., 2013). In this model, both the mediated pathway via peer relationships and via academic attainment were significant. Although mediators were assessed at an earlier time point than depression symptoms, this does not guarantee that these factors preceded depression symptoms. However, regressions adjusted for earlier childhood emotional problems showed that childhood ADHD was still associated with depression at 17.5 years. Mediation analyses adjusted for depressive symptoms at 14 years – prior to the measurement of peer relationships or academic attainment – also remained very similar. However, this sensitivity check should be interpreted with caution, as depression at 14 would almost certainly be affected by the exposure and thus act as an intermediate confounder. Furthermore, although academic attainment data was only available at 16 years, the peer problems mediation analysis was repeated using data collected at earlier time points. Peer problems at age 9.5 years (prior to the typical age of onset of depression) still mediated the association between ADHD symptoms at age 7.5 years and depression symptoms at age 13 years, accounting for over 20% of the total relationship. There was attrition of participants in ALSPAC, which is a common problem with longitudinal cohorts (Spratt et al., 2010). Childhood ADHD symptoms predicted missingness at 17.5 years, meaning those with ADHD may be under-represented. Indeed, the prevalence of ADHD diagnosis in the current study (0.47%) was lower than reported in the UK population of children (1.5%) (Green et al., 2005). However, this would likely result in attenuation of associations if there was an effect on results. The inclusion of confounder variables in analyses (socioeconomic status, maternal age at birth and sex) that predicted missingness from depression data helped to address bias that may be caused by missing data (Groenwold, Donders, Roes, Harrell, & Moons, 2012). To investigate impact of further bias arising from missing data, analyses were

repeated with Inverse Probability Weights applied. Results remained very similar, suggesting that the impact of missing data was minimal (Seaman & White, 2013).

Although not necessarily a limitation, it is worth noting that the mediation effects observed via peer relationships and academic attainment may represent person-effects on the environment, vice versa, or both (Rutter, Pickles, Murray, & Eaves, 2001). As ADHD and depression are genetically correlated (Demontis et al., 2019; Wray et al., 2018), shared genetic liability with the mediators cannot be ruled out as an explanation of results. It is also important to note that young people with ADHD have been found to under-report their depressive symptoms (Fraser et al., 2018), which may lead to an underestimation of associations.

2.4.4. Strengths

Strengths of the current study included the use of longitudinal data spanning 10 years, allowing the mediation of the relationship between ADHD and depression to be investigated across childhood to adolescence, which are key risk periods for ADHD and depression, respectively (Kessler et al., 2005; Thapar et al., 2012, 2017). Longitudinal data also allowed time-lags between measurement of the exposure, mediator and outcome variables, which is a central part of investigating mediation (Selig & Preacher, 2009). The large population sample used in the current study avoided the selection bias that can occur in studies of only those at the severe end of the disorder group, as is the case in previous clinical studies (Meinzer et al., 2014).

2.4.5. Implications

An increased risk of clinically significant depressive symptoms was observed in children with ADHD in this study, highlighting the importance of monitoring this group for depression. Such monitoring may allow early identification and treatment of depression. The association between ADHD and depressive symptoms was mediated in part by peer relationships (even when accounting for potential effects of bullying) and academic attainment. Interventions targeting the impact of children's ADHD on their peer relationships and academic attainment may have the added benefit of reducing depression risk, in addition to treating core ADHD symptoms. There are a number of existing psychosocial interventions available for those with

ADHD that target social skills and academic skills (Evans, Owens, Wymbs, & Ray, 2018; Haack, Villodas, McBurnett, Hinshaw, & Pfiffner, 2017; Pfiffner et al., 2014) that may have the potential to reduce depression risk, though this needs to be formally tested. However, existing interventions targeting social skills have shown limited success thus far in children with ADHD (Mikami, 2010).

For future research, a detailed investigation of the specific components of peer relationship difficulties that increase depression risk in young people with ADHD would allow further insight into the most appropriate targets for intervention. The different features of friendship that might be important in the association between ADHD and depression is investigated in chapter 3.

2.4.6. Conclusions

The current study in a longitudinal population cohort shows that childhood ADHD symptoms are associated with increased risk of clinically-significant depressive symptoms in late adolescence. This adds to a growing body of research highlighting the need for depression monitoring in young people with ADHD. The association between ADHD and depressive symptoms was mediated in part by peer problems and academic attainment. This highlights peer relationship and academic attainment difficulties as potential targets for depression prevention and intervention in children with ADHD.

Chapter 3: A longitudinal study of the role of different features of friendships and the parent-child relationship in the association between ADHD and depression

This chapter is an amended version of a published paper:

Powell, V., Riglin, L., Ng-Knight, T., Frederickson, N., Woolf, K., McManus, C., Collishaw, S., Shelton, K. H., Thapar, A., & Rice, F. (in press). Investigating friendship difficulties in the pathway from ADHD to depressive symptoms. Can parent-child relationships compensate? *Research on Child and Adolescent Psychopathology*.

Following the observed mediation of the association between ADHD and depression by peer relationship difficulties in chapter 2, the current study chapter sought to investigate different elements of friendship in more detail. The aim was to identify which specific aspects of friendship may act as mediators of the association between ADHD and depression. This short-term longitudinal study in a school-based sample in the UK investigated the potential mediating effect of different features of friendship (presence of friends, quality of friendships and the characteristics of the classroom friendship group) in the association between ADHD and subsequent depression. In addition, whether any mediating effects via friendship might be mitigated or moderated by parent-child relationship quality was tested. Analyses were conducted in 1712 pupils in their first year of secondary school (year 7; children aged 11-12 years) with data on ADHD symptoms and friendships (end of the first term of year 7) and depressive symptoms seven months later (end of year 7). ADHD symptoms were associated with having fewer friends, lower friendship quality and being part of a more disruptive classroom friendship group. Presence and quality of friendships were negatively associated with depressive symptoms. Friendship quality was found to mediate the association between ADHD and subsequent depressive symptoms. There was some suggestive evidence that mediation via friendship quality was moderated by the quality of parent-child relationships, whereby mediated effects attenuated slightly as children reported warmer, less hostile parent-child relationships.

3.1. Introduction

As discussed in chapter 1, friendship difficulties are associated with both ADHD and depression in separate studies (Blachman & Hinshaw, 2002; Goodyer et al., 1989) and thus are one potential explanation of the prospective association between ADHD and depression. In the study detailed in chapter 2, a composite measure of peer problems that included items on having good friends, being liked by others and playing and socialising with others mediated the prospective association between ADHD and depression. However, the effect of ADHD on different features of friendships and which features are important in conferring later depression risk is not clear. The role of parents is also often not considered in studies of ADHD and friendship (Mikami, 2010), but it is possible that any effects of friendship difficulty might be compensated for by a good quality parent-child relationship (Stocker, 1994) as discussed in chapter 1. Thus, the current study aimed to expand upon existing literature and the findings in chapter 2 by investigating different features of friendship (presence of friends, quality of friendships and characteristics of the classroom friendship group) in the prospective association between ADHD and depression. In addition, whether parent-child relationship quality moderated any mediated effects via friendship was also investigated. The relevant extant literature is detailed below, before outlining the aims of the current study.

3.1.1. Friendships

ADHD impacts on many aspects of a young person's life (Harpin, 2005), including friendships (Mikami, 2010). Studies comparing children with an ADHD diagnosis to typically developing controls show that children with ADHD are likely to have fewer stable friendships (Blachman & Hinshaw, 2002; Marton et al., 2015). Poor quality friendships may be risk factors for subsequent depression (Goodyer et al., 1989).

One potential explanation of the prospective association of ADHD and depression is that social stressors that commonly accompany ADHD, such as friendship difficulties, lead to an increased risk of depression (Capaldi, 1992), potentially by creating feelings of failure or lowered self-esteem (Cole, 1990;

Patterson & Stoolmiller, 1991). Interpersonal stress is an important precipitator of depression, particularly during adolescence (Flynn & Rudolph, 2011) – a period when individuals spend increasing amounts of time with friends (Blakemore, 2018; Larson & Richards, 1991). Studies have shown that bullying (Roy et al., 2015), social functioning and popularity (Humphreys et al., 2013) and peer relationship difficulties (chapter 2) contribute to the prospective relationship of ADHD and depressive symptoms in young people. However, a detailed investigation of friendship features including presence of friends, friendship quality and characteristics of the friendship group (Bukowski et al., 1996) and how these are associated with ADHD and impact on later depression is lacking (Mikami, 2010). It is possible that certain aspects of friendship difficulty might be more important than others in the association of ADHD and depression. For instance, a previous study conducted in secondary school children found that while retaining your best friend over time was not associated with emotional outcomes, retaining poor quality friendships over time with your top three friends was associated with subsequent emotional problems (Ng-Knight et al., 2019). Identification of factors that might explain the relationship between ADHD and depression, as well as factors that moderate risk, could help pinpoint new ways of supporting young people with ADHD.

3.1.2. The Context of School

School is a key context where children make friends (Ng-Knight et al., 2019). Classroom expectations may often be a poor ‘fit’ for those with ADHD, which can exacerbate poor social outcomes for this group (Richardson et al., 2015). The transition from primary to secondary school is a period of change (Chung et al., 1998) when good friendships can protect against poor mental health (Ng-Knight et al., 2019), but also when there is a natural disruption to established friendships and a need to establish new ones.

3.1.3. Parent-Child Relationships

In addition to friendships, it is important to consider children’s other sources of social support including parent-child relationships, which can mitigate against poor mental health outcomes in the presence of adversity (Brennan, Le Brocque, &

Hammen, 2003; Collishaw et al., 2016, 2007; Lewandowski et al., 2014) and may compensate for a lack of friends (Stocker, 1994). Warmer relationships with parents are also associated with more satisfactory friendships in young people (Deković & Meeus, 1997), and the influence of parental behaviour on the child's friendships may be particularly important in children with ADHD (Mikami et al., 2010). Thus, it is possible that any mediating effects of friendship in the association of ADHD and depression could be moderated by the quality of the parent-child relationship. However, parent-child relationships are often not considered in studies of ADHD and friendship. This is especially the case for the father-child relationship (Cabrera et al., 2018). Investigating the influence of relationships with both mother and father is important, as they may exert differential influences on children's friendships (Flynn, Felmlee, Shu, & Conger, 2018; Updegraff, McHale, Crouter, & Kupanoff, 2001).

3.1.4. The Current Study

The aim of this study was to investigate which aspects of friendship (presence of friends, friendship quality and characteristics of friends) are important in increasing vulnerability to depressive symptoms in those with elevated ADHD symptoms. A secondary aim of this study was to investigate whether any indirect effects via elements of friendship were moderated by mother-child or father-child relationship quality. A follow-up exploratory research question was whether indirect effects differed according to gender, as the features of friendship that young people value can differ between females and males (Hall, 2010). The study included children in the first year of secondary school followed over a 7-month timespan.

3.2. Methods

3.2.1. Sample

The School Transition Adjustment Research Study (STARS; Ng-Knight et al., 2016) includes pupils recruited from nine secondary schools in Greater London selected to be representative of schools in the local region in terms of socioeconomic disadvantage, exam pass rates and proportions of pupils from

minority ethnic backgrounds. Ethical approval was granted by the University College London Research Ethics Committee. Informed assent was obtained for the participating children and parents were given the opportunity to opt-out. Baseline data were collected during the second half of the first term of year 7 (children aged 11-12 years; pupil and teacher reports) and follow-up data 7 months later in the summer term of year 7 (pupil reports) via questionnaires completed in classroom settings. At baseline, 1712 children participated (53.5% male; response rate=87.0%). For 80.1% of these children, teachers returned questionnaires reporting on the child's mental health (n=1372). For 1020 of these 1372 children (74.3%), teachers completed the section rating the children's baseline ADHD symptoms. Of the 1020 children, self-rated depressive symptom data at follow-up were available for 901. Of these, there were 752 (50.3% male) for whom data were additionally available on friendship and sociodemographic variables. As described subsequently in 3.2.4., to address bias that might be caused by missingness, missing data were imputed for covariates and outcome using Multiple Imputation by Chained Equations (MICE; White, Royston, & Wood, 2011) with 100 imputations, which formed the analysis sample (n=1712).

3.2.2. Measures

ADHD Symptoms

ADHD symptoms were measured at baseline with the teacher-rated ADHD subscale (hyperactivity-inattention) of the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997). Five items were rated "Not True" (0), "Somewhat True" (1) or "Certainly True" (2) (total score range=0-10). The teacher-rated hyperactivity-inattention subscale has good sensitivity and specificity for detecting DSM-IV (American Psychiatric Association, 1994) ADHD in school-aged children (Pritchard, 2012).

Depressive Symptoms

Depressive symptoms were assessed at follow-up with the self-rated Short Moods and Feelings Questionnaire (SMFQ; Angold et al., 1995). Thirteen items were

rated “Not true” (0), “Somewhat true” (1), or “True” (2) (total score range=0-26). The SMFQ is a well-validated, reliable measure of depression in adolescents with high sensitivity and specificity for detecting major depressive disorder (MDD) (Thapar & McGuffin, 1998).

Friendship Presence

At baseline and follow-up, children were asked to name up to three friends in order of preference as their top three friends. The following variables were derived: number of friends at baseline (range=0-3), stability of best friend (from the start to the end of the school year; 0=no, 1=yes) and stability of ‘top three friends’ (stability of any of the three top friends; 0=no, 1=yes). This method of deriving friendship stability has been used previously in the STARS study (Ng-Knight et al., 2019).

Friendship Quality

For their best friend, children completed a 15-item version of the Friendships Qualities Scale at baseline (FQS; Bukowski, Hoza, & Boivin, 1994). This consisted of 5 subscales: companionship, conflict, closeness, help and security. Items were rated on a 5-point Likert scale from “Not at all” (0) to “Very much” (4). Positive scales (companionship, closeness, help and security) were summed and then negative scales (conflict) subtracted to generate a maximum total quality score of 48 (Cronbach alpha=0.80). In addition, friendship quality across the top three friends was measured at baseline by a single rating for each of these friends on a 5-point smiley face rating scale from 0 (least satisfied) to 4 (most satisfied). Scores for the top three friends were summed to give an overall score (maximum=12).

Classroom Friendship Group Characteristics

Sociometric methods were used to identify classroom friendship groups at baseline. In classroom groups, children were asked to draw on paper a diagram describing “which children in your class hang around together” by circling groups of pupils who are friends (example shown in Appendix 3.1). Social Cognitive Mapping software (SCM; Cairns & Cairns, 1994; Hamm, Farmer, Dadisman, Gravelle, & Murray, 2011) was used to identify classroom friendship groups – a reliable, valid

tool for this purpose (Cairns, Cairns, Neckerman, Gest, & Gariépy, 1988; Cairns, Leung, Buchanan, & Cairns, 1995). To describe the characteristics of the classroom friendship group, this was linked to information on the behavioural and emotional characteristics of children in that group: i) the self-rated SDQ total difficulties score (Goodman, 1997), and ii) cooperative and disruptive behaviour rated by peers who indicated from a list of the children in their class who they felt matched these descriptions (example shown in Appendix 3.1; the Guess Who peer-nomination method; Coie & Dodge, 1988; Parkhurst & Asher, 1992). Classroom friendship group characteristics were derived for each child by averaging the scores of the other pupils in their friendship group (the score of the individual was not included so as to avoid group scores being biased by the individual's own score). The mean number of individuals in a classroom friendship group was 5 (maximum: 15). 5.3% of children were social isolates (i.e. did not have a classroom friendship group) so their scores could not be calculated.

Parent-Child Relationship Quality

At baseline, children who reported being in contact with their mother and/or father (or equivalents, e.g. step-parent, carer) in the last month completed a measure assessing their perception of each parent's warmth and hostility towards them using the Iowa family interaction rating scale (Melby & Conger, 2001). The warmth scale consisted of six items (example: "Acts loving and affectionate toward you") rated on a 7-point Likert scale from "Never" (0) to "Always" (6) (score range=0-36; Cronbach's alpha for mother score=0.90; Cronbach's alpha for father score=0.92). The hostility scale consisted of 4 items (example: "Criticises you or your ideas") rated in the same way (score range=0-24; Cronbach's alpha for mother score=0.79; Cronbach's alpha for father score=0.82).

Confounders

Analyses were adjusted for sex and socioeconomic and ethnic factors associated with depression (Gilman et al., 2002; Williams et al., 2015). These were socioeconomic disadvantage (free school meals status), Black Minority Ethnic status and English as a first language (data collected from school records). All analyses

presented are adjusted for all confounders by including confounder variables in the models as covariates.

3.2.3. Data Analysis

Associations of ADHD, Features of Friendship and Depression

ADHD symptoms were standardised meaning a point increase in SDQ hyperactivity score was equivalent to a standard deviation unit increase. Linear regression was used to test the association between ADHD symptoms and depressive symptoms 7 months later. Separate linear and logistic regressions were used as appropriate to test associations between ADHD symptoms and indicators of three friendship elements (presence/stability, quality and characteristics of friends), and to test associations of these friendship indicators (standardised if continuous) with depressive symptoms. Regressions included the school class as a random effect to account for potential hierarchical data structure or clustering.

Indirect Effects via Friendship in the ADHD-Depression Association

To test whether the different features of friendship contributed to the association of ADHD and depressive symptoms, indirect effects were tested separately using the `sureg` STATA command. `Sureg` conducts Seemingly Unrelated Regressions (Zellner, 1962), from which indirect (mediated) and conditional indirect (moderated mediation) effects can be derived in original and imputed data (UCLA Statistical Consulting Group, n.d.). Any friendship variables found to have significant indirect effects were tested simultaneously in a multiple mediator model. As indirect effects via friendship may be influenced by gender (Hall, 2010), a sensitivity analysis testing moderated mediation by child gender was conducted using `sureg`.

Moderation of Indirect Effects by Parent-Child Relationships

Moderated mediation was tested using `sureg` to investigate whether any indirect effects via friendship varied according to the warmth or hostility of parent-child relationships. The model used tested combined moderation of the pathway from ADHD to friendship and the pathway from friendship to depression (Preacher,

Rucker, & Hayes, 2007). Indirect effects at the mean level of the moderator and 1 standard deviation above and below this were calculated and plotted. For each moderator, significance tests (Z-tests) of the difference between the observed indirect effect at the mean level of the moderator compared to the mean level of the moderator -1SD (for hostility) or +1SD (for warmth) were conducted. To investigate which path(s) in the indirect effects were being moderated, models with an interaction effect on the path between ADHD and friendship or the path between friendship and depression only were additionally tested.

3.2.4. Missing Data

To address potential bias arising from missingness in the data, all analyses were conducted on an imputed dataset. Due to the variety of socio-demographic variables available in the STARS data which predict missingness, the assumption can be made that missing information is dependent on observed data. Therefore, Multiple Imputation by Chained Equations was conducted with the 'ice' command in STATA 13 to impute missing data for outcome and covariates (White et al., 2011). The imputation model included all analysis variables, recent contact with mother and father variables, the child's social isolate status, and socio-demographic and school engagement variables that predicted missingness (missingness analysis is shown in Appendix 3.2), in addition to predictors of the exposure and outcome. This included earlier measures of child-rated behavioural and emotional problems (total SDQ score taken in the first term of year 7) to predict the exposure of teacher rated ADHD symptoms (first term of year 7), and child-rated depressive symptoms (in the first term of year 7) to predict the outcome of child-rated depressive symptoms (in the last term of year 7). The imputation model was used to predict missing data across 100 imputed datasets. Monte-Carlo errors were less than 10% of the standard error and FMI (fraction of missing information) values were no larger than 0.71. These are important checks to ensure low variability and high reproducibility in multiple imputation (White et al., 2011). After imputation, all analyses were re-ran and estimates combined across the 100 imputations using Rubin's rules (Rubin, 2004).

3.3. Results

3.3.1. Descriptive Statistics

Descriptive statistics for the sample and for females and males separately are shown in Table 3.1.

Table 3.1. Descriptive statistics for ADHD, depression and features of friendship

Variable	Overall mean (SE) / proportion (%)	Female mean (SE) / proportion (%)	Male mean (SE) / proportion (%)
ADHD	1.97 (0.07)	1.33 (0.08)	2.53 (0.11)
Depression	3.36 (0.12)	3.85 (0.19)	2.94 (0.16)
Presence of friends	2.90 (0.01)	2.93 (0.01)	2.87 (0.02)
Stability: best friend	39.6%	42.1%	37.5%
Stability: top three friends	62.3%	65.2%	59.8%
Quality: best friend	34.81 (0.21)	37.14 (0.28)	32.78 (0.30)
Quality: top three friends	10.84 (0.04)	10.81 (0.05)	10.86 (0.05)
Classroom friendship group: total difficulties	7.99 (0.20)	7.18 (0.22)	8.70 (0.24)
Classroom friendship group: cooperativeness	0.51 (0.01)	0.54 (0.01)	0.47 (0.01)
Classroom friendship group: disruptiveness	0.12 (0.005)	0.07 (0.005)	0.17 (0.01)
Number of people in classroom friendship group	4.98 (0.07)	4.59 (0.08)	5.33 (0.10)

n=1712 (53.5% male). ADHD attention deficit/hyperactivity disorder, SE standard error

3.3.2. Associations of ADHD, Features of Friendship and Depression

Teacher-rated ADHD at baseline was associated with naming fewer friends and lower friendship quality at baseline, both of which were associated with increased depressive symptoms at follow-up. ADHD symptoms were also associated with being part of a classroom friendship group that had higher total difficulties, and was rated as less cooperative and more disruptive at baseline. Stability of the best friendship from baseline to follow-up was inversely associated with depressive symptoms (Table 3.2). Teacher-rated ADHD symptoms were associated with depressive symptoms 7 months later ($b=0.48$ (95% CI 0.17, 0.79) $p=0.002$).

Table 3.2. Associations of ADHD symptoms, friendship variables and depressive symptoms

Friendship variable	ADHD symptoms association with variable (<i>b</i> (95% CI) <i>p</i>)	Variable association with depressive symptoms (<i>b</i> (95% CI) <i>p</i>)	Indirect effect via variable between ADHD and depressive symptoms (<i>b</i> (95% CI) <i>p</i>)
Presence of friends	-0.05 (-0.08, -0.02) 0.002	-0.65 (-1.24, -0.07) 0.029	0.03 (-0.004, 0.06) 0.095
Stability: best friend	OR=0.92 (0.80, 1.06) 0.267	-0.57 (-1.07, -0.06) 0.027	0.01 (-0.01, 0.03) 0.262
Stability: top three friends	OR=0.96 (0.82, 1.12) 0.568	-0.32 (-0.84, 0.21) 0.235	0.004 (-0.01, 0.02) 0.530
Quality: best friend	-0.75 (-1.29, -0.20) 0.008	-0.72 (-0.97, -0.47) <0.001	0.06 (0.01, 0.11) 0.011
Quality: top three friends	-0.15 (-0.25, -0.05) 0.003	-0.69 (-0.94, -0.44) <0.001	0.07 (0.02, 0.11) 0.008
Classroom friendship group: total difficulties	0.94 (0.61, 1.27) <0.001	0.17 (-0.10, 0.43) 0.211	0.02 (-0.05, 0.08) 0.633
Classroom friendship group: cooperativeness	-0.03 (-0.04, -0.02) <0.001	-0.03 (-0.29, 0.23) 0.798	-0.01 (-0.06, 0.04) 0.663
Classroom friendship group: disruptiveness	0.03 (0.02, 0.04) <0.001	0.15 (-0.12, 0.42) 0.262	-0.01 (-0.05, 0.08) 0.743

n=1712. ADHD attention deficit/hyperactivity disorder, *b* unstandardized beta, *CI* confidence interval, *OR* odds ratio

3.3.3. Indirect Effects via Friendship in the Association between ADHD and Depression

ADHD and depressive symptoms were associated directly and indirectly via friendship quality, both for best friend and top three friends, when tested separately (Table 3.2). They showed independent effects when tested simultaneously in a multiple mediator model (Table 3.3), each accounting for approximately 9% of the total effect of ADHD symptoms on subsequent depressive symptoms. Sensitivity analyses suggested that the friendship quality sub-scales of higher friendship conflict and lower friendship security (ability to disclose problems to friend and reconcile after disagreement) drove this effect (Appendix 3.3).

The indirect effect of ADHD to depressive symptoms via friendship quality was larger for females than males (Table 3.4).

Table 3.3. Indirect effects via friendship quality in the association of ADHD and depressive symptoms in a multiple mediator model

Effect	<i>b</i> (95% CI)	<i>p</i>	Percentage of total effect mediated
Indirect Effect Via Best Friendship Quality	0.04 (0.01, 0.08)	0.024	9.05%
Indirect Effect Via Top Three Friendships Quality	0.05 (0.006, 0.09)	0.024	9.48%
Total Indirect Effect	0.09 (0.03, 0.15)	0.002	18.53%
Direct Effect	0.39 (0.09, 0.70)	0.011	-
Total Effect	0.48 (0.18, 0.79)	0.002	-

n=1712. ADHD attention deficit/hyperactivity disorder, *b* unstandardized beta, *CI* confidence interval

Table 3.4. Moderation by gender of indirect effects via friendship quality

Mediator	Indirect effect (<i>b</i> (95% CI) <i>p</i>) in		Difference in indirect effect (<i>b</i> (95% CI) <i>p</i>) in males versus females	
	males	females	males	females
Quality: best friend	0.03 (-0.01, 0.07) 0.147	0.08 (-0.003, 0.17) 0.059	0.05 (-0.04, 0.15) 0.254	
Quality: top three friends	0.001 (-0.03, 0.03) 0.936	0.14 (0.02, 0.26) 0.020	0.14 (0.02, 0.26) 0.025	

Indirect effects between ADHD and depressive symptoms via best friendship quality and top three friendships quality (tested simultaneously in multiple mediator model) in males, females and the difference between genders ($n=1712$). *ADHD* attention deficit/hyperactivity disorder, *b* unstandardized beta, *CI* confidence interval

3.3.4. Moderation of Indirect Effects by Parent-Child Relationships

For this analysis, data from children who reported being in recent contact with their mother and/or father were used. Most (98.0%) children reported that they had been in contact with their mother in the last month and 92.5% with their father. Indirect effects via top three friendships quality attenuated ($p=0.040$) as mother-child relationship warmth increased (Table 3.5; Figure 3.1). Results were suggestive of this moderating effect by mother warmth acting on both paths in the indirect effect via top three friendships quality between ADHD and depressive symptoms (Figure 3.2; Appendix 3.4). Indirect effects via top three friendships quality also attenuated slightly as father-child hostility decreased, though this observation did not reach the conventional threshold for statistical significance ($p=0.084$) (Table 3.5; Figure 3.1).

All results were very similar before and after imputation (Appendix 3.5).

Table 3.5. Moderation by parental warmth and hostility of indirect effects via friendship quality

Moderator	Z-test of difference in indirect effect via best friendship quality at mean level of moderator versus mean+1SD (for warmth) or mean-1SD (for hostility)	Z-test of difference in indirect effect via top three friendships quality at mean level of moderator versus mean+1SD (for warmth) or mean-1SD (for hostility)
Mother warmth	$z=-0.02, p=0.981$	$z=2.05, p=0.040$
Mother hostility	$z=-0.35, p=0.725$	$z=-0.07, p=0.945$
Father warmth	$z=0.04, p=0.964$	$z=0.28, p=0.783$
Father hostility	$z=0.41, p=0.685$	$z=1.73, p=0.084$

Z-tests of difference between indirect effect via best friendship quality and top three friendships quality in the association of ADHD and depressive symptoms at mean level of moderator versus mean±1SD (n=1712). Parent variables were tested separately as moderators of a multiple mediator model (best friendship and top three friendships quality entered simultaneously). The model tested included interaction effects on the path between ADHD symptoms and friendship quality and on the path between friendship quality and depressive symptoms. *ADHD* attention deficit/hyperactivity disorder, *SD* standard deviation

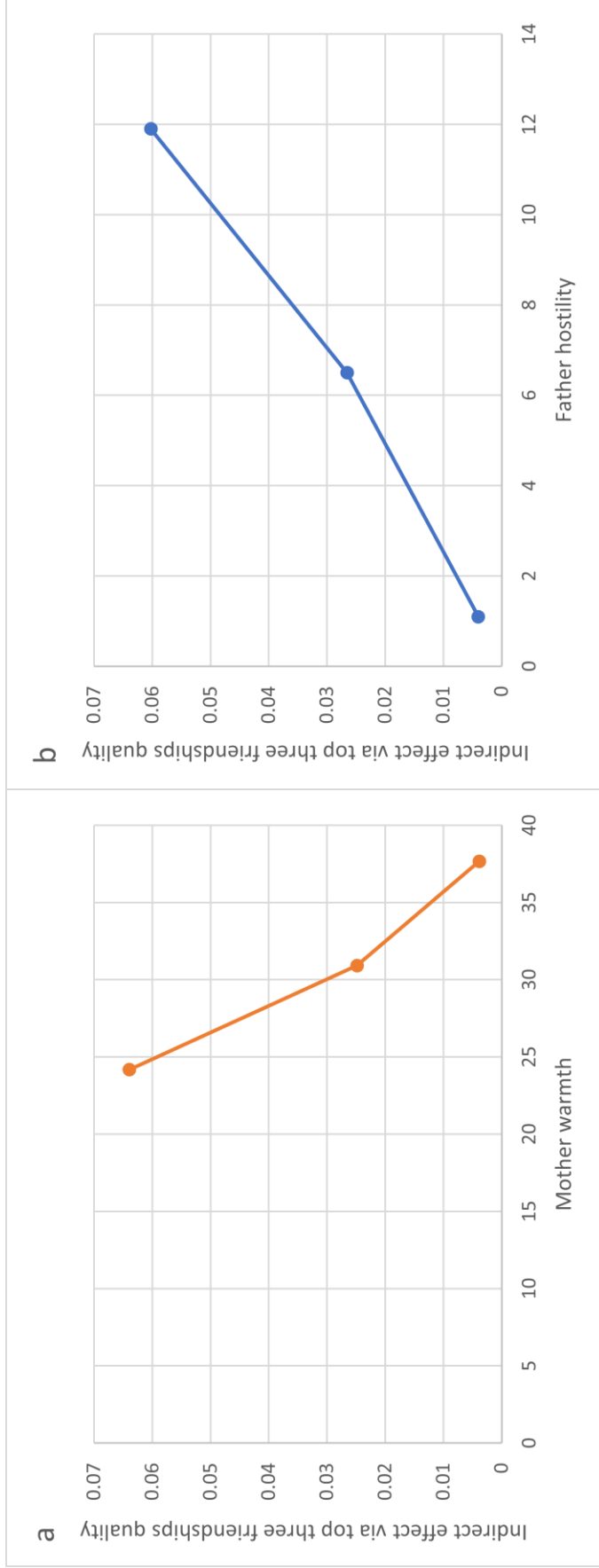


Figure 3.1. Moderation by parent-child relationship quality of mediation by friendship quality. Moderated mediation analysis suggested that when mother warmth increased, the indirect effect (beta) via quality of friendship with top three friends between ADHD and depressive symptoms attenuated (a). When father hostility decreased, the indirect effect via quality of friendship with top three friends also attenuated slightly (b), though this did not meet conventional thresholds for statistical significance. The model tested included interaction effects on the path between ADHD symptoms and friendship quality and on the path between friendship quality and depressive symptoms. Indirect effect betas at the mean of the moderator and the mean ± 1 standard deviation are plotted ($n=1712$). *ADHD* attention deficit/hyperactivity disorder

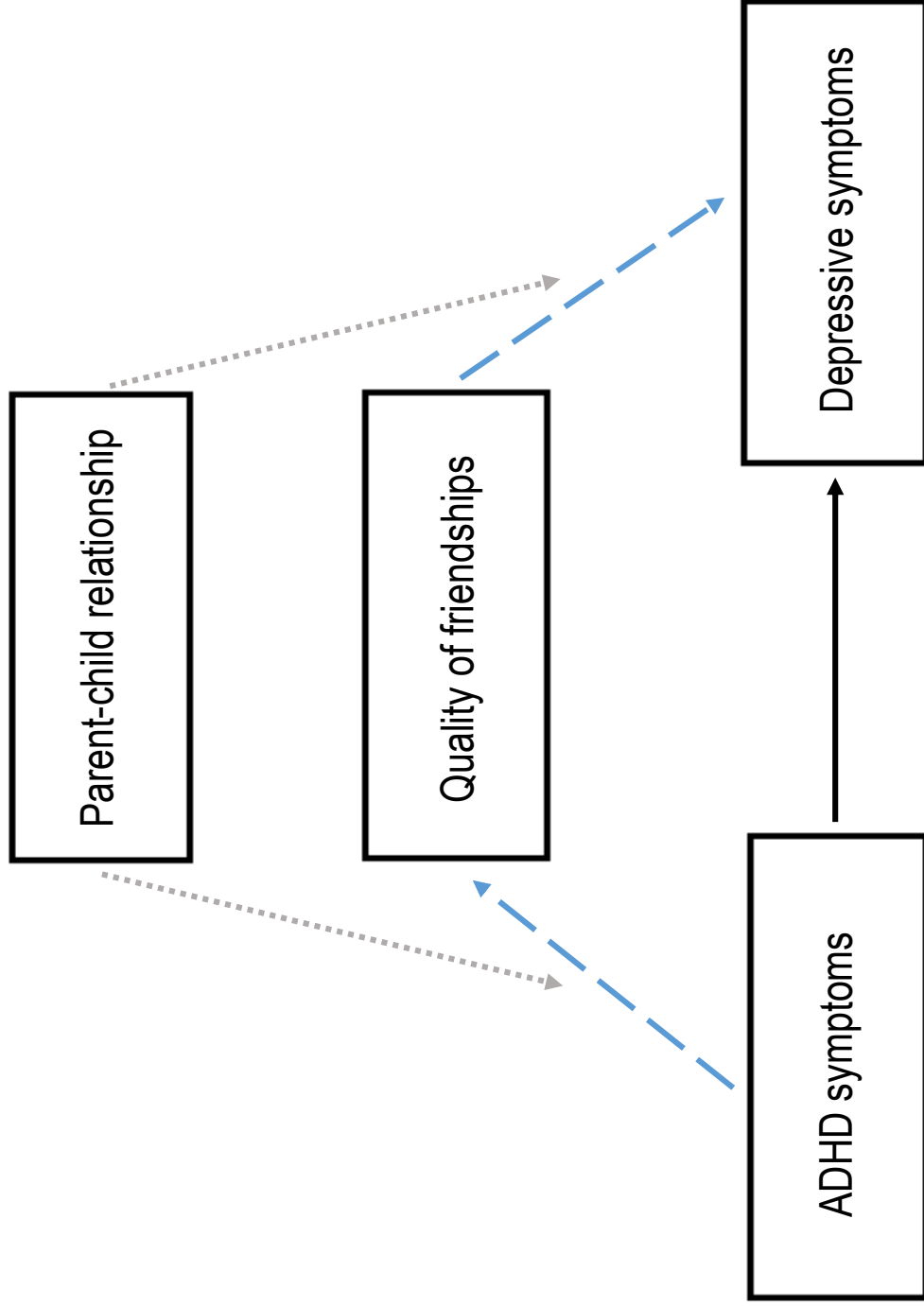


Figure 3.2. Moderated mediation model depicting the role of parent-child relationship quality and friendship quality in the link between ADHD and depression. Results supported a model whereby friendship quality accounted for part of the association between ADHD and depressive symptoms (black arrow) via mediated pathways (blue arrows). There was some suggestive evidence to suggest that the indirect effect via top three friendships quality might be moderated by parent-child relationships (grey arrows), whereby warmer, less hostile relationships with mothers and fathers slightly decreased the size of the indirect effect. *ADHD* attention deficit/hyperactivity disorder

3.4. Discussion

To my knowledge, this is the first detailed investigation of how different aspects of friendships are involved in the prospective association of ADHD and depressive symptoms. The potential moderating effect of parent-child relationship quality on any indirect effects via friendship in the prospective association of ADHD and depression was also investigated. In a representative longitudinal study of children, ADHD symptoms were associated with children having fewer friends and having lower quality friendships, which were both also associated with depressive symptoms. ADHD symptoms only were also associated with having a classroom friendship group that had more total difficulties, was more disruptive and less cooperative. Retaining best friendships across the study period was inversely associated with depression symptoms. These findings are in accord with case-control studies that found an association between ADHD and having fewer friends and more friendship conflict and aggression (Blachman & Hinshaw, 2002), and an association between poor friendship quality and depression (Goodyer et al., 1989; La Greca & Harrison, 2005). A previous study also conducted in the STARS sample found somewhat similar findings for friendship stability, where retaining poor quality friendships was associated with higher levels of emotional problems (Ng-Knight et al., 2019). Despite these varied associations, only friendship quality was identified as a pathway through which ADHD symptoms were associated with subsequent depressive symptoms. This mediation effect was observed for the quality of the best friendship and quality of top three friendships. The indirect effect via top three friendships quality varied slightly in magnitude according to the warmth and hostility of parent-child relationships, suggesting that positive parent-child relationships might mitigate some of the adverse effects in the indirect pathway of ADHD to depressive symptoms via poor quality friendships.

3.4.1. Mediation of the Association of ADHD and Depression via Friendship Quality

The findings on friendship quality align with theories of social difficulty explaining some of the link between early psychopathology and subsequent depression (Capaldi, 1992). The findings of the current study suggest this is also a

pathway that links ADHD to depression symptoms. Friendship quality as a form of perceived social support might reduce depression risk in those with elevated ADHD symptoms via increasing a sense of connectedness and self-esteem, or by buffering against life stresses and adversity (H. Y. Lee et al., 2019; Rueger et al., 2016), which are likely to be elevated in those with ADHD (Harpin, 2005). Sensitivity analyses showed that conflict and security with friends (ability to disclose problems to friend and reconcile after disagreement) appeared to be the specific elements of best friendship quality that were important in the pathway from ADHD to depressive symptoms. Elevated conflict with friends has been reported for children with ADHD (Blachman & Hinshaw, 2002) and poor quality friendships may be risk factors for depressive outcomes in school aged children (Goodyer et al., 1989).

Larger indirect effects via friendship quality were observed in females than males. This aligns with previous evidence of females valuing aspects of friendship quality such as companionship and intimacy more highly than males (Hall, 2010). Interpersonal stress may be more prevalent and predictive of depression in adolescent females than males (Shih, Eberhart, Hammen, & Brennan, 2006). This could particularly be the case in females with ADHD, who may experience more peer relationship difficulties than males with ADHD (Elkins, Malone, Keyes, Iacono, & McGue, 2011). However, it seems likely that the indirect effects observed are important to consider for both genders.

3.4.2. Moderation by Parent-Child Relationship Quality of Mediated Effects via Friendship Quality

There was some evidence of moderated mediation suggesting that indirect effects of top three friendships quality on the link between ADHD and depressive symptoms decreased slightly as self-reports of mother-child relationship warmth increased and father-child relationship hostility decreased, though the evidence for father hostility did not reach the conventional significance threshold. This draws attention to the need to consider the child's social support across different contexts such as the parent-child relationship, including fathers, who are understudied in the literature (Cabrera et al., 2018; Mikami, 2010). Findings were suggestive of mother

warmth moderating both the first part of the mediated pathway (ADHD to top three friendships quality path) and the second part of the mediated pathway (top three friendships quality to depression path) as shown in Figure 3.2. This aligns with previous findings of an association between parental behaviour and child peer relationships in children with ADHD (Mikami et al., 2010), in addition to studies that have found parent-child relationships may be able to compensate for a lack of friends (Stocker, 1994) and mitigate against poor mental health in the presence of adversity (Brennan et al., 2003; Collishaw et al., 2016, 2007; Lewandowski et al., 2014). The findings should also be considered in light of the potential effects of person-environment correlation, whereby individuals with certain traits are more likely to be exposed to certain situations, in addition to evocative effects whereby an individual is more likely to “create” certain situations and evoke responses from others that reinforce their behaviour (Caspi, Bem, & Elder Jr., 1989; Rutter et al., 1997). For example, in some cases, children with ADHD may find themselves more likely to experience difficulties in their relationship with their parents, which might reinforce poor social interactions with friends (and vice versa), thus increasing later depression risk.

However, these moderated mediation findings should be interpreted with caution given that results were not consistent across mother and father or between warmth and hostility. Nevertheless, this may be explained in part by previous findings that suggest mothers and fathers may have differential effects on the friendships of their adolescent children, including mother supportive behaviour, father problem-solving behaviour and both mother and father hostile behaviour influencing their adolescent children’s interaction styles with peers, for example (Flynn, Felmlee, Shu, & Conger, 2018; Updegraff, McHale, Crouter, & Kupanoff, 2001). Moderated mediation results in the current study were also inconsistent across the two friendship quality measures used. While some evidence of moderation by mother warmth was observed for the indirect effect via friendship quality with the top three friends, no moderation by parent-child relationship quality was observed for the indirect effect via friendship quality with the best friend. Moderation effects by gender were also only observed for the indirect effect via the

quality of the top three friendships. Measurement differences in the two friendship variables used in the present study may have impacted on findings, as a previous study also conducted in STARS found that a variable measuring quality of top three friendships was more conducive to finding evidence of interactions than the quality of the best friendship only variable (Ng-Knight et al., 2019).

3.4.3. Limitations

Limitations include the use of teacher reports of child ADHD symptoms which provide a reliable measure of ADHD symptoms in school, but most clinical research and practitioners rely primarily on parental reports of ADHD. Reliance on teacher ratings only might affect results, as teachers have been found previously to under-rate children's ADHD symptoms compared to parent ratings (Antrop, Roeyers, Oosterlaan, & Van Oost, 2002; Sollie, Larsson, & Mørch, 2012). Despite the longitudinal design used, there is a possibility that reverse causation contributed to observed associations. However, strong evidence that ADHD precedes depression in a potentially causal relationship has been found in a recent study (Riglin et al., 2020). Although indirect effects were tested, this is not mediation analysis *per se*, due to the exposure and mediator being measured contemporaneously (Selig & Preacher, 2009). This study had missing data, a common problem in longitudinal data (Spratt et al., 2010). However, tests were adjusted for confounders that predicted missingness, helping to address potential bias arising from missing data (Groenwold et al., 2012). Additionally, Multiple Imputation was conducted and results remained very similar in imputed data, suggesting bias caused by missingness was minimal (Spratt et al., 2010). Those with ADHD may under-report their depressive symptoms and may over-estimate their social competency, which could affect the observed associations (Fraser et al., 2018; Ohan & Johnston, 2011). In addition, those with depression may under-rate their social ability (Whitton, Larson, & Hauser, 2008). Although this could affect the self-reported friendship presence and quality results, peer-rated classroom data was also used to measure the characteristics of the friendship group, which might help to mitigate against any effect of illusory biases. ADHD was associated with characteristics of the classroom friendship group (a peer-rated variable), though it did not act as a mediator in the current study.

3.4.4. Strengths

Strengths include use of a representative school-based sample during the first year of secondary school with detailed information from multiple informants on different features of friendship, in addition to parent-child relationship quality. School life is important in adolescent mental health and stressors such as school transition can precipitate anxiety and depression (Rice, Frederickson, & Seymour, 2011; West, Sweeting, & Young, 2010), and may be particularly challenging for those with ADHD (Langberg et al., 2008; Richardson et al., 2015).

3.4.5. Implications

Implications of this work include pinpointing quality of friendships and parent-child relationships as important to consider clinically in those with ADHD for reducing depression risk. Many peer relationship-focused interventions, which have mainly focused on peer acceptance and social skills thus far, have shown little success in children with neurodevelopmental disorders (Mikami, 2010). Promising directions for the development of enhanced programmes include those involving a parental component focused on dyadic friendship building (Gardner et al., 2019). Schools' arrangements regarding awareness of friendship groups (e.g. keeping together or separating friends) are also important in ensuring children feel settled at the beginning of secondary school (Keay, Lang, & Frederickson, 2015), and may need additional consideration in children with ADHD. Practical implications for children with ADHD in mitigating later risk of emotional difficulties may also involve focusing on interventions to strengthen parent-child relationships (Abikoff et al., 2015; Meinzer, Felton, Oddo, Rubin, & Chronis-Tuscano, 2020). Interventions aiming to improve parent-child interactions can have beneficial effects on the mental health of both child and parent (Sonuga-Barke, Daley, Thompson, Laver-Bradbury, & Weeks, 2001).

3.4.6. Conclusion

In a large school-based sample, ADHD symptoms were associated with subsequent depressive symptoms partly via decreased friendship quality, suggesting that this aspect of friendship is one potential mechanism by which ADHD symptoms

increase risk for depressive symptoms. Positive features of parent-child relationships seemed to slightly alleviate the indirect effect via the top three friendships quality, highlighting the importance of considering different sources of social support in the child's life.

Chapter 4: A genome-wide association study meta-analysis investigating regions of shared genetic association in ADHD and MDD

This chapter is an amended version of a published pre-print:

Powell, V., Martin, J., Thapar, A., Rice, F. & Anney, R. (under review). Investigating regions of shared genetic variation in attention deficit/hyperactivity disorder and major depressive disorder: A GWAS meta-analysis. *Manuscript under review for publication. Preprint available on bioRxiv at <https://doi.org/10.1101/2020.04.22.054908>*

In the earlier empirical chapters in this thesis, I investigated potential social mediating mechanisms contributing to the association between ADHD and depression. However, such mechanisms can be influenced by genetic factors via gene-environment interplay. Indeed, both ADHD and depression are influenced by genetic characteristics and demonstrate genetic overlap. In this chapter, I therefore investigated genetic overlap between ADHD and depression and aimed to investigate genomic regions of shared variation in ADHD and MDD that might contribute to the observed genetic correlation between the two conditions. This was done by conducting a meta-analysis of genome-wide association (GWA) studies of ADHD and MDD, using the most well-powered GWA study available for ADHD (20,183 cases and 35,191 controls) and for MDD (135,458 cases and 344,901 controls). SNPs that were genome wide significant ($p < 5 \times 10^{-8}$) in the meta-analysis that were also strongly associated ($p < 5 \times 10^{-4}$) with each disorder separately were followed up to investigate their potential mechanism in the genetic overlap of ADHD and MDD. First, these putatively pleiotropic SNPs were examined for nearby protein coding genes. Next, they were tested for effects on gene expression as expression quantitative trait loci (eQTL; i.e. whether they affect the level of messenger RNA produced was tested) in human tissues. Finally, index SNPs were tested for additional associations across a broad range of phenotypes to examine the extent of pleiotropy and to identify potential risk mechanisms involving related traits to ADHD and MDD. Fourteen linkage disequilibrium-independent SNPs that were genome wide significant in the meta-analysis ($p < 5 \times 10^{-8}$) were also associated with each disorder independently ($p < 5 \times 10^{-4}$). Nine of these SNPs were not highlighted

previously in either of the individual GWA studies. Nine of the fourteen SNPs acted as eQTL and two as eQTL in brain tissues. Index SNPs were associated with additional phenotypes examined, particularly those related to mental health, which serves as further evidence for the potential role of these SNPs in psychiatric phenotypes.

4.1. Introduction

In chapters 2 and 3, potential social mediating mechanisms were investigated as possible explanations of the association between ADHD and depression, including difficulties with friendship and academic attainment. As discussed in chapter 1 however, the association of ADHD and depression is likely due to a combination of environmental and genetic factors, and social mediating pathways can be influenced by gene-environment interplay. Thus, the genetic overlap of ADHD and major depressive disorder (MDD; used synonymously with ‘depression’ here) is investigated in the current chapter. Although it is known that ADHD and MDD are familial and heritable disorders that are genetically correlated (Demontis et al., 2019; Flint & Kendler, 2014; Thapar, 2018; Wray et al., 2018), the specific regions of the genome that might account for this overlap are unclear. Therefore, the current study sought to examine the genetic overlap of ADHD and MDD to identify regions of the genome that might contribute to this overlap by conducting a genome-wide association (GWA) study meta-analysis. It is important to note that while the studies detailed chapters 2 and 3 were conducted in samples of children and young people, the GWA studies available for the meta-analysis in the current study are based on samples of children and adults for ADHD and samples of adults for MDD. The existing literature on the genetic overlap of ADHD and MDD is discussed below and the study aims are outlined.

4.1.1. The Genetic Overlap of ADHD and MDD

As ADHD and depression are both heritable (Demontis et al., 2019; Flint & Kendler, 2014; Thapar, 2018; Wray et al., 2018), shared genetic risk is one factor that could explain part of the association between ADHD and depression. Early evidence supporting the genetic overlap of ADHD and depression came from twin studies, which observed a genetic correlation ranging from 0.23 to 0.77 for ADHD and depression with the magnitude of association varying according to age and sex (T. J. Chen et al., 2016; Cole et al., 2009; Lahey et al., 2011; Rydell et al., 2017; Schmitz & Mrazek, 2001). More recently, evidence of the genetic overlap of ADHD and depression has also come from GWA studies of ADHD and MDD, which report an

estimated ADHD-MDD genetic correlation of $r_g=0.42$ ($SE=0.03$) (Demontis et al., 2019; Wray et al., 2018). Studies that use polygenic scores derived from the ADHD GWA study have found that ADHD polygenic score is associated with depression symptoms in a twin sample of children (Brikell et al., 2018), depression symptoms in an adolescent population sample (Rice et al., 2019) and depression diagnosis in an adult population sample (Du Rietz et al., 2018). In addition, the most recent GWA study meta-analysis of eight psychiatric disorders (anorexia nervosa, ADHD, autism spectrum disorder, bipolar disorder, MDD, obsessive-compulsive disorder, schizophrenia, and Tourette syndrome) by the Cross Disorder Group of the Psychiatric Genomics Consortium (PGC) (P. H. Lee et al., 2019) also reported a robust genetic correlation between ADHD and depression ($r_g=0.44$, $SE=0.03$). As Lee et al., (2019) focussed on investigating cross-disorder effects across eight psychiatric disorders and thus reported based on statistics across all eight diagnoses, key findings are likely to miss regions that impact only on ADHD and MDD due to a lack of evidence across the other six diagnoses. These include GWA studies with greater statistical power than observed in the ADHD and MDD GWA studies (e.g. bipolar disorder), meaning that observed results may be over-weighted for such diagnoses. The overlap between ADHD and depression might also be explained by risk mechanisms involving other phenotypes that have not been previously studied. For instance, psychiatric phenotypes including early irritability and anxiety have been shown to be antecedents of depression, including in those with ADHD (Eyre et al., 2017; Rice et al., 2017; Stringaris, Cohen, Pine, & Leibenluft, 2009).

4.1.2. The Current Study

In the current study, the aim was to identify genomic regions that might explain the genetic overlap of ADHD and depression. A GWA study meta-analysis of ADHD and MDD was conducted, aiming to identify associated SNPs with contribution to both disorders. The secondary aim was to follow up these putatively pleiotropic SNPs by investigating biological mechanisms including whether they affected gene expression, and to investigate associations between the SNPs and a broad range of additional GWA study phenotypes.

4.2. Methods

4.2.1. Samples and Measures

Published GWA study summary statistics of ADHD (Demontis et al., 2019) and MDD (Wray et al., 2018) were used. GWA study data were downloaded from <https://www.med.unc.edu/pgc/results-and-downloads/>. Additional local quality control of the downloaded data was performed to align genome strand, genome build (hg19) and marker nomenclature (HRC1.1) across the studies. All analysis was limited to autosomal SNPs.

Attention Deficit/Hyperactivity Disorder: Demontis et al., 2019

Demontis and colleagues identified 12 genome-wide significant loci associated with ADHD by combining 12 cohorts (20,183 cases and 35,191 controls), mainly of European and North American ancestry and one of Chinese ancestry. The Danish population-based cohort (iPSYCH) used health records from the Danish Psychiatric Central Research Register to identify those individuals diagnosed with ICD-10 ADHD. The remaining 11 cohorts consisted of 4 parent-offspring trio cohorts and 7 case-control cohorts in which individuals with ADHD were recruited from clinics, hospitals, or medical registers, and were diagnosed using standard tools administered by trained researchers or clinicians. Imputation of non-genotyped markers was conducted using the 1000 Genomes Project Phase 3 reference panel. Heterogeneous ancestry in samples has been shown to give rise to population stratification bias in genome-wide analyses (Berg et al., 2019). Thus, analysis was restricted to samples of European ancestry only, leaving 19,099 cases and 34,194 controls.

Major Depressive Disorder: Wray et al., 2018

Wray and colleagues identified 44 genome-wide significant loci associated with MDD by combining 7 case-control cohorts (135,458 cases and 344,901 controls). The first cohort was a mega-analysis of 29 European ancestry samples where MDD cases were required to meet DSM-IV, ICD-9 or ICD-10 criteria using

structured diagnostic interviews, clinician-administered checklists or a review of medical records. The 6 additional cohorts were also of European ancestry where cases were defined according to DSM-IV, ICD-9 or ICD-10 diagnoses of MDD derived via interviews, self-report depressive symptoms or treatment seeking, and national or hospital treatment records. The published data includes an MDD cohort from the 23andMe study. Due to data restrictions, the 23andMe cohort was excluded from analysis, leaving a sample of 59,851 cases and 113,154 controls.

4.2.2. Analysis

SNP-based Heritability and Genetic Correlation

SNP-based heritability (SNP h^2) and the genetic correlation of the ADHD and MDD GWA studies were calculated using the LD-score approach (Bulik-Sullivan et al., 2015). Estimates were calculated on the liability scale using a population prevalence of 0.05 for ADHD and 0.15 for MDD. Summary data were harmonised to common build, strand and nomenclature and SNP h^2 estimates calculated limited to the HapMap-3 SNP subset provided by the LDSC software.

GWA Study Meta-analysis to Identify Regions of Joint Association

A number of GWA study meta-analysis approaches exist for investigating cross-phenotype associations and pleiotropy (van Rheenen et al., 2019). In the current study, an adapted GWA study meta-analysis was performed to identify regions of joint association between ADHD and MDD. Therefore, the maximum SNP effect was meta-analysed in a GWA study summary-data-based meta-analysis. The meta-analysis was performed using a fixed-effects inverse variance-weighted model using METAL (Willer, Li, & Abecasis, 2010) with ADHD used as the index. A fixed-effects model rather than a random-effects model was chosen to maximise power to detect SNPs associated with ADHD and MDD (Evangelou & Ioannidis, 2013). A genome-wide significance threshold of 5×10^{-8} was used.

Unlike standard meta-analytic approaches aiming to increase SNP discovery, the aim of the current study was to identify regions of common association between ADHD and MDD regardless of the direction of the effect. Strong associations in

opposing directions are of biological interest and may also be expected where one trait is a counter measure of the second (e.g. wellbeing and depressive symptoms). Such associations might cancel each other out in a standard meta-analytic approach where the effect at one allele only (either the reference or alternative allele) between different studies is meta-analysed. Therefore, the adapted meta-analysis performed in the current study is in essence two meta-analyses examining the same effect: one where the effect at the reference allele for trait 1 is matched to the effect at the reference allele for trait 2, and the opposite effect where the effect at the reference allele for trait 1 is matched to the effect at the alternative allele for trait 2. In other words, the meta-analysis was conducted twice with the alleles or signs (positive/negative) of the effects flipped to allow detection of association signals independent of direction of effect in ADHD and MDD. The maximized test-statistic from either the same- or opposite-direction comparisons were then extracted for further interrogation.

For each of the identified SNPs from the ADHD-MDD meta-analysis, the association findings were compared against the original ADHD and MDD GWA studies. Based on these comparisons, associations were categorised into three classes: Model 1, 2 and 3. Model 1 is defined as a genome wide significant meta-analysis association where the p-value for ADHD GWA study is smaller than both the MDD GWA study and meta-analysis p-values, thus appearing to be more robustly implicated in ADHD than the combination of both phenotypes. Model 2 is the converse of Model 1, where the p-value is smallest for the MDD GWA study, thus identifying SNPs that appear to be more robustly associated with MDD. Model 3 is defined as a genome wide significant meta-analysis association where the meta-analysis p-value is smaller than both the ADHD and MDD GWA study p-values. Model 3 is suggestive of a variant contributing to both phenotypes and highlights potential regions of joint association between ADHD and MDD. Thus, while all Model 1 and 2 SNPs would have been highlighted previously by the individual ADHD and MDD GWA studies, Model 3 is the model of interest in the current study because this model identifies potential regions of shared association in ADHD and MDD as stated in the study aim. Thus, all SNPs meeting Model 3 criteria are reported. To limit the

identification of putatively stochastic Model 3 associations, reporting was limited to SNPs that showed an ADHD and MDD maximum p-value of 5×10^{-4} .

SNPs that met Model 3 criteria were Linkage Disequilibrium (LD) pruned using PLINK (version 1.07; Purcell et al., 2007). LD statistics for pruning were derived from the European super population 1000 genomes project phase 3 reference genotypes. “LD ranges” were defined as regions around the index association containing SNPs with $r^2 \geq 0.2$ with the primary SNP and $p < .05$.

Due to concerns in the literature regarding over-reliance on p-values (Sterne & Davey Smith, 2001), the meta-analysis was repeated using effect size estimates (z-score thresholds) to define Model 1, 2 and 3 SNPs (Appendix 4.1: Table 4.1a).

Annotation of Association Signals within Identified Regions

To aid in the biological interpretation of the associated markers, the index SNPs, SNPs in high LD with the index SNP, and LD ranges were annotated with data related to both physical and functional landmarks. SNPs in high LD were defined as those SNPs with $r^2 > 0.8$ with the index SNP within the European super population 1000 genomes project phase 3 reference genotypes. Gene transcript and cis-eQTL annotations were investigated as described below.

Gene transcripts. Transcript annotations were assigned based on overlap with the LD-ranges (with a border of 35kb 5' and 5kb 3' to the transcript boundaries) using the Homo sapiens GRCh37.87 gene sets (downloaded from ftp://ftp.ensembl.org/pub/grch37/release-90/gtf/homo_sapiens/Homo_sapiens.GRCh37.87.gtf.gz).

eQTL. To test if index variants affected gene expression, cis-eQTL (expression quantitative trait loci that coincide with the location of underlying gene) annotations were assigned to index SNP and SNPs in high LD using a database that catalogued eQTL data from 48 adult human tissue types (GTEx version 7; downloaded from <https://www.gtexportal.org/home/>; GTEx Consortium et al., 2017). All cis-eQTL with a tissue specific association ($P < 1 \times 10^{-5}$) were mapped. Where more than one SNP linked to the index SNP contained an eQTL for a tissue, the strongest association was reported.

Associations with Additional Genome Wide Association Study Phenotypes

Regions of genome wide significant association in the meta-analysis (LD ranges containing index association of $p < 5 \times 10^{-8}$) were mapped to strong associations (LD ranges containing index association of $p < 1 \times 10^{-5}$) for a set of 37 reference GWA studies of human phenotypes. These GWA studies are for reasonably well-powered, heritable, complex human traits that could be of relevance to ADHD and MDD, for example, as part of a causal cascade. This also allowed checking of how pleiotropic identified variants are, i.e. whether they are specific to ADHD and MDD, associated with psychiatric traits more widely, or are associated ubiquitously across various phenotypes. The 37 studies covered 5 categories of traits: mental health (13 traits), personality (5 traits), cognitive (3 traits), anthropometric (4 traits) and 'other' (12 traits). The 'other' category included traits relating to physical activity, smoking and health conditions of the skin, digestive, genitourinary, metabolic, immune and nervous systems. All GWA study LD ranges were calculated as described previously and overlaps were mapped using bedtools (<https://bedtools.readthedocs.io/>). In addition, the association at the index SNPs (rather than the LD ranges of the SNP) against all 37 GWA studies was directly assessed. All SNPs were p-corrected < 0.05 . Bonferroni correction based on 37 independent tests was applied (Appendix 4.2). A full list of the GWA studies used in this analysis is included in Appendix 4.1 (Table 4.1b).

4.3. Results

4.3.1. SNP Heritability and Genetic Correlation

After quality control of the ADHD summary data, 5,907,045 SNPs remained. ADHD SNP h^2 measured on the liability scale was estimated as $h^2 = 0.22$ (0.02). After quality control of the MDD summary data, 7,104,680 SNPs remained. MDD SNP h^2 on the liability scale was $h^2 = 0.15$ (0.01). Genetic correlation between ADHD and MDD was estimated as $r_g = 0.52$ (0.04) (Genetic covariance: 0.08 (0.01); LD-score intercept: 0.18 (0.01)).

4.3.2. Identification of Regions Showing Evidence of Common Association

Fourteen SNPs were identified that met Model 3 criteria in the combined analysis, i.e. they were associated with both MDD and ADHD to a similar degree (sample size per SNP range of 120,401 to 191,525). That is they were associated at genome wide significance level in the combined analysis, the p-value was lower in the combined analysis compared to the individual GWA studies, and the p value was $<5 \times 10^{-4}$ for ADHD and MDD separately (Table 4.1). Each of the 14 SNPs demonstrated concordant directions of effect for ADHD and MDD. Nine of the 14 SNPs were novel in that they were not previously identified as being genome wide significant or within regions that harbour genome wide significant association for ADHD or MDD (Appendix 4.1: Table 4.1c). For each of the 14 index SNPs, the regions that contained them were associated at the genome wide significant level in at least one of the 37 reference GWA studies as well as with ADHD and MDD GWA studies (Appendix 4.1: Table 4.1d). Moreover, these associations were also observed for the same SNP (Appendix 4.2). Follow-up analyses were performed for each of these 14 index SNPs, which is described below and in Appendices 4.1 – 4.3. For 2 of the SNPs which were of greatest interest as they had the strongest (smallest p-value) meta-analysis signal (rs12658032) and the strongest evidence that it acted as a brain eQTL (rs8084351), detailed figures of key results are also presented. Detailed results for all other SNPs are shown in the Appendices (Appendices 4.1 – 4.3).

Table 4.1. Summary of genome-wide significant associations for SNPs identified as contributing to both ADHD and MDD

SNP	Position	Ref	Alt	OR (ADHD)	P (ADHD)	OR (MDD)	P (MDD)	OR (Combined)	P (Combined)	LD Range	Protein Coding Genes Overlapping LD Range
rs12658032	chr5:103904226	A	G	1.07 (1.05-1.10)	1.2e-07	1.05 (1.03-1.07)	1.2e-10	1.06 (1.04-1.07)	1.5e-16	chr5:103671867..104082179	
rs4593766	chr1:73773043	T	C	1.05 (1.02-1.08)	6.4e-05	1.04 (1.03-1.06)	1.7e-08	1.04 (1.03-1.06)	4.9e-12	chr1:73666614..73991792	
rs61867322	chr10:106647839	A	G	0.93 (0.90-0.96)	7.2e-06	0.95 (0.94-0.97)	5.3e-06	0.95 (0.93-0.96)	6.4e-10	chr10:106529451..106797515	SORCS3
rs2509805	chr11:57650796	T	C	1.05 (1.02-1.08)	2.7e-04	1.04 (1.02-1.06)	5.3e-07	1.04 (1.03-1.06)	6.4e-10	chr11:57641883..57661032	
rs113901452	chr5:44816452	A	G	1.10 (1.05-1.16)	1.4e-04	1.08 (1.04-1.11)	1.0e-06	1.08 (1.06-1.11)	8.1e-10	chr5:44816452..44861664	MRPS30
rs1371048	chr2:145753166	T	G	0.94 (0.91-0.97)	4.8e-05	0.96 (0.94-0.97)	6.1e-06	0.95 (0.94-0.97)	2.3e-09	chr2:145701992..145753166	
rs8084351	chr18:50726559	A	G	1.04 (1.02-1.07)	4.1e-04	1.03 (1.02-1.05)	1.2e-06	1.04 (1.02-1.05)	2.4e-09	chr18:50716945..50737950	DCC
rs139161896	chr12:89802804	A	G	1.15 (1.08-1.22)	8.8e-05	1.10 (1.06-1.14)	5.1e-06	1.11 (1.08-1.15)	3.2e-09	chr12:89721105..89904596	DUSP6 POC1B
rs2029591	chr3:49646981	T	C	1.07 (1.04-1.11)	1.7e-05	1.04 (1.02-1.06)	2.8e-05	1.05 (1.03-1.07)	5.9e-09	chr3:49193081..49890967	AMIGO3 AMT APEH BSN C3orf62 C3orf84 CAMKY CCDC36 CCDC71 CDHR4 DAG1 FAM212A GMPPB GPX1 IP6K1 KLHDC8B MST1 NICN1 RHOA RNF123 RP11-3B7.1 TCTA TRAIIP UBAT USP4
rs2433018	chr15:47677596	A	G	0.94 (0.91-0.97)	3.5e-05	0.96 (0.94-0.98)	2.8e-05	0.95 (0.94-0.97)	1.1e-08	chr15:47659445..47685378	SEMA6D
rs12226775	chr11:49179289	T	C	1.10 (1.05-1.14)	1.8e-05	1.05 (1.02-1.08)	6.4e-05	1.06 (1.04-1.08)	1.8e-08	chr11:48234357..49873791	FOLH1 OR4A47 OR4B1 OR4C3 OR4C5 OR4S1 OR4X1 OR4X2 TRIM49B TRIM64C FAM172A
rs71639293	chr5:92995013	A	G	1.07 (1.04-1.11)	5.0e-05	1.04 (1.02-1.06)	4.0e-05	1.05 (1.03-1.06)	2.6e-08	chr5:92995013..92995013	
rs16827974	chr3:117837222	A	G	1.07 (1.04-1.10)	3.3e-05	1.04 (1.02-1.05)	6.8e-05	1.04 (1.03-1.06)	3.1e-08	chr3:117826733..117903064	
rs17775184	chr14:98647550	T	C	1.06 (1.03-1.10)	9.6e-05	1.04 (1.02-1.05)	5.2e-05	1.04 (1.03-1.06)	4.7e-08	chr14:98645610..98667928	

Protein coding genes located in the immediate region of each SNP are reported. ADHD attention deficit/hyperactivity disorder, MDD major depressive disorder, SNP single nucleotide polymorphism, OR odds ratio, LD linkage disequilibrium

Two of these 14 index SNPs (rs12658032 and rs4593766) had previously shown strong evidence for association with the individual ADHD or MDD GWA studies. The first of these SNPs, rs12658032, ($OR_{meta}=1.06(1.04-1.07)$; $P_{meta}=1.54 \times 10^{-16}$) was the strongest association observed, with a genome-wide significant association observed in MDD and a strong association for ADHD (see Table 4.1 & Figure 4.1). The SNP is mapped to chromosome 5q21.2 in a region showing no protein-coding annotation and no evidence of eQTL ($P < 10^{-5}$) (Appendix 4.1: Table 4.1e-f). rs12658032 shows SNP-level associations in additional mental health-related GWA studies in the same direction of effect as observed in the ADHD and MDD GWA studies, including depressive symptoms and bipolar disorder, as well as anorexia in the opposing direction of effect (Figure 4.2 & Appendix 4.2). The region is also associated with years of education, birthweight, BMI and waist circumference (Appendix 4.1: Table 4.1d).

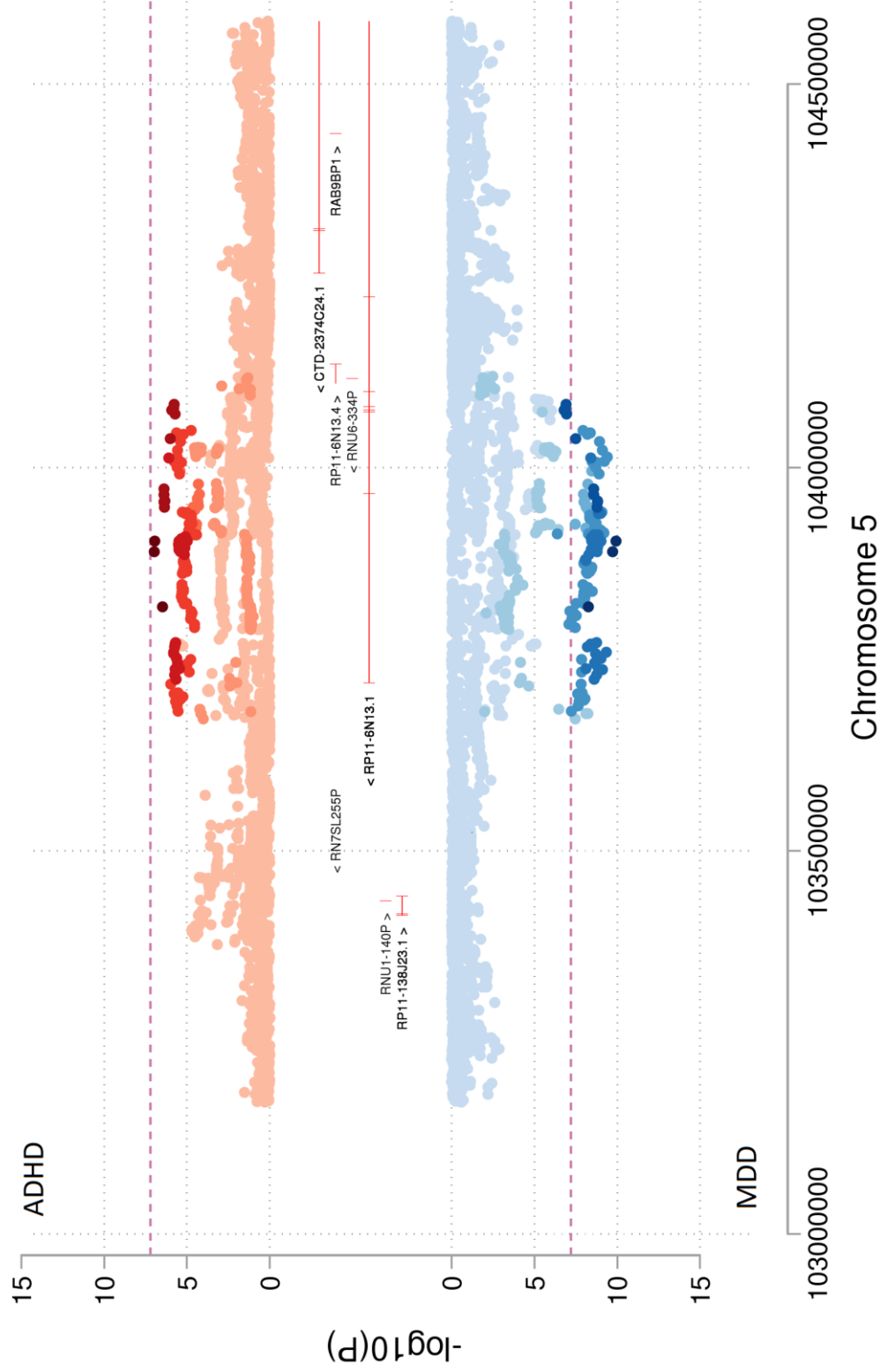


Figure 4.1. Miami plot showing the association of SNP rs12658032 with ADHD compared to MDD. Miami plot from the meta-analysis of ADHD and MDD GWA studies. SNP rs12658032 on chromosome 5 was associated with both ADHD ($p=1.15 \times 10^{-7}$) as shown in red and with MDD ($p=1.18 \times 10^{-10}$) as shown in blue to a genome-wide significant level and was also genome-wide significant in the meta-analysis ($p=1.54 \times 10^{-16}$). This SNP was located in a protein-coding gene desert. Non-protein-coding genes are shown in red. Genes are defined according to residence within the LD block of index SNP. The x-axis is chromosomal position in base pairs and the y-axis is the p value ($-\log_{10} p$ value) of the association of the SNP with both disorders. *ADHD* attention deficit/hyperactivity disorder, *MDD* major depressive disorder, *SNP* single nucleotide polymorphism, *LD* linkage disequilibrium

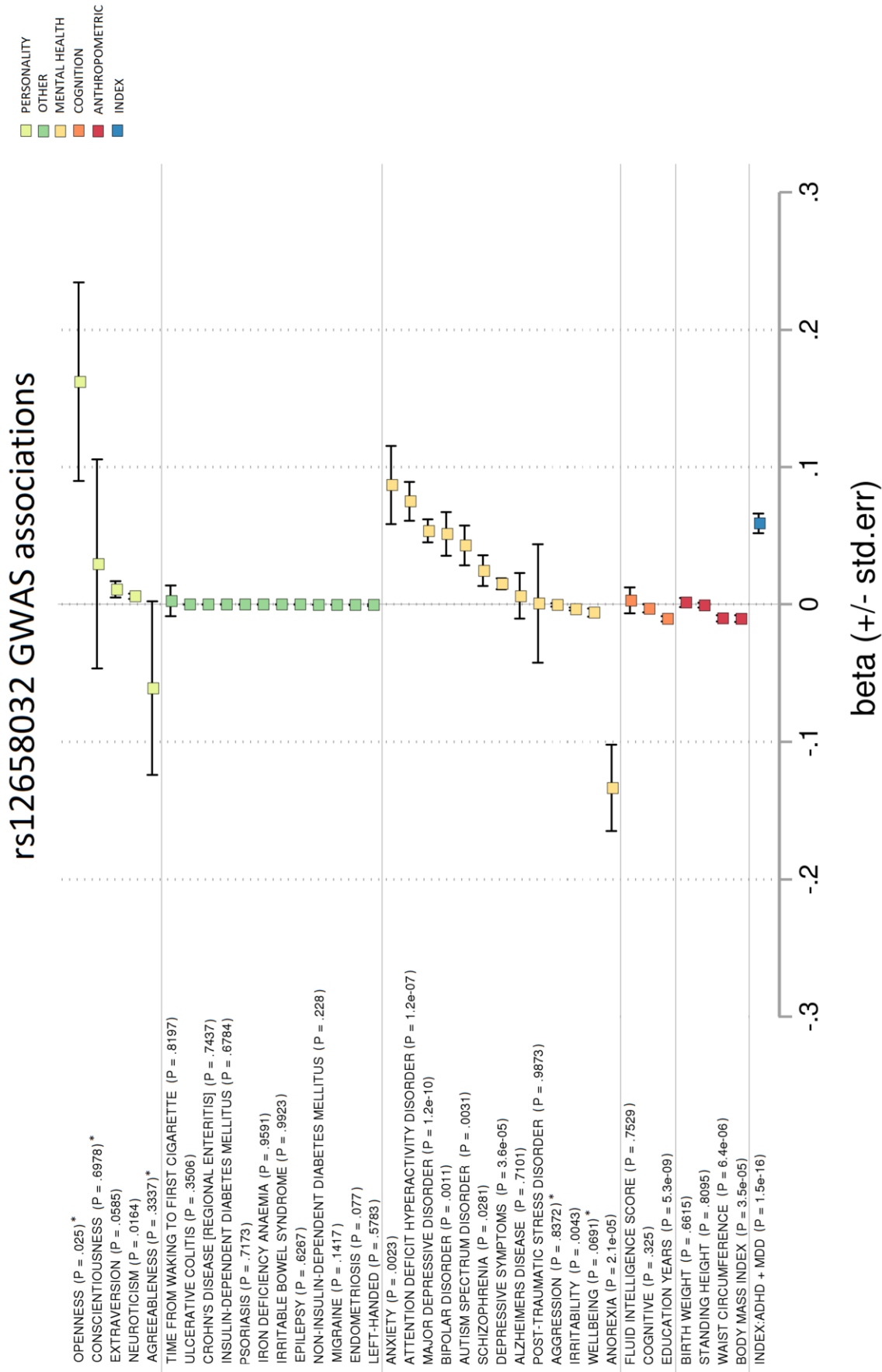


Figure 4.2. Forest plot showing additional associations of rs12658032. To investigate pleiotropy, rs12658032 was tested for associations across 37 phenotypes covering various aspects of health and functioning. rs12658032 was associated mainly with mental health phenotypes. To a lesser extent, it was associated with cognition and BMI. p = non-corrected p-value. * = results unavailable for rs12658032 so a proxy SNP – rs1592757 – was used. ADHD attention deficit/hyperactivity disorder, MDD major depressive disorder, GWAS genome-wide association study

The second of these strongly associated SNPs, rs4593766, is mapped to chromosome 1p31.1 ($OR_{meta}=1.04(1.03-1.06)$; $P_{meta}=4.9 \times 10^{-12}$) and is similarly located in a region showing no protein-coding annotation and no evidence of brain related eQTL (Table 4.1 & Appendix 4.1: Table 4.1e-f). rs4593766 demonstrates SNP-level associations in mental health related GWA studies in addition to ADHD and MDD, such as anxiety and schizophrenia (Appendix 4.2). The region is also associated with years of education, birthweight, BMI and waist circumference (Appendix 4.1: Table 4.1d).

Nine of the 14 index SNPs were found to be (or be in high LD with) cis-eQTL (Appendix 4.1: Table 4.1e-f). Two of these index SNPs (rs2029591 and rs8084351) are linked to brain-eQTL. rs2029591 ($OR_{meta}=1.05(1.03-1.07)$; $P_{meta}=5.9 \times 10^{-9}$) is mapped to chromosome 3p21.31 and is physically co-located over many genes (Table 4.1). rs2029591 showed evidence as an eQTL for *AMT*, *FAM212A*, *GPX1*, *NCKIPSD* and *RNF123* across multiple brain tissues (Appendix 4.1: Table 4.1e-f). As an example, *NCKIPSD* encodes a protein involved in the building and maintenance of dendritic spines and modulates neuronal synaptic activity (Cho et al., 2013). rs2029591 shows SNP-level associations with additional phenotypes including cognitive traits, BMI and various mental health traits including irritability and bipolar disorder (Appendix 4.2).

rs8084351 ($OR_{meta}=1.04(1.02-1.05)$; $P_{meta}=2.4 \times 10^{-9}$) is mapped to chromosome 18q21.2 and is physically co-located over the *DCC* gene (Table 4.1 & Figure 4.3). *DCC* encodes a receptor involved in guiding neuronal growth and is highly expressed in the brain (Li et al., 2004). rs8084351 showed evidence as an eQTL for *DCC* in the cerebellum ($b=-0.39$, $SE=0.08$, $p=4.60 \times 10^{-6}$) (Appendix 4.1: Table 4.1e-f). In addition to MDD and ADHD, rs8084351 is also associated at the SNP-level with cognitive traits, years of education, neuroticism and mental health traits such as irritability, depressive symptoms and schizophrenia (Figure 4.4 & Appendix 4.2).

Alongside the majority of the SNPs reported in this analysis (i.e. rs61867322, rs2509805, rs113901452, rs1371048, rs8084351, rs139161896, rs2029591, rs2433018, rs12226775, rs71639293, rs16827974 and rs17775184), rs8084351 is an example of a novel finding having been observed below the standard genome-wide

significance reporting threshold in both the MDD and the ADHD GWA studies (Table 4.1 & Figure 4.3). These SNPs when combined in this meta-analysis reveal a strong combined signal (Table 4.1 & Figure 4.5).

Detailed description of the annotations for the additional identified markers are given in Appendix 4.3. Meta-analysis results remained similar when effect size estimates (z-score thresholds) were used to define Model 1, 2 and 3 SNPs instead of p-value thresholds (Appendix 4.1: Table 4.1a).

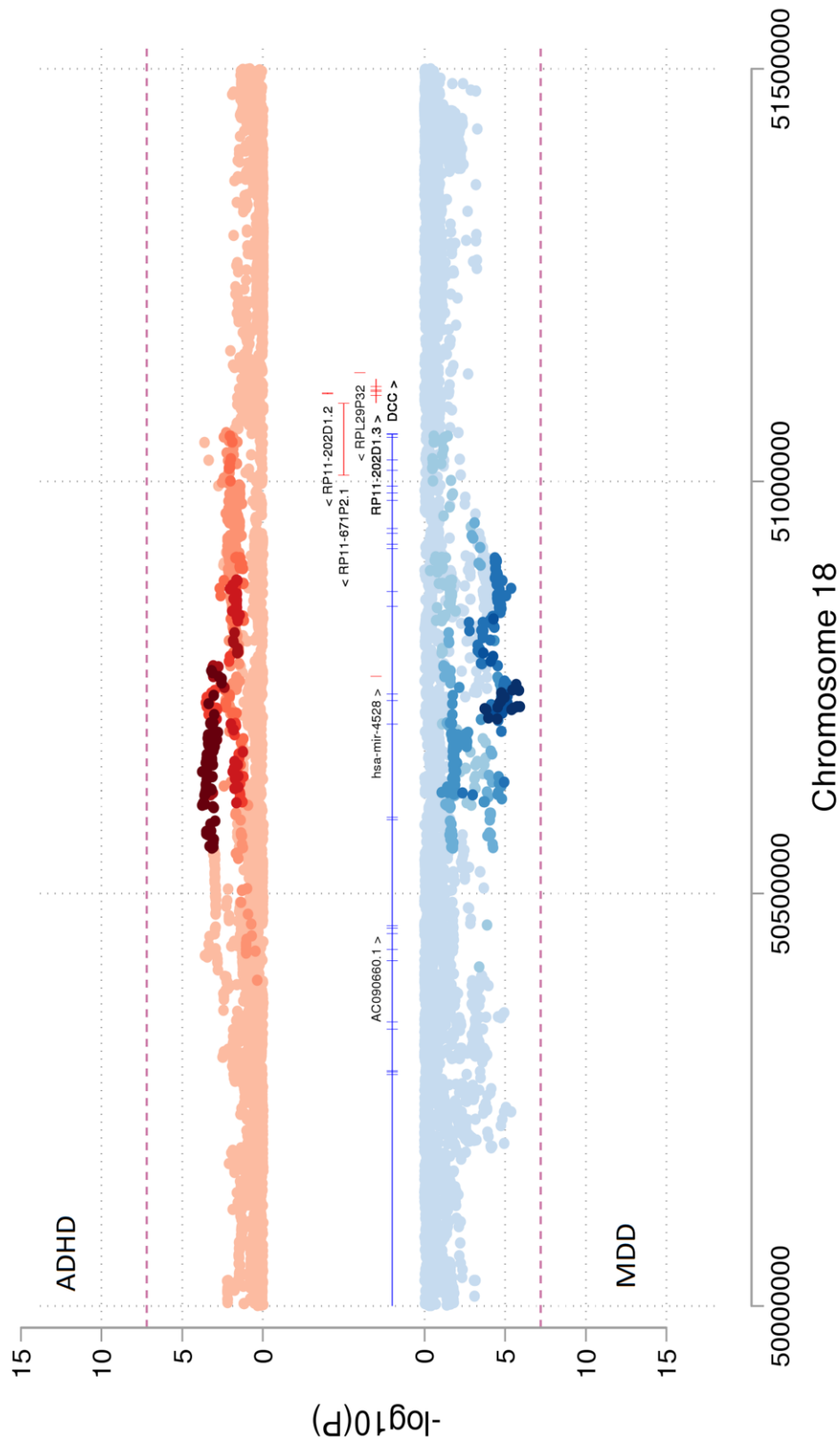


Figure 4.3. Miami plot showing the association of SNP rs8084351 with ADHD compared to MDD. As shown in the Miami plot, the SNP rs8084351 on chromosome 18 had a subthreshold association with both ADHD ($p=4.11 \times 10^{-4}$) as shown in red and with MDD ($p=1.24 \times 10^{-6}$) as shown in blue. Genes in the surrounding region of 5×10^7 to 5.15×10^7 base pairs included *DCC*. Genes are defined according to residence within the LD block of the index SNP. Protein-coding genes are shown in blue. Non-protein-coding genes are shown in red. The x-axis is chromosomal position in base pairs and the y-axis is the p value ($-\log_{10} p$ value) of the association of the SNP with both disorders. *ADHD* attention deficit/hyperactivity disorder, *MDD* major depressive disorder, *SNP* single nucleotide polymorphism, *LD* linkage disequilibrium, *DCC* deleted in colorectal cancer

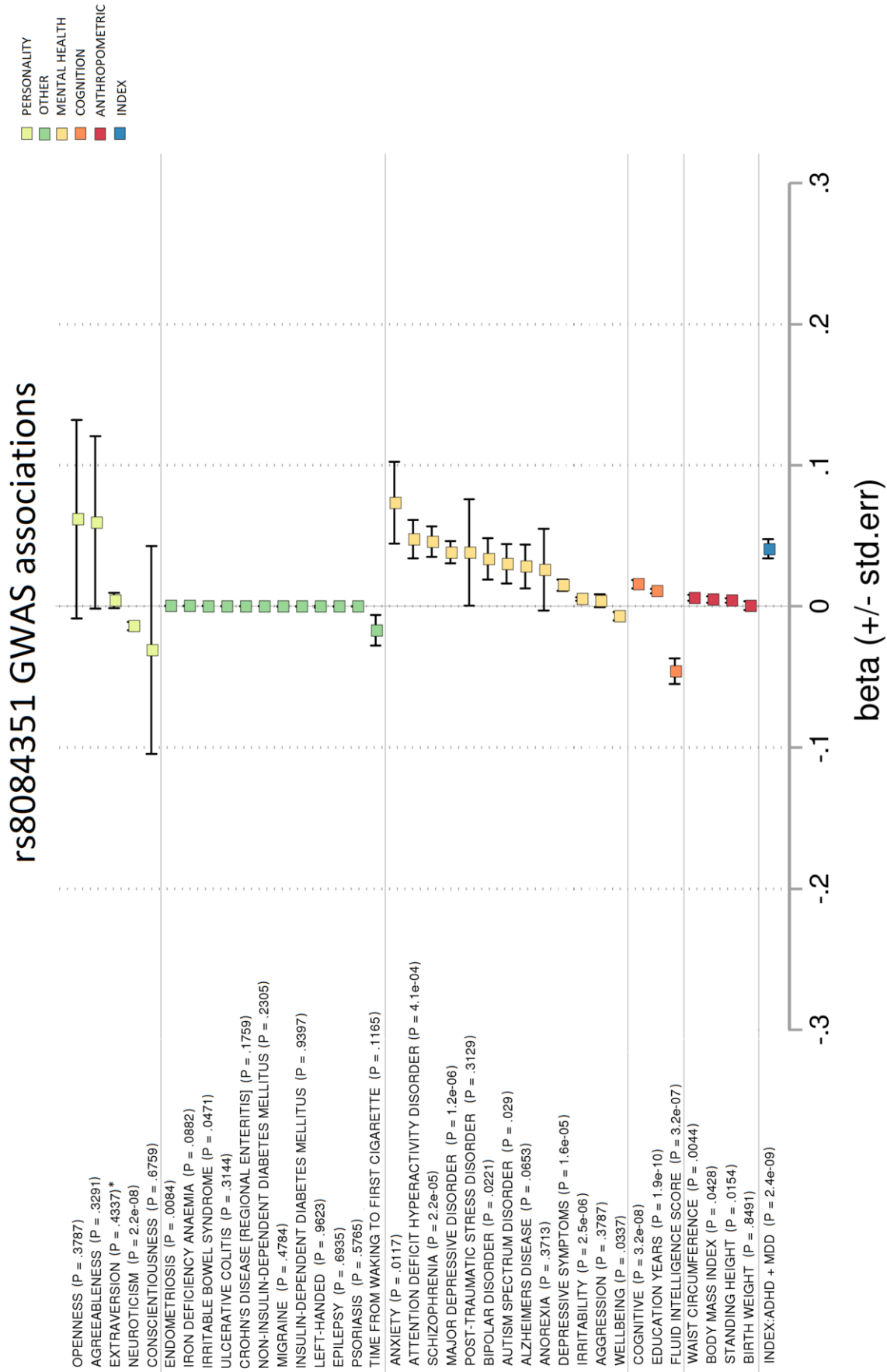


Figure 4.4. Forest plot showing additional associations of rs8084351. To investigate pleiotropy, rs8084351 was tested for associations across 37 phenotypes covering various aspects of health and functioning. rs8084351 was associated mainly with mental health phenotypes. It also demonstrated associations with cognition and neuroticism. p = non-corrected p-value. * = results unavailable for rs8084351 so a proxy SNP – rs7505145 – was used. ADHD attention deficit/hyperactivity disorder, MDD major depressive disorder, GWAS genome-wide association study

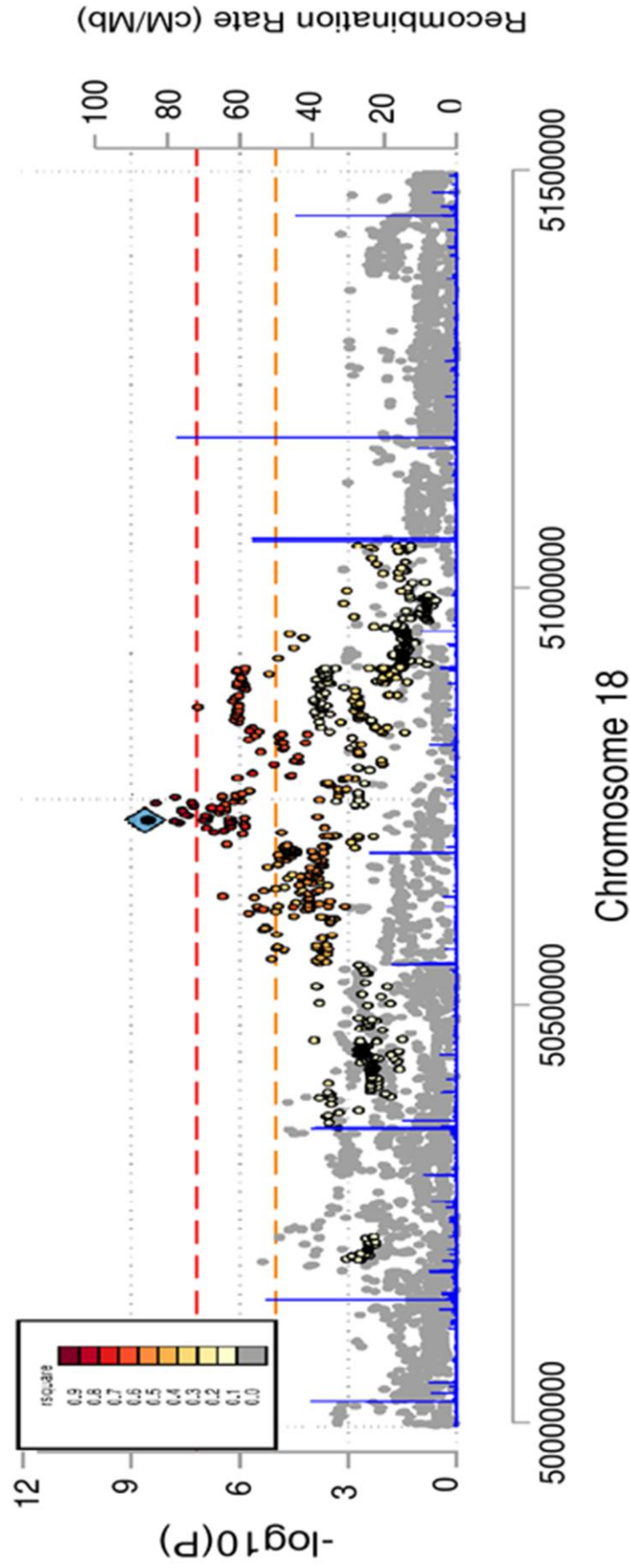


Figure 4.5. Locus plot showing the association of SNP rs8084351 with the meta-analysis. Although rs8084351 had a subthreshold association with both ADHD ($p=4.11 \times 10^{-4}$) and MDD ($p=1.24 \times 10^{-6}$), it was genome-wide significant in the meta-analysis ($p=2.39 \times 10^{-9}$), as shown in the locus plot. The x-axis is chromosomal position in base pairs and the y-axis is the p value ($-\log_{10} p$ value) of the association of the SNP with the meta-analysis. *ADHD* attention deficit/hyperactivity disorder, *MDD* major depressive disorder, *SNP* single nucleotide polymorphism

4.4. Discussion

The current study describes a GWA study meta-analysis to identify SNPs with a joint contribution to ADHD and MDD. Fourteen such LD-independent SNPs were identified. Concordant directions of effect for ADHD and MDD were observed for all 14 SNPs. Five of the SNPs were in high LD with nearby SNPs reported as genome-wide significant in the individual MDD or ADHD GWA studies (Demontis et al., 2019; Wray et al., 2018). The remaining 9 SNPs had not been previously reported in either the individual ADHD or MDD GWA study. None of the identified SNPs were genome-wide significant in *both* the ADHD and MDD GWA study individually. Nine of the 14 index SNPs were found to act as eQTL and two as eQTL in brain tissue. For each index SNP, associations were also tested across 37 GWA studies selected to represent well-powered GWA studies of mental health, cognition, personality, anthropometric and other heritable traits to explore the pleiotropy of each identified SNP. In general, for each of the identified SNPs, deviation from the null was observed across traits within the mental health category.

4.4.1. Key Findings

Annotation of GWA study findings can add supporting data through revealing the genes and potential biological processes linked to associated SNPs. For the traits under investigation in this study, each SNP and the associated region (including other SNPs in high LD to the index SNP) were annotated for transcripts and eQTL. Essentially, the approach was to identify SNPs showing evidence of a relationship to genes related to brain function or neurodevelopment, or gene expression in trait relevant tissues (i.e. brain). The top finding (rs12658032) revealed neither of these properties. The region that includes rs12658032 is associated with multiple traits and therefore warrants further interrogation. A recent study reported a SNP in this region (rs1363105, a SNP in LD with rs12658032) that was associated with ADHD, MDD, ASD and anorexia (P. H. Lee et al., 2019). In the current study, rs12658032 was associated with various mental health-related phenotypes in addition to ADHD and MDD, including anxiety, which is genetically correlated with both ADHD and depression (e.g. Demontis et al., 2019; Wray et al., 2018) and has a high reported

rate of comorbidity with both disorders (Angold, Costello, & Erkanli, 1999). In addition, rs12658032 was associated with indicators of body weight including waist circumference (Appendix 4.1: Table 4.1d). One potential explanation of this finding is that waist circumference might be a shared risk factor between ADHD and MDD that rs12658032 influences. Two recent separate studies have found evidence supporting a causal influence of ADHD on obesity (Leppert et al., 2019) and of body fat on depression (Speed, Jepsen, Børglum, Speed, & Østergaard, 2019) using Mendelian randomisation techniques.

Nine of the identified SNPs were novel in that they had not been reported previously in the individual ADHD or MDD GWA study. For example, rs8084351 on chromosome 18 demonstrated a modest subthreshold association with ADHD and a subthreshold association with MDD. However, a strong genome-wide significant association was observed for rs8084351 in the meta-analysis of ADHD and MDD. Findings such as this one highlight the increased power of meta-analysis to detect variants that contribute to multiple traits. It might also suggest that while variants such as rs8084351 do not greatly contribute to the phenotype of ADHD or MDD individually, they are important in the overlap of these two disorders. When testing the association of rs8084351 across 37 GWA studies covering a broad range of phenotypes, rs8084351 was additionally associated in GWA studies of other mental health phenotypes, cognition measures and education related phenotypes. Cognition or education could be an example of a shared risk factor or effect of ADHD and MDD that rs8084351 contributes to. In chapter 2, educational attainment was found to mediate the prospective association between ADHD and depression. This SNP (rs8084351) was also found to affect expression of *DCC* in cerebellar brain tissue, which is noteworthy as ADHD and MDD are both considered to be brain disorders. *DCC* encodes a transmembrane receptor for netrin 1 and guides axonal growth of neurones towards sources of netrin 1 (Li et al., 2004). Mutations in *DCC* have been shown to result in disruption of the midline-bridging neuronal commissures of the brain, causing horizontal gaze palsy, scoliosis and intellectual disability (Jamuar et al., 2017).

One additional SNP (rs2029591) was found to be an eQTL for brain expression. There was evidence that rs2029591 is an eQTL for multiple genes across multiple tissues. In brain tissue, rs2029591 is an eQTL for *AMT*, *FAM212A*, *GPX1*, *NCKIPSD* and *RNF123*. Of these five genes, there is literature to support a potential role in brain disorder for *AMT*, *FAM212A* and *NCKIPSD*. *AMT* forms part of the enzymatic system responsible for glycine cleavage in mitochondria (Applegarth & Toone, 2006). *AMT* mutations are associated with glycine encephalopathy – a rare condition associated with brain abnormality and learning difficulties among other traits. However, *AMT* showed evidence of expression across many different tissues and was not specific to the brain. *FAM212A* and *NCKIPSD* showed brain-specific expression. Mutation in the genomic region of *FAM212A* has been observed in a child with CNS abnormalities (Haldeman-Englert et al., 2009). *NCKIPSD* has been evidenced to be involved in the building and maintenance of dendritic spines and modulation of synaptic activity in neurones (Cho et al., 2013).

4.4.2. Associations with Additional Genome Wide Association Study Phenotypes

The phenomenon whereby common genetic association is observed between two or more traits is called pleiotropy. There are several types of pleiotropy and mechanisms that give rise to it (van Rheenen et al., 2019). In the current study, regions of pleiotropy were identified based on the GWA study of ADHD and GWA study of MDD. However, overlap exists in the symptoms of different mental health disorders and overlapping genetic associations may not be limited to ADHD and MDD. In addition, genetically mediated behavioural mechanisms involving related traits might influence the link between ADHD and MDD. In order to explore the extent of pleiotropy, identified regions were screened against 37 additional GWA studies. As expected, regions were identified that show common association across multiple psychiatric disorders. Some of the relationships may be in part due to examining highly correlated traits (e.g. cognition and fluid intelligence scores, depressive symptoms and MDD, or waist circumference and BMI). Some of the associations may be affected by misclassification bias or confounding. Misclassification may arise between related psychiatric presentations. For example, it is common that those with bipolar disorder are first given a diagnosis of MDD in

the early stages of treatment seeking due to diagnostic uncertainty (Lish, Dime-Meenan, Whybrow, Price, & Hirschfeld, 1994). An example of confounding would be where a common SNP association is observed for education and ADHD, only because ADHD is associated with both the SNP and education independently and not through a causal pathway. Models such as vertical pleiotropy offer an alternate explanation through the role of intermediate traits. For example, rs8084351 was associated with numerous mental health phenotypes as well as years of education. Vertical pleiotropy would be where rs8084351 directly influences traits related to ADHD, which influences years of education, which could in turn impact upon MDD risk in a causal cascade, for example. Horizontal pleiotropy could be an alternative or additional explanation of results, whereby rs8084351 would directly influence all three traits (education, ADHD and MDD in this example).

4.4.3. Limitations

There were five instances where the associated regions identified from the meta-analysis overlapped with regions found to harbour genome-wide significant associations in the individual ADHD or MDD GWA study. Although the SNP with the strongest association in the meta-analysis in addition to strong associations with ADHD and MDD individually is focussed upon in the current study, the assumption that the shared association is driven by a common SNP could be a potential limitation in the interpretation. Specifically, the SNP with the strongest association may not represent the same causal variant being shared between ADHD and MDD. The associations could potentially represent 'spurious pleiotropy', whereby two different SNPs in the ADHD and MDD GWA studies are in high LD with one another (van Rheenen et al., 2019). Additionally, the MDD GWA study used in this study has a much larger sample size than the ADHD GWA study used. This might create a statistical power imbalance that potentially biases meta-analysis results in favour of the larger discovery GWA study (MDD). Indeed, for 11 of 14 reported associations, lower p-values were observed for MDD than ADHD. However, GWA study power also increases as the heritability of the trait under study increases (Sullivan, Daly, & O'Donovan, 2012), and the observed heritability of ADHD ($h^2=0.22$ (0.02)) is higher than that of MDD ($h^2=0.15$ (0.01)). To reduce over interpretation of genome-wide

significant SNPs due to stochastic processes driven by the better statistically powered GWA study, interpretation was limited to SNPs whereby a lower but modest minimum association ($P < 5 \times 10^{-4}$) was observed in both studies individually. There are concerns in the literature regarding reliance on p-values (Sterne & Davey Smith, 2001) and thus the meta-analysis was repeated using effect size estimates (z-scores) to define Model 1, 2 and 3 SNPs. Results were very similar, with the z-score approach detecting 13 Model 3 SNPs – all of the 14 SNPs found using the p-value approach except the weakest association (rs17775184).

A known limitation of meta-analysis of GWA study summary data is the potential bias arising from sample overlap. The ADHD and MDD GWA study data were generated from multiple cohorts and it is possible that the contributing cohorts share individuals. My understanding of the extent of sample overlap in this study is that, for PGC samples, there is no evidence of case overlap and there appears to be nominal overlap of 4% of MDD controls with ADHD controls (personal communication; PGC Data Access Committee). For iPSYCH, the numbers of overlapping individuals between the ADHD and MDD GWAS are not publicly available, but there may be some overlap of cases and of controls. 17,841 of the MDD controls were from iPSYCH, meaning that up to 15% of MDD controls could overlap with ADHD iPSYCH controls. Some of the ADHD cases in iPSYCH ($n=14,584$) may have comorbid psychiatric disorders (Schork et al., 2019), however, the exact number of ADHD cases with comorbid MDD was not specified in published work using these data (Schork et al., 2019). Sample overlap could theoretically inflate effect sizes, but given the small extent of overlap, any potential inflation is likely be small. We were unable to adjust the meta-analysis for sample overlap due to the focus of this study on summary statistics. Additional issues to consider are the choice and availability of GWA study data. Some of the GWA studies are primarily based on clinical diagnosis (e.g. Demontis et al., 2019; Wray et al., 2018) whereas others used data sourced solely from the UK Biobank (Sudlow et al., 2015). Classification and diagnosis in the UK Biobank are often based on self-report which may be less stringent or reliable than clinical diagnoses, particularly for conditions that are episodic like MDD (Malhi & Mann, 2018). Although not necessarily a limitation, it is

important to note that the 23andMe cohort of the MDD GWA study was excluded in the current study due to data access restrictions. With this cohort removed, MDD heritability ($h^2=0.15$ (0.01)) was higher than reported in the original GWA study (Wray et al., 2018; $h^2=0.09$ (0.004)). The genetic correlation between ADHD and MDD was also higher ($r_g=0.52$) relative to the genetic correlation reported when 23andMe is included ($r_g=0.42$) (Demontis et al., 2019; Wray et al., 2018). One explanation is that the self-reported phenotype used by 23andMe captures a broader spectrum of clinical severity and increases heterogeneity, in comparison to clinician derived diagnosis used by contributors to the non-23andMe MDD GWA study cohorts (Wray et al., 2018). Finally, it is important to note that the ADHD and MDD GWA studies summary data used here were of a European ancestry only, restricting the generalisability of the findings.

4.4.4. Strengths

Strengths of this study include the use of the most recent and well powered GWA studies of MDD (Wray et al., 2018) and ADHD (Demontis et al., 2019) in an adapted meta-analysis, which provides a novel approach for investigating SNPs that make a joint contribution to the two disorders, compared to previous cross disorder GWA study meta-analyses of numerous psychiatric disorders (e.g. Lee et al., 2019). The exploration of multiple phenotypes in the study by Lee et al. (2019) requires evidence across multiple GWA studies and thus might miss regions only impacting ADHD and MDD. Indeed, only 5 of the 14 genomic regions identified in the current study were identified in the study by Lee et al. (2019) (the LD ranges of rs12658032, rs4593766, rs61867322, rs2509805, rs8084351), and thus 9 additional regions were identified in the current study. The screening of other GWA study associations of index SNPs and regions, instead of standard literature review approaches, allowed investigation free from reporting-bias of the associations of the SNPs identified in the meta-analysis with a broad range of phenotypes.

4.4.5. Future Research Directions and Implications

Future research directions include in-depth functional analysis of the genomic regions identified in the current study to further investigate their biological

mechanisms in the overlap of ADHD and MDD. Additionally, Mendelian randomisation-based techniques would be helpful to infer whether or not the identified variants are causal in ADHD, MDD and/or their overlap. Such techniques would also provide helpful insights into the type of pleiotropy (e.g. horizontal and vertical) behind the pleiotropic associations observed in this study. A greater understanding of the divergence and commonalities of genetic contributions to psychiatric disorders may better inform current diagnostic boundaries.

4.4.6. Conclusions

In conclusion, this study highlights fourteen LD-independent SNPs contributing to the genetic overlap of ADHD and MDD, nine of which are novel in that they did not meet genome-wide significance reporting thresholds in either the ADHD or MDD GWA study alone. In contrast to existing cross disorder papers, the current study focuses specifically on ADHD and MDD using a novel method to highlight shared SNPs regardless of direction of effect. The results build upon existing evidence of the genetic correlation of ADHD and MDD by revealing the regions of the genome that potentially explain some of the overlap observed between the disorders. Findings suggest that there might be some unique genetic architecture to the overlap of ADHD and MDD. eQTL results support the biological relevance of certain identified SNPs to mental health phenotypes. The index SNPs seem to be largely specific to mental health related phenotypes rather than other phenotype classes, supporting the existence of common genetic pathways amongst psychiatric disorders.

Chapter 5: A study of ADHD in adults with recurrent depression and impact on clinical presentation of depression

This chapter is an amended version of a published pre-print:

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In addition to examining different factors that might contribute to the association of ADHD and depression in chapters 2, 3 and 4, it is also important to consider the effect ADHD might have on depression presentation. This was the aim of the current study conducted in a longitudinal cohort of adults with recurrent depression. First, the prevalence of ADHD in this sample was investigated. The association of ADHD with a number of clinical features of depression presentation was then tested, in addition to exploring how ADHD influenced the treatment or management of depression in this group. Analyses were conducted in 148 women aged 42 to 67 who completed the fourth assessment of a longitudinal study including an ADHD screening measure. 12.8% of the recurrently depressed women had ADHD symptoms above the validated clinical cut point for the scale and 3.4% met DSM-5 diagnostic criteria for ADHD. None of the women reported having been diagnosed with ADHD by a clinician. ADHD was associated with earlier age of depression onset, greater depression associated impairment, greater recurrence of depressive episodes and increased persistence of subthreshold depression symptoms over the study period and increased odds of self-harm or suicide attempt. ADHD symptoms were associated increased odds of hospitalisation and receiving non-standard anti-depressant medication.

5.1. Introduction

In chapters 2 to 4, potential explanations of the association of ADHD and depression were investigated. However, as discussed in chapter 1, it is also important to consider whether ADHD might influence the presentation of depression. Depression is highly heterogeneous in its presentation and there is some evidence that children with ADHD and depression may be at higher risk of worse depression outcomes, such as hospitalisation, compared to those with depression alone (e.g. Biederman et al., 2008). Nevertheless, the existing literature investigating the effect of ADHD on depression presentation mainly comes from samples of children and young people. Neurodevelopmental disorders such as ADHD which are not identified in childhood can be missed in adults, especially among women (Martin et al., 2018). There is emerging evidence to suggest that recurrent adult depression may mask underlying neurodevelopmental disorders including ADHD that are missed in clinical practice (McIntosh et al., 2009). Thus, the study described in the current chapter sought to investigate the prevalence of ADHD and the impact on depression presentation in a sample of recurrently depressed women in mid-life. The extant literature related to this study is detailed below, before outlining the study aims.

5.1.1. ADHD and Depression Presentation

Depression is a highly heterogeneous disorder that varies in its origins and clinical presentation (Fried & Nesse, 2015; Kendler et al., 1996; Weissman et al., 1986). Young people with ADHD and depression are at higher risk of early-onset, recurrent depression (Riglin et al., 2020) as well as suicide and psychiatric hospitalisation compared to those with depression alone (Biederman et al., 2008). A national register-based study also found that those with comorbid ADHD and depression were at an increased risk of antidepressant resistance compared to those with depression alone (M.H. Chen et al., 2016). ADHD can persist into adulthood in some individuals, with more persistent cases showing an association with more comorbid mental health problems (Agnew-Blais et al., 2016; Riglin et al., 2016). One four-year follow-up study of depressed adults and community controls found an increased odds of probable ADHD in those with longer lasting, more severe

depressive episodes and in those with a reported depression age of onset before 21 years (Bron et al., 2016).

5.1.2. Neurodevelopmental Contribution to Depression

Some studies have found evidence to suggest that there is a neurodevelopmental contribution to some forms of depression. One such study of a population sample followed from birth to young adulthood found that an earlier-onset, more chronic class of depression was associated with a higher level of neurodevelopmental traits, including ADHD symptoms, ADHD genetic risk and schizophrenia genetic risk (Rice et al., 2019). Other epidemiological studies also report similar associations between early onset depression and neurodevelopmental traits (Jaffee et al., 2002; van Os et al., 1997).

5.1.3. The Current Study

In this longitudinal study spanning 13 years, the aim was to investigate ADHD in women with recurrent depression. The sample was a longitudinal study of adults with a history of recurrent depression (defined as at least two episodes of MDD according to DSM-IV criteria) with detailed data on clinical features of depression over four phases of data collection. At the fourth phase, ADHD was additionally assessed. First, the prevalence of ADHD in this group was investigated. Next, a number of clinical features of depression identified in the literature as potentially associated with ADHD were examined. These included age of depression onset, severity of impairment, depression recurrence, suicide and self-harm attempts and psychotic affective symptoms. Finally, the association of ADHD symptoms with clinical management and treatment of depression was explored. Hospitalisation for depression and non-standard antidepressant medication were examined as outcomes that may indicate a poor treatment response or a complex clinical presentation.

5.2. Method

5.2.1. Sample

Data came from the Early Prediction of Adolescent Depression (EPAD) study – a prospective longitudinal study of recurrently depressed parents and their offspring based in the UK (Mars et al., 2012). The baseline sample included 337 parents with recurrent unipolar depression (two or more lifetime Major Depressive Disorder (MDD) episodes confirmed at interview) and their offspring. Families were assessed at 4 time points between April 2007 and September 2020 via interview and questionnaire. The average length of follow up was 16 months between the first and second waves, 13 months between the second and third, and 8 years between the third and fourth. The current study focuses primarily on the fourth assessment wave, carried out between 2018 and 2020. Complete data from waves 1 through 4 were available from 197 families. Study design and participation rates are summarised in Figure 5.1. Reasons for the lower retention rate between the third and fourth assessment waves include: death of participants, loss to follow-up and withdrawal from the study. Of the 197 participating families at wave 4, 148 mothers (mean age: 53, range: 42 – 67) with complete data on their own ADHD symptoms, clinical features of their depression and sociodemographic variables formed the primary sample. Though the main analysis was conducted in these 148 women only, analyses were repeated with fathers additionally included (5 fathers; n=153). Ethical approval was granted by the Multi-Centre Research Ethics Committee for Wales and from the School of Medicine Ethics Committee, Cardiff University. Written informed consent and assent was gained from each of the participants at each wave. More detailed information about recruitment, assessments and sample characteristics at assessment waves 1 to 3 can be found elsewhere (Mars et al., 2015, 2012).

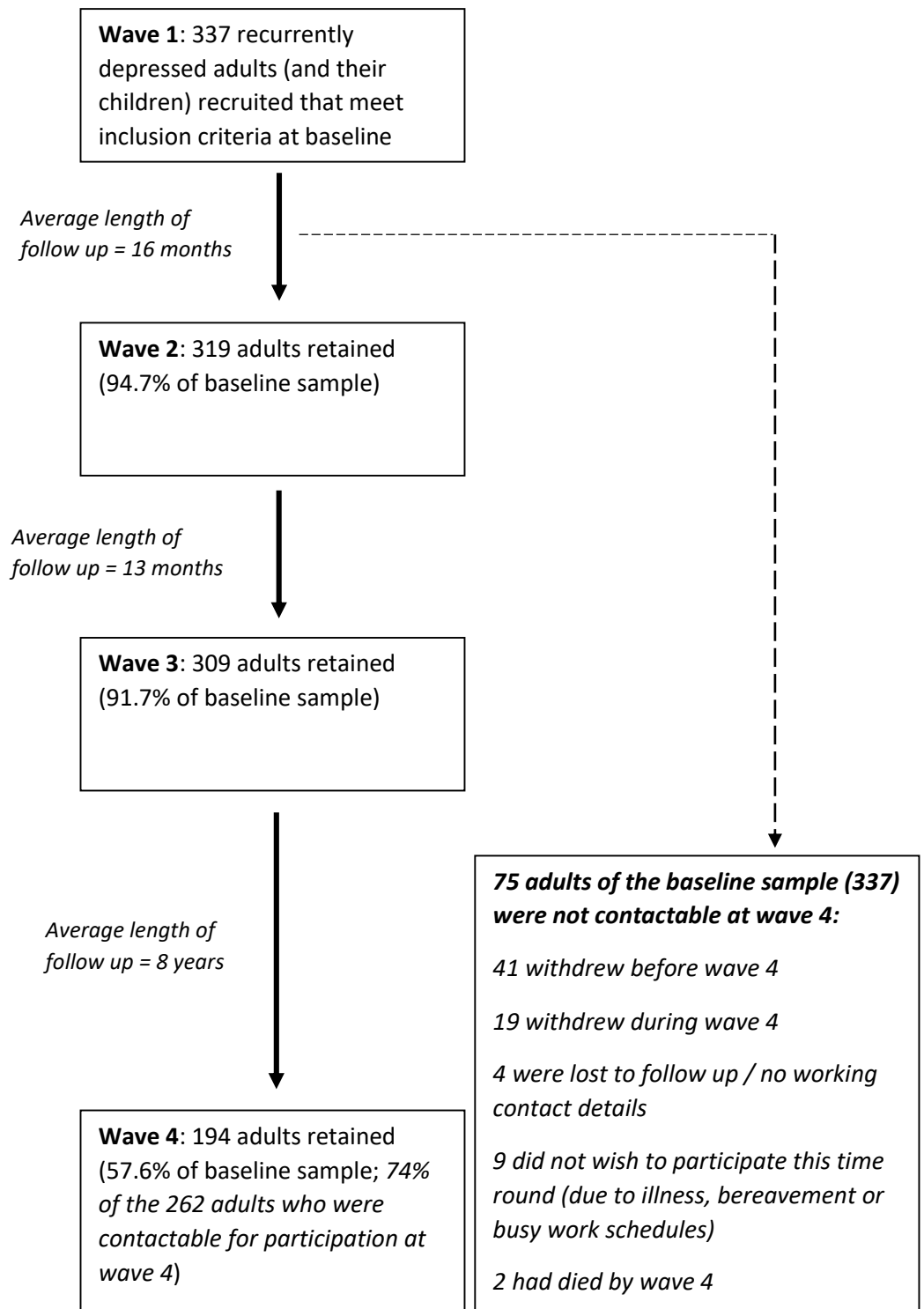


Figure 5.1. Study design and participation rates across assessment waves of the EPAD study. The Early Prediction of Adolescent Depression (EPAD) study took place over four assessment waves between April 2007 and September 2020 via interview and questionnaire. Numbers of participants reported are those participating at each wave via questionnaire, interview or both. Only 262 adults were contactable at wave 4. Reasons for this include loss of up to date contact details, withdrawal from the study, death and declining to participate due to ill health, bereavement or other commitments such as work (n=75). Of the 262 contactable participants at wave 4, 68 were unresponsive despite multiple communication attempts.

5.2.2. Overview of Assessment Procedure

The sample was recruited mainly from general practice surgeries in South Wales (78%). Additional participants were recruited using a database of individuals who had been identified as having previous unipolar depression, via community mental health teams and advertisements in local media and primary care centres (Mars et al., 2012). The original aim of the study was to conduct a cross-generational study to examine the offspring of parents with recurrent depression, so all participants had biologically related offspring living at home in the age range of 9 to 17 years at the time of initial recruitment. Recruited adults were screened over the telephone to ensure they met inclusion criteria: suffered from re-current unipolar depression (at least 2 episodes, which were later confirmed using diagnostic interview). Adults were not required to be experiencing a depressive episode at the time of recruitment.

At each assessment wave (1 through 4), the Schedule for Clinical Assessment (SCAN; Wing et al., 1990) was used to assess adult DSM-IV MDD based on symptoms and impairment reported in the preceding month. All cases meeting criteria for diagnosis in addition to subthreshold cases were reviewed by two psychiatrists and diagnoses were made according to clinical consensus. At the baseline assessment, participants were additionally asked to report on their worst ever and second worst ever episodes of depression and associated impairment. They were also asked to retrospectively report on various clinical features of their depression including age of onset. A life history calendar approach was used for all retrospectively reported information to aid recall (Belli, 1998). At assessment waves 2 through 4, participants were asked to report on episodes of depression they had experienced since the previous assessment wave and to report on associated impairment. Participants additionally completed a questionnaire booklet which included questions relating to sociodemographic information, family structure and relationships, and psychiatric symptom measures such as the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961).

5.2.3. Measures

Adult ADHD

Participants completed the Adult ADHD Investigator Symptom Rating Scale (AISRS; Spencer et al., 2009) via questionnaire at wave 4. The AISRS consists of 18 items based on the DSM-5 (American Psychiatric Association, 2013) symptoms of ADHD. Symptoms were rated on a 4-point scale of “Never/Rarely” (0), “Sometimes” (1), “Often” (2) and “Very often” (3) and summed to give a total symptom score (possible range: 0-54). Participants were asked at what age they could recall these symptoms starting and to indicate whether the symptoms impacted on functioning in a number of areas of life. Participants were classed as meeting DSM-5 (American Psychiatric Association, 2013) criteria for adult ADHD diagnosis if they reported at least 5 current symptoms (reported as happening “Often” or “Very often”), an age of onset of these problems prior to 12 years old and associated impairment in home, work or social life. Those meeting the AISRS clinical cut point by scoring 24 or higher (Silverstein et al., 2018) were classed as having elevated ADHD symptoms. Participants were also asked to report on their recent and current service use and any diagnoses they had received from a clinician using a questionnaire adapted from the Children’s Services Interview (Ford, Hamilton, Dosani, Burke, & Goodman, 2007; Potter et al., 2012). Continuous ADHD symptoms and binary ADHD symptoms according to the AISRS clinical cut-point were the two exposure variables used in analyses. ADHD DSM-5 diagnosis and reports of diagnosis by a clinician are used only for the descriptive statistics in the current study.

Clinical Features of Depression

Age of onset. Participants were asked at baseline interview how old they were when they had their first episode of MDD. Age of onset was dichotomised so that onset at 25 years old or earlier was classed as early-onset depression based on previous studies (e.g. Power et al., 2017).

Severity. Impairment associated with depression was measured using the Global Assessment of Functioning (GAF; American Psychiatric Association, 1994),

which was assessed for the worst ever episode reported by the participant at baseline interview and at each subsequent assessment phase for current/recent depression. A binary measure was derived capturing whether participants had ever had a GAF score ≤ 50 during the study period with GAF scores below or equal to 50 indicating serious impairment in work or social life (American Psychiatric Association, 1994).

Episode recurrence. A count variable of the recurrence of depressive episodes across the study period was derived. This included a count of the number of assessment points at which participants met clinical criteria for MDD plus the number of times participants reported being depressed since the last assessment wave (possible range=0-7).

Subthreshold persistence. In addition to recurrence of depressive episodes, chronicity of subthreshold symptoms over time is common and impairing (Fergusson et al., 2005; Judd et al., 1998). Thus, as an indicator of persistence of depression symptoms over time, self-report questionnaire measures of depressive symptoms at waves 1 through 4 were used to derive a measure of subthreshold depression persistence. These were the Patient Health Questionnaire (PHQ; Kroenke, Spitzer, & Williams, 2001) at waves 1 and 4 and the Beck Depression Inventory (BDI; Beck et al., 1961) at waves 2 and 3. Both questionnaires are valid and reliable measures of depressive symptoms (Kroenke et al., 2001; Strober, Green, & Carlson, 1981). Depressive symptom scores were calculated at each wave. Those falling into the “intermediate” symptoms group (i.e. between the “none/mild” and “severe” group: scoring 5-19 on the PHQ or 10-29 on the BDI) were defined at each wave based on the cut points validated for the PHQ and BDI (Beck, Steer, & Garbin, 1988; Kroenke et al., 2001). A count of the number of times symptoms were intermediate was derived (possible range=0-4).

Suicide and self-harm attempt. The SCAN (Wing et al., 1990) was used to assess self-harm or suicide at each wave with the question “Have you thought about harming yourself or even made an attempt at suicide during the last month?”. Participants responses were coded as ‘absent’ (0), ‘intrusive thoughts but no attempt’ (1), ‘injured self but no serious harm resulted’ (2), ‘injured self and serious

harm resulted' (3) or 'made an attempt at suicide designed to result in death' (4). A binary variable capturing whether participants had ever reported self-harm or suicide attempts at any of the four assessment waves was derived.

Psychotic affective symptoms. A binary variable capturing whether participants had ever endorsed psychotic affective symptoms during the SCAN (Wing et al., 1990) at waves 1 to 4 was derived. Psychotic affective symptoms assessed were delusions of guilt, delusions of catastrophe, hypochondriacal delusions and auditory hallucinations.

Hospitalisations. Participants reported the number of times they had ever been hospitalised due to depression at baseline, and the number of times they had been hospitalised since the last assessment wave at waves 2 and 3. At wave 4, participants were not asked explicitly to report the number of hospitalisations, but they were asked to give details of what treatment they had received during any depressive episodes. From this information, a binary variable was derived capturing whether participants had ever been hospitalised due to depression.

Antidepressant medication. At wave 4, participants reported on which medications they were currently taking, including medication for depression. Based upon UK NICE clinical guidelines for management of adult depression (National Institute for Health and Care Excellence (NICE), 2009), a binary variable of no depression treatment or standard depression treatment (use of an SSRI) versus non-standard depression medication (use of an antidepressant other than an SSRI, use of two or more antidepressants, or an antidepressant augmented with lithium or an antipsychotic) was derived. The use of non-standard antidepressant medication might indicate either poor response to standard, first-line antidepressants (SSRIs), or the need to address complexities in a patient's depression presentation (National Institute for Health and Care Excellence (NICE), 2009).

Confounders

All regressions presented are adjusted for sociodemographic factors associated with depression that might confound associations (Gilman et al., 2002). The confounders adjusted for are questionnaire self-reported financial status (how

“well off” participants rate themselves compared to others they know, from “much better off” (0) to “much worse off” (4)) and educational attainment (assessed as having attained qualifications at end of compulsory education, e.g. GCSEs or equivalent qualifications Yes/No) at assessment wave 4.

5.2.4. Analysis

Association between ADHD and Clinical Features of Depression

A series of linear and logistic regressions were conducted as appropriate to test the association of ADHD symptoms and clinical features of depression. Continuous ADHD symptoms were standardised so that a one-unit increase was equivalent to a standard deviation increase. All regressions were repeated with ADHD entered as a binary variable (above or below the AISRS clinical cut point (≥ 24) for ADHD) to test whether the depression presentation was significantly different between those above and below the cut-point.

5.2.5. Sensitivity Analysis

In a small number of the participating families in the EPAD study, the father was the index parent. Analyses were therefore repeated with these males (n=5) additionally included to check whether results differed compared to results in females only.

5.2.6. Missing Data

Regressions were repeated with Inverse Probability Weights (IPW) applied to assess possible bias arising from potential non-random missing data (Seaman & White, 2013). This involved weighting the analysis sample by the inverse probability of being missing. Variables measured at the first wave were examined as predictors of missingness from the analysis sample, including baseline reports of financial income, education, number of children, anxiety or depression problems and comorbid illness (Appendix 5.1). These formed the missingness model from which the weights were created. Minimal missing data on these predictors were singly imputed as the modal value (all predictors had <13% of values missing). The Hosmer-

Lemeshow test showed no indication of poor fit for the missingness model (Hosmer-Lemeshow $\chi^2(8)=6.94$, $p=0.543$). Weights ranged from 1.29 to 22.73. Regression analyses were conducted again with the IPW weights applied to address potential bias caused by missing data. IPW is a reliable approach to dealing with missing data, particularly in longitudinal cohorts where participants can have missing data for multiple variables (Seaman & White, 2013).

5.3. Results

5.3.1. Descriptive Statistics

In the primary sample of recurrently depressed females ($n=148$), 12.8% ($n=19$) had elevated ADHD symptoms, indicated by having an AISRS score above the validated clinical cut point (≥ 24), and 3.4% ($n=5$) met DSM-5 diagnostic criteria for adult ADHD. None of the women in the study however, reported having been diagnosed with ADHD by a clinician. Descriptive statistics are shown in Table 5.1.

Table 5.1. Descriptive statistics for ADHD symptoms and features of depression presentation and management

Variable	Mean (SD) / % (n)	Range
ADHD symptoms	11.19 (10.02)	0 - 50
Age of onset of depression / % onset \leq 25 years	26.01 (7.98) / 45.3% (67)	8 - 46
Ever had GAF score \leq 50 (Severe impairment associated with depression)	73.0% (108)	Binary: 0=No, 1=Yes
Number of MDD episodes during study	2.42 (1.69)	0 - 7
Subthreshold depression persistence	1.97 (1.34)	0 - 4
Ever hospitalised	17.6% (26)	Binary: 0=No, 1=Yes
Use of non-standard antidepressants	20.3% (30)	Binary: 0=No, 1=Yes
Ever attempted self-harm or suicide during study	4.1% (6)	Binary: 0=No, 1=Yes
Ever had psychotic affective symptoms during study	12.8% (19)	Binary: 0=No, 1=Yes

Descriptive statistics in complete case mothers (n=148). ADHD attention-deficit/hyperactivity disorder, MDD major depressive disorder, GAF Global Assessment of Functioning, SD standard deviation

5.3.2. Association between ADHD and Clinical Features of Depression

In regressions where ADHD symptoms were measured as a continuous score, ADHD symptoms were associated with an earlier age of onset of depression (≤ 25 years), and associated with severe impairment ($GAF \leq 50$; Table 5.2). ADHD symptoms were also positively associated with MDD episode recurrence over the 13-year period of the study, and with a measure capturing persistence of subthreshold depressive symptoms over the study period. ADHD symptoms were associated with increased odds of reporting self-harm or suicide attempt during the study period, but not with psychotic affective symptoms.

In addition, ADHD symptoms were associated with increased odds of ever being hospitalised. ADHD symptoms were associated with non-standard antidepressant medication use, which may be indicative of poor response to first-line antidepressants or a complex clinical presentation. The frequencies of different medication types used in the sample are reported in Table 5.3. In the primary sample ($n=148$), 63.5% ($n=94$) reported taking psychiatric medication and 19.6% ($n=29$) reported taking more than one psychiatric medication.

Table 5.2. Association of adult ADHD symptoms (continuous and dichotomised) with clinical features of depression

Clinical feature of depression	Association with self-reported adult ADHD symptom score			Association with dichotomised self-reported adult ADHD symptoms (above clinical cut-point versus below)		
	b or OR (95% CI)	p-value	n	b or OR (95% CI)	p-value	n
Depression age of onset of 25 or before	OR=-1.45 (1.02, 2.05)	0.040	148	OR=2.09 (0.74, 5.88)	0.163	148
Ever had GAF score \leq 50 (Severe impairment associated with depression)	OR=1.73 (1.08, 2.75)	0.021	148	- - -	- - -	- - - ^a
Number of MDD episodes during study	b=0.74 (0.51, 0.98)	<0.001	148	b=1.93 (1.17, 2.69)	<0.001	148
Subthreshold depression persistence	b=0.22 (0.01, 0.43)	0.044	148	b=0.29 (-0.368, 0.948)	0.385	148
Ever hospitalised	OR=1.94 (1.29, 2.91)	0.001	148	OR=4.58 (1.58, 13.25)	0.005	148
Use of non-standard antidepressants	OR=2.04 (1.35, 3.09)	0.001	148	OR=5.85 (1.99, 17.23)	0.001	148
Ever attempted self-harm or suicide during study	OR=3.46 (1.46, 8.21)	0.005	148	- - -	- - -	- - - ^b
Ever had psychotic affective symptoms during study	OR=0.89 (0.56, 1.40)	0.603	148	OR=0.92 (0.22, 3.98)	0.916	148

ADHD symptoms were dichotomised using the clinical cut point of the Adult ADHD Investigator Symptom Rating Scale AISRS (≥ 24).^a All participants above the cut point for ADHD had a GAF score below 50, so the association of dichotomised ADHD and depression impairment could not be tested due to complete separation issues.^b The association between dichotomised ADHD and suicide or self-harm attempts could not be tested due to small cell sizes. Results in complete case women are shown (n=148). ADHD attention-deficit/hyperactivity disorder, MDD major depressive disorder, GAF Global Assessment of Functioning, b unstandardized beta, CI confidence interval, OR odds ratio

Table 5.3. Categories of psychiatric medications reported at assessment wave 4 of the EPAD study

Psychiatric drug category	N	% of 148
Selective serotonin reuptake inhibitors (SSRIs)	70	47.3
Other serotonin reuptake inhibitors (SNRIs or SARIs)	15	10.1
First generation antidepressants (tricyclics or MOAIs)	11	7.4
Atypical antidepressants (tetracyclics)	4	2.7
Antipsychotics	7	4.7
Lithium	4	2.7
Mood stabilisers/anti-epileptic	5	2.7
Anti-anxiety (benzodiazapines, propranolol and buspirone)	11	7.4
Insomnia medication (hypnotics)	4	2.7
Gabapentinoids	10	6.8

Psychiatric medication use reported at assessment wave 4 in complete case women (n=148). *SSRI* selective serotonin reuptake inhibitor, *SNRI* serotonin-norepinephrine reuptake inhibitors, *SARI* serotonin antagonist and reuptake inhibitors, *MOAIs* monoamine oxidase inhibitors

The same associations were tested with ADHD as a binary rather than continuous variable to assess whether the depression presentation of those above the AISRS clinical cut-point for ADHD was significantly different to those below the cut-point. ADHD symptoms above the clinical cut point were associated with increased recurrence of depressive episodes, increased odds of hospitalisation and taking non-standard depression medication. ADHD above the clinical cut-point was also associated with a 2-fold increased odds of early onset depression, but this did not reach conventional thresholds for significance. The association between binary ADHD and severe impairment could not be tested due to complete separation issues (i.e. all participants above the cut point for ADHD had had a GAF score below 50), and the association with suicide and self-harm attempts could not be tested due to small cell sizes.

5.3.3. Sensitivity Analysis and Inverse Probability Weighting

Results remained similar with IPW applied (Appendix 5.2) and when participating males (n=5) were included (Appendix 5.3). However, the association of ADHD symptoms and subthreshold persistence attenuated after IPW was applied.

5.4. Discussion

5.4.1. Key Findings

In this prospective, longitudinal study of recurrently depressed women, the prevalence of ADHD and the effect of comorbid ADHD on the clinical phenotype of depression was investigated. Of the sample of 148 women, 12.8% were found to have elevated ADHD symptoms and 3.4% met DSM-5 diagnostic criteria for ADHD. These are higher than estimates reported in general population samples of adults (2.5%; Simon, Czobor, Bálint, Mészáros, & Bitter, 2009). None of these cases of high ADHD symptoms appeared to be currently clinically recognised however, as no participants reported having been diagnosed with ADHD. ADHD was associated with earlier age of depression onset, higher depression associated impairment as indexed by GAF scores, a greater number of depressive episodes over the study assessment

period and increased persistence of subthreshold depression symptoms. ADHD symptoms were also associated with increased odds of self-harm or suicide. ADHD symptoms were associated increased odds of hospitalisation and receiving non-standard anti-depressant medication, potentially indicative of non-response to standard SSRI antidepressants or a more complex clinical presentation.

The findings of the current study suggest that a proportion of adults in mid-life with a history of early-onset, recurrent depression that has been severely impairing may have undetected ADHD. Previous studies have shown associations of ADHD in childhood and adolescence with more severe depressive outcomes in young adulthood, such as depression recurrence, suicide and hospitalisation (Biederman et al., 2008; Riglin et al., 2020). There is also evidence from a national register-based study that those with ADHD and depression may be at higher odds of antidepressant resistance than those with depression alone (M.H. Chen et al., 2016). A four-year follow-up study of depressed adults and controls found that odds of probable ADHD were higher when depression episodes were longer and when participants reported more severe episodes and an age of onset of depression before 21 (Bron et al., 2016). However, no studies to date have examined recurrently depressed adults in mid-life. Therefore, the current study builds on existing literature by examining the effect of ADHD on a number of features of depression presentation in this group. Despite the high rates of ADHD reported in this sample, no cases seemed to have been clinically recognised with an ADHD diagnosis. ADHD is not typically assessed in adult clinical settings. However, those with high ADHD symptoms were more likely to be taking non-standard depression medication, which might suggest that these individuals have been recognised by clinicians as having a more complex depression presentation or resistance to first-line antidepressant treatment (National Institute for Health and Care Excellence (NICE), 2009).

There is much heterogeneity observed in the presentation of depression (Fried & Nesse, 2015; Kendler et al., 1996; Weissman et al., 1986), including wide variation in the age at first onset and chronicity of illness. The findings of the present study suggest that part of this may be accounted for or indexed by comorbid ADHD in some cases. It is possible that some individuals, even if they do not fulfil diagnostic

criteria for ADHD, have a more 'neurodevelopmental type' of depression characterised by early onset, persistence of symptomatology over time and overlap with neurodevelopmental traits, including ADHD symptoms (Jaffee et al., 2002; Rice et al., 2019; van Os et al., 1997). For instance, one study found that an earlier onset, more chronic class of depressive symptoms from childhood to early adulthood (age 18) was associated with more neurodevelopmental traits (ADHD traits, pragmatic language skills and autistic traits) and ADHD genetic risk scores (Rice et al., 2019). Other studies also suggest that the genetic architecture of earlier onset depression may be more neurodevelopmental in nature and tends to be more strongly associated with neurodevelopmental genetic risk (Musliner et al., 2019; Power et al., 2017; Thapar & Riglin, 2020). The present study is important and novel because it examines adults in mid-life with recurrent diagnosed depression from a longitudinal cohort spanning 13 years.

It is important to note that in contrast to studies where the age of onset of depression is measured prospectively (e.g. Jaffee et al., 2002; Rice et al., 2019; van Os et al., 1997), depression age of onset in the current study of recurrently depressed adults is measured using retrospective report. This might affect results by capturing a specific subgroup within individuals with early onset depression. For instance, those with early onset depression may have symptoms that desist by early adulthood or that persist into adulthood (e.g. Jaffee et al., 2002). Thus, in the current study of recurrently depressed adults, those who report an early onset of depression represent a persistent subgroup of those with early-onset depression. In addition, national survey studies of adolescents and adults have found that only a subgroup of individuals with depression have severe associated impairment and distress (Kessler et al., 2012; Merikangas et al., 2010). Based on the current study findings, individuals with depression and comorbid ADHD appear more likely to fall into this subgroup of severely impaired depressed cases. This has important public health implications for targeting interventions.

5.4.2. Limitations

Limitations of this work include the measurement of ADHD that was based on a questionnaire measure. In addition, this study focussed on women with adolescent

children who had participated in a longitudinal study of recurrent depression and were recruited mainly from primary care settings, so the findings may not apply to males or other groups, for example in-patient samples. The rate of ADHD observed may be influenced by specific characteristics of the present sample. Thus, rates of ADHD may be higher in this sample because individuals all had recurrent depression. However, given that ADHD is associated with multiple social and educational impairments (Harpin, 2005), those with comorbid ADHD also may be under-represented in this sample. As age of onset was reported retrospectively in this study, results may be affected by recall bias (Drews & Greeland, 1990). In addition, the retrospective data did not allow for reliable differentiation between childhood, adolescent or early adulthood onset depression within the early-onset group, which have been found to behave differently in terms of associations and persistence when age of onset is inferred using prospectively collected data (Rice et al., 2019). As is common in longitudinal cohort studies, there was some attrition of the sample over time. Analysis of baseline factors associated with drop-out at wave 4 (Appendix 5.1), showed that while factors such as lower socioeconomic status and education were associated with attrition, other factors associated with severity of depression and history of depression treatment were not. These included the percentage of the participant's life that they had been unwell since depression onset and previous non-pharmacological treatment for depression (including talking therapies and electroconvulsive therapy). This might suggest that those with more severe depression may be more likely to stay in the current study, which is likely due to the inclusion criteria of the EPAD study, namely that the participant had experienced at least 2 prior episodes of depression. Nevertheless, to account for any potential bias arising from attrition, analyses were adjusted for variables associated with missingness, helping to address potential bias due to missing data (Groenwold et al., 2012). In addition, regression results when inverse probability weights were applied remained similar, suggesting bias due to missingness was minimal (Seaman & White, 2013).

5.4.3. Strengths

Strengths of the current study include the use of a prospective cohort of recurrently depressed adults with detailed information available on the participants' clinical history and presentation.

5.4.4. Implications

These findings have important clinical implications. They suggest that in women with early onset, recurrent depression in adulthood, the possibility of depression masking underlying ADHD needs to be considered. Effective treatment of ADHD along with depression could improve functioning and associated depression symptoms. Even for those who do not meet diagnostic criteria for ADHD, higher ADHD symptoms appear to index a worse clinical picture. It is possible that they represent a 'neurodevelopmental type' of depression presentation, including earlier age of onset, increased severity and recurrence. Therefore, they may require more frequent follow-up for management of depression. It will be important for future studies to examine whether this group might respond to different types of depression treatment to those that are typically used for depression such as cognitive behavioural therapy and SSRI antidepressants.

5.4.5. Conclusions

To conclude, in a sample of recurrently depressed adults, ADHD was associated with an earlier age of depression onset, higher depression impairment, episode recurrence and subthreshold persistence. ADHD symptoms were also associated with increased odds of suicide or self-harm attempt. ADHD symptoms were associated with increased odds of hospitalisation and receiving non-standard depression medication, indicating non-response to first-line antidepressant treatment or a complex clinical presentation. Higher ADHD symptoms appear to index a worse clinical presentation for depression. Findings suggest that in women with early onset, recurrent depression, the possibility of underlying ADHD masked by depression needs to be considered.

Chapter 6: General Discussion

6.1. Overview

The overall aim of this thesis was to investigate the relationship between ADHD and depression and to test the role of a number of potential contributing factors. Though there is growing evidence that ADHD is associated with increased depression risk, the potential explanatory mechanisms underlying this association are unclear (Meinzer et al., 2014). Possible explanations include a direct effect of ADHD on depression risk in addition to a combination of shared environmental and genetic risk factors (Caron & Rutter, 1991; T. J. Chen et al., 2016; J. Cole et al., 2009; Lahey et al., 2011; Rydell et al., 2017; Schmitz & Mrazek, 2001). However, it is worth noting that genetic influences may be relevant to apparently environmental processes through gene-environment correlation (Rutter et al., 2001). Thus, I aimed to consider different explanations of the association between ADHD and depression in this thesis. Potential mediating mechanisms tested as possible explanations of the association between ADHD and depression were school attainment, friendships and parent-child relationships. The genetic overlap between ADHD and depression was examined to try and identify specific shared regions of the genome and the way in which these genomic regions might contribute to the association of ADHD and depression. Finally, the impact of ADHD on the clinical phenotype of depression was investigated. These aims were addressed in four empirical study chapters that each used a different sample suited to addressing the study aims.

The study chapter aims were:

1. To investigate the prospective association between ADHD at age 7 and depression symptoms 10 years later, and to test whether school attainment and peer relationships explain part of this association.
2. In a separate sample with detailed information on peer relationships, I tested which components of friendship were important in the association of ADHD and depression symptoms. I also tested whether the parent-child relationship could compensate for any friendship difficulties that mediated the association between ADHD and depression as a secondary aim.

3. To investigate the genetic correlation of ADHD and depression by identifying the specific regions of the genome that might contribute to the genetic overlap and to investigate potential mechanisms of these regions.

4. To investigate the impact of ADHD symptoms on the clinical phenotype of depression in an adult sample of individuals with recurrent depression.

The summary and interpretation of the findings of each chapter are discussed below, before a discussion of the strengths, limitations and implications of the work of this thesis, in addition to suggestions for future research.

6.2. Summary and Interpretation of Findings

6.2.1. Academic Attainment and Peer Relationships

The first aim of this thesis was to investigate the prospective association of ADHD and depression in childhood and adolescence – important risk periods for these disorders (Kessler et al., 2005; Thapar et al., 2017) – and to investigate whether school attainment and peer relationships explained part of this prospective association. This was investigated in chapter 2, which presents a study conducted in 2161 participants from ALSPAC – a longitudinal UK population sample, spanning 10 years from childhood to adolescence. School attainment and peer relationships were investigated as there is evidence that these are disrupted separately in ADHD (Birchwood & Daley, 2012; Blachman & Hinshaw, 2002; Kessler et al., 2014; Marton et al., 2015) and depression (Cole, 1990; Goodyer et al., 1989; Rahman et al., 2018; Riglin et al., 2014), but relatively few studies have examined how these factors might explain the link between ADHD and depression (Meinzer et al., 2014).

First, the study described in chapter 2 found a positive association between ADHD symptoms at 7 years and depression symptoms at 17 years. This adds to the growing body of literature mainly in clinical samples that supports a prospective association between ADHD and depression (Gundel et al., 2018; Meinzer et al., 2014), by testing the association in a population sample across a long follow-up period that included the key stages of childhood and adolescence. Since conducting

the study described in chapter 2, another study has been published that utilises the same cohort (ALSPAC), which found that ADHD symptoms at age 7 were associated with recurrent depression in early adulthood (age 18 to 25), reporting a similar magnitude of association (Riglin et al., 2020). The study described in chapter 2 also found that part of the association between ADHD and depression was mediated by academic attainment and peer relationship problems at age 16. Academic attainment explained 20.13% and peer problems explained 14.68% of the association between ADHD and depression. A sensitivity check was conducted to test whether the observed mediation by peer relationship problems was driven by the effect of bullying, as this has previously been shown to mediate the association of ADHD and depression (Roy et al., 2015). Peer relationship problems remained a significant mediator even when the item assessing bullying was removed from the measure. These results suggest that ADHD can lead to difficulties in academic attainment and with peers, which in turn increases subsequent depression risk in a mediated pathway. A previous study found that the prospective association between attention problems and depressive symptoms was mediated by social problems at school (a latent variable capturing social functioning and popularity), but not by stress related to general academic functioning (Humphreys et al., 2013). Another study found that being bullied or disliked by peers accounted for part of the prospective association between ADHD and depression symptoms (Roy et al., 2015). Both of those studies used measures of how liked (accepted) or disliked (rejected) children were. While these measures can capture how liked a child is on a group level (i.e. popularity), measures that instead capture children's friendships have previously been found to be more predictive of later depression and anxiety (Narr et al., 2019). Thus, the study presented in chapter 2 extends previous findings by highlighting academic attainment (assessed by performance in end of secondary school examinations) and peer problems other than social functioning, popularity and bullying (including self-reports of having good friends, feeling liked by others, playing or socialising with others and whether those you get on with are your own age) as potential mediators of the association between ADHD and depression. The findings also lend support to a number of theories that describe feelings of failure or a lack of competency in areas

such as friendships and school work as risk factors for depression (Capaldi, 1992; Cole et al., 1996; Patterson & Stoolmiller, 1991).

In summary, the study presented in chapter 2 adds to the growing evidence of a prospective association between ADHD and depression and highlights academic attainment and peer relationships as potential mediators of this association. However, peer relationships in this study were captured by a composite measure, and a more detailed investigation of friendships in the association of ADHD and depression is lacking (Mikami, 2010). Therefore, this was investigated in the next study chapter.

6.2.2. Features of Friendship and The Parent-Child Relationship

The second aim of this thesis was to investigate peer relationships in more detail by testing which components of friendship are important in the association of ADHD and depression symptoms. An additional aim was to investigate whether quality of the parent-child relationship compensated for any friendship difficulties mediating the association between ADHD and depression. This was tested because there is some evidence that a good quality parent-child relationship may be able to compensate for the adverse effect of a lack of friends on children's emotional functioning (Stocker, 1994). This was investigated in chapter 3, which presents a short-term longitudinal study of 1712 pupils from nine schools across the Greater London region of the UK in their first year of secondary school. The features of friendship that were investigated included the presence and stability of best friendships over the school year, the quality of best friendships, and the characteristics of the child's classroom friendship group.

The study found that ADHD and depression were differentially associated with various aspects of friendship when tested separately, but only friendship quality was a significant mediator of the prospective association between ADHD and depression symptoms 7 months later. ADHD was significantly associated with having fewer friends, friendships that were lower quality and being a part of a classroom friendship group where members had greater (self-rated) mental health difficulties according to the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997) and

were more disruptive and less cooperative according to peer-reports. Presence, stability and quality of friendships were negatively associated with depression. This expands on existing literature evidencing that those with ADHD have fewer stable friendships (Blachman & Hinshaw, 2002) and that poor quality friendships are a risk factor for depression (Goodyer et al., 1989), by documenting in detail the associations of ADHD and depression with a wide range of features of friendship, and by testing their potential mediating role in the association of ADHD and depression. Friendship quality was the only significant mediator of the association between ADHD and depression symptoms, suggesting that lower quality friendships are important in explaining the association between ADHD symptoms and subsequent depressive symptoms, at least in this short-term longitudinal study. In particular, the conflict and security elements of the friendship quality measure seemed to be important in the association of ADHD and depression, as these were significant mediators when each subscale of the friendship quality scale was tested. The security subscale assesses the ability to disclose problems to your friend and reconcile following disagreements. The finding that conflict in friendships mediated the link between ADHD and depression is somewhat consistent with previous findings of increased friendship conflict and aggression in those with ADHD in a case-control study (Blachman & Hinshaw, 2002). The mediating effect of friendship quality was stronger for females than for males. Previous literature that shows that females might value aspects of friendship such as companionship more highly than males (Hall, 2010). Interpersonal stress is also more common in adolescent females and more highly associated with depression compared to in males (Shih et al., 2006). This is particularly important to consider in females with ADHD. In a previous study, females with predominantly inattentive ADHD were found to experience more peer problems, including a lack of positive-influence peers, in comparison to boys with inattentive ADHD (Elkins et al., 2011). Potential explanations of this include attention problems impacting on the ability to notice social cues that perhaps contribute to a sense of companionship, which is an important part of female friendships (Hall, 2010).

There was some suggestive evidence that parent-child relationship quality may act as a moderator of mediation via top three friendships quality, whereby the mediation effect via friendship quality attenuated slightly as mother warmth increased and father hostility decreased, though the moderating effect of father hostility did not reach conventional thresholds for significance. These findings expand upon the current literature that supports a mediating role of the parent-child relationship in the association of ADHD and depression (Humphreys et al., 2013; Meinzer et al., 2020), by investigating moderating effects of parent-child relationships on mediating effects via friendship. In addition, the study presented in chapter 3 investigates the effect of the children's relationship with their mothers and also fathers, who are understudied in the literature (Cabrera et al., 2018; Mikami, 2010). The findings of chapter 3 highlight the need to consider the social support available to the child across multiple contexts, including with parents and with friends, and how this might be impaired by ADHD symptoms and may increase vulnerability to depression. The findings add to the previous literature that suggests good quality social support can mitigate against depression risk in the presence of adversity more broadly (Collishaw et al., 2016; H. Y. Lee et al., 2019).

In summary, the study presented in chapter 3 highlights quality of relationships with best friends and the interaction of this with parent-child relationship quality as important factors to consider in the association between ADHD and depression. This builds upon the work detailed in chapter 2, where a composite measure of peer-relationship problems was found to mediate the prospective association between ADHD and depression, by highlighting friendship quality as an important part of friendship problems to consider. It also draws attention to the various aspects of friendship that may be adversely affected in those with ADHD symptoms, including a lack of friendships, decreased quality of friendships and increased likelihood of being a part of peer groups with increased mental health and behavioural difficulties.

Although genetic and environmental effects in combination were not tested in the studies of this thesis, the potential effect of person-environment correlation on the findings observed in chapters 2 and 3 should be noted. While the mediators

and moderators investigated can be considered as situations that those with ADHD are at an increased risk of being exposed to, children with ADHD might in some cases also be more likely to contribute to the creation of such situations, for example, through evocative effects (Caspi et al., 1989). For instance, children with ADHD may be more likely to evoke certain reactions from their parents, which could in turn detrimentally effect the quality of this relationship and also the child's subsequent interactions with their friends. An example of this is the observation that parent-child hostility is reduced when children are receiving drug treatment for ADHD compared to no treatment (Barkley & Cunningham, 1979). Person-environment correlation is influenced in part by an individual's genetically influenced behaviour and is an example of an indirect genetic effect whereby genes can influence a phenotype via exposure to an environmental factor (Rutter et al., 1997). I consider the contribution of genetics to the association of ADHD and depression in the next section, which discusses the findings in chapter 4.

6.2.3. Genetic Overlap

In addition to potential environmental factors that might contribute to the association between ADHD and depression that are examined in chapters 2 and 3, genetic factors also need to be considered as both ADHD and MDD are heritable and are genetically correlated with each other (Demontis et al., 2019; Wray et al., 2018). The third aim of this thesis was to investigate the genetic correlation of ADHD and depression and to identify specific regions of the genome that might contribute to this genetic overlap. This was investigated in chapter 4 – a genome-wide association (GWA) study meta-analysis of the most recent ADHD and MDD GWA studies (Demontis et al., 2019; Wray et al., 2018). SNPs that were significantly associated with the meta-analysis that I performed ($p=5 \times 10^{-8}$) and associated to a lesser extent with ADHD and MDD separately ($p=5 \times 10^{-4}$), were highlighted as putative regions of shared genetic variation in ADHD and MDD. These thresholds were used in an attempt to identify SNPs contributing to both ADHD and MDD, rather than meta-analysis signals driven predominantly by one of these GWA studies. Identified SNPs then underwent annotation analysis to identify nearby protein coding genes and whether SNPs affected gene expression as expression quantitative trait loci in human

tissues (eQTL). SNPs that were found to act as an eQTL in brain tissue were of particular interest, given that both ADHD and MDD are regarded as disorders of the brain. SNPs were also examined for association across 37 other GWA studies to investigate the extent to which the SNPs might be pleiotropic across different phenotype categories including psychiatric, cognitive, anthropometric and other health conditions. This allowed checking of whether associated SNPs were specific to ADHD and MDD, wider psychiatric traits, or more broadly associated across different trait classes. In addition to examining the extent of pleiotropy, this also allowed the potential mechanisms of association to be explored through identifying potential shared risk factors. For example, many of the SNPs identified as contributing to ADHD and MDD in chapter 4 were associated with other traits that have been found to be associated with both ADHD and depression in separate studies in the literature, for example, body fat (Leppert et al., 2019; Speed et al., 2019) and cognition or education (Birchwood & Daley, 2012; Riglin et al., 2015). These observations in chapter 4 could represent horizontal pleiotropy (the SNP, or gene that the SNP affects, is directly associated with all traits separately), vertical pleiotropy (the SNP is associated with one of the associated traits, which in turn increases risk of the other associated trait) or a combination of the two (van Rheenen et al., 2019).

Fourteen putatively shared SNPs in the meta-analysis of ADHD and MDD were identified, nine of which were novel in that they had not been highlighted in the previous individual GWA studies (Demontis et al., 2019; Wray et al., 2018). This study builds upon previous findings of a genetic correlation between ADHD and MDD (Demontis et al., 2019; Wray et al., 2018), by highlighting potential regions of the genome responsible for this overlap. It also builds upon a previous GWA study meta-analysis of eight psychiatric disorders (including ADHD and MDD) which identified only 5 of the 14 genomic regions identified in the current study (the LD ranges of rs12658032, rs4593766, rs61867322, rs2509805, rs8084351) (P. H. Lee et al., 2019). The previous study investigated multiple traits including well-powered and large GWA studies (e.g. schizophrenia) and thus findings are likely to be dominated by signals for these traits, while findings for less powered GWA studies such as ADHD are likely to be omitted or down-weighted due to a lack of evidence across the other

diagnoses. By focusing on ADHD and MDD only, the study in chapter 4 identifies an additional 9 SNPs that might contribute to the genetic overlap of these two disorders. However, it should be noted that the same issue to a lesser extent applies to the study in chapter 4, as the ADHD and MDD GWA studies vary considerably in sample size.

Investigation of nearby genes to index SNPs and whether SNPs acted as eQTLs allowed elucidation of which variants showed evidence of being related to genes involved in neurodevelopment or brain function, and whether they affected gene expression in trait relevant tissues (i.e. mRNA levels in the brain). Nine of the 14 SNPs were found to affect gene expression, two of them in brain tissue. For example, rs8084351 on chromosome 18 showed a subthreshold association with ADHD and MDD separately, but was genome wide significant in the meta-analysis. This demonstrates the increased power to detect genetic variants by using meta-analysis. The SNP rs8084351 was found to affect expression of *DCC* (Deleted in Colorectal Cancer) in cerebellar brain tissue – a gene involved in neuronal growth (Li et al., 2004). In addition, all of the 14 SNPs demonstrated additional associations with related psychiatric, cognitive and education phenotypes and minimal associations with any other phenotype categories, suggesting specificity to psychiatric and related outcomes. Findings also support previous findings of genetic contributions to psychiatric disorders transcending diagnostic boundaries (e.g. P. H. Lee et al., 2019). There may be multiple explanations of the genetic pleiotropy observed in this study (van Rheenen et al., 2019). One example is the association of rs12658032 (among other index SNPs) with years of education, in addition to ADHD and MDD. One potential explanation of this observation is vertical pleiotropy, whereby rs12658032 is associated with ADHD, which in turn is negatively associated with years in education, which increases subsequent depression risk in a causal cascade. In addition, it is possible that rs12658032 also exerts direct effects on all three traits (horizontal pleiotropy). In chapter 2, I found that academic attainment mediated the prospective association between childhood ADHD and adolescent MDD. Taken together, the findings of chapters 2 and 4 highlight that multiple effects may potentially be contributing to observed associations: vertical genetic pleiotropy,

horizontal genetic pleiotropy, in addition to potential social mediating mechanisms whereby a mediated pathway via friendship and academic attainment occurs over the course of development.

In summary, the study presented in chapter 4 highlights 14 regions of the genome that potentially contribute to the genetic correlation of ADHD and MDD, nine of which were not highlighted by the previous individual GWA studies. The study also highlights the impact of nine of these SNPs on gene expression, helping to elucidate the way in which these SNPs might act biologically. The additional associations of index SNPs with related traits are also highlighted. Findings might suggest that there is some unique genetic architecture to the overlap of ADHD and MDD.

6.2.4. The Impact of ADHD on Depression Clinical Phenotype

In addition to the first three thesis aims which focussed on investigating mediating mechanisms and genetic explanations of the association between ADHD and depression, the aim of the fourth study of this thesis was to investigate how ADHD affects the clinical phenotype of depression. Though there is some evidence that ADHD may affect the presentation of depression in children (e.g. Biederman et al., 2008), the impact of ADHD on depression phenotype in adults is not clear. This was investigated in chapter 5, which presents a study of 148 recurrently depressed females from a prospective, longitudinal cohort of recurrently depressed adults spanning 13 years.

The study found that the prevalence of those meeting criteria for ADHD diagnosis was high in the recurrently depressed adults compared with the reported prevalence in the general population (Simon et al., 2009). Despite this, probable cases of ADHD did not seem to be clinically recognised in this sample, as no participants reported having been diagnosed with ADHD by a clinician. ADHD is not typically assessed in adult clinical settings, although those with high ADHD symptoms were more likely to be on non-standard depression medication (based on UK clinical guidelines), which might indicate that a clinician had recognised a complex clinical presentation or resistance to first line (i.e. SSRI) depression medication (National

Institute for Health and Care Excellence (NICE), 2009). ADHD symptoms in the recurrently depressed adults were also associated with various features of depression clinical phenotype. ADHD symptoms were associated with an earlier reported age of onset for depression (≤ 25 years), more severe impairment and greater depression recurrence. ADHD symptoms were also associated with increased odds of self-harm or suicide. ADHD symptoms were associated with aspects of clinical management, including increased odds of being hospitalised in addition to increased odds of being on non-standard depression medication. The findings align with previous studies in children and adolescents that found young people with ADHD are at higher risk of early onset, highly impairing and recurrent depression in young adulthood (Biederman et al., 2008; Riglin et al., 2020), as well as suicide compared to those with depression alone (Biederman et al., 2008). A previous 4-year follow-up study in adults (aged 21 to 69 years) also found an increased risk of probable ADHD in those with longer depressive episodes and in those with an age of onset before 21 compared to after (Bron et al., 2016). The study presented in chapter 5 makes an important contribution to the existing literature by investigating the association of ADHD symptoms in midlife (aged 42 to 67 years) with various aspects of depression phenotype using detailed clinical measures of depression assessed on multiple occasions in a prospective cohort followed for 13 years. The findings suggest that even for those who do not meet diagnostic criteria for ADHD, higher ADHD symptoms appear to index a worse clinical presentation, which might represent a 'neurodevelopmental type' of depression presentation, including earlier onset, increased severity and recurrence. For instance, previous studies of depression according to age of onset have found that an earlier onset, more persistent depression is associated with elevated neurodevelopmental traits (Jaffee et al., 2002; van Os et al., 1997), including ADHD symptoms (Rice et al., 2019). The findings presented in chapter 5 also align with emerging evidence that suggests that adult major depressive disorder might mask underlying ADHD that is missed in clinical practice (e.g. McIntosh et al., 2009). This might be particularly important to consider in females, as neurodevelopmental disorders may be more likely to be missed in females compared to males (Martin et al., 2018).

In summary, the final study of this thesis detailed in chapter 5 finds that the prevalence of adult ADHD is high in a cohort of recurrently depressed adults and that ADHD symptoms affect the clinical presentation of their depression. Findings suggest that increased adult ADHD symptoms may index a more recurrent and severe depression with an earlier age of onset, increased odds of suicide or self-harm attempt, hospitalisation and non-standard depression medication use. While chapters 2 and 3 investigated potential explanations of the association of ADHD and depression in childhood and adolescence, chapter 4 highlights the impact of ADHD on depression presentation in a sample of adults. Despite the high rate of ADHD and depression comorbidity observed in samples of children and adolescents (Angold, Costello, & Erkanli, 1999), comorbidity between depression and ADHD is not typically assessed in adult samples. The findings of chapter 4 highlight the need to consider the association of ADHD and depression in adults in addition to children and adolescents.

6.3. Limitations

It is important to view the findings of this thesis in the context of a number of limitations. Limitations specific to each study are discussed in each study chapter. More general limitations are discussed here.

Although the work of this thesis provides a number of insights into potential explanations of the association between ADHD and depression across varying samples, the results are not able to confirm a causal effect between ADHD, mediating factors and depression. To infer causality a number of requirements of study design must be fulfilled including observation of an association, a time precedent and ruling out spurious association (Rutter, 2007). Although the findings of this thesis support an association between ADHD and depression and are tested in a longitudinal design in chapters 2 and 3, ruling out spuriousness is more complex. All associations presented in this thesis are adjusted for various potential confounders such as sociodemographic background. However, there is a possibility that unmeasured confounders might exist that would explain the association of ADHD and depression or the associations with mediators. This unmeasured

confounding in addition to measurement error in confounders creates residual confounding, which is a major challenge in observational studies (Rice, Langley, Woodford, Davey Smith, & Thapar, 2018). An additional challenge is the possibility of reverse causation contributing to the observed association between ADHD and subsequent depression. However, a recent study using Mendelian Randomisation (MR) analysis supported a causal effect of ADHD genetic liability on depression risk in a longitudinal population cohort (Riglin et al., 2020). MR uses genetic liability as a proxy for the exposure of interest and thus is more robust to confounding than traditional observational studies (Bowden et al., 2016). This and other study designs that may be useful for inferring causality are discussed as future research directions in section 6.4.

Although a strength of this thesis is the varying samples and studies used, it is important to consider the disadvantages of different samples and how they might affect results. For instance, while a longitudinal design is useful for helping to infer the direction of effects and providing the opportunity to test associations in relevant developmental periods of life, one common limitation of prospective longitudinal studies is attrition. This loss to follow-up of participants and resulting missing data can bias observed results (Spratt et al., 2010). For instance, in mental health research it is often the case that the participants at higher risk of psychopathology including increased genetic risk are more likely to drop out than other participants (Martin et al., 2016; Taylor et al., 2018). A number of reliable statistical methods exist to address the potential bias arising from missing data which are utilised in the studies presented in chapters 2, 3 and 5. Inverse Probability Weighting (IPW) is particularly suited to longitudinal cohorts where participants can have missing data for multiple variables (e.g. due to non-participation at an assessment wave; Seaman & White, 2013), as is in the case in the ALSPAC cohort in chapter 2 and the EPAD cohort in chapter 5. Thus, in chapters 2 and 5, IPW was used whereby participants more similar to those who have dropped out are given greater weight in analysis than other participants (Seaman & White, 2013). The weights are derived from a missingness model, which is specified by investigating various potential predictors of missingness, such as socioeconomic status, adversity and gender. In chapter 3,

Multiple Imputation (MI) was used due to its high computational efficacy when incomplete cases have some available data, as was the case in this study, where many of the children who had complete self-rated data did not have complete teacher-rated data (Seaman & White, 2013; Spratt et al., 2010). In MI, values for missing participants are imputed using a model consisting of variables that predict missingness and variables that predict the outcome variables that are subject to missing data (Spratt et al., 2010). The imputation is conducted numerous times to allow for a degree of uncertainty about the missing data, for example, 100 imputations were used in chapter 3. Both IPW and MI are reliable methods for handling missing data (Seaman & White, 2013). In the study chapters utilising these methods (2, 3 and 5), results remained similar before and after IPW or MI, suggesting that potential bias arising from missingness was minimal.

The samples used in chapter 4 might also have affected results. The studies used may have biased the genetic variants detected as contributing to the overlap of ADHD and MDD due to differences in the size and therefore potentially the power of the ADHD and MDD GWA studies. For instance, in a previous cross-disorder meta-analysis of multiple large GWA studies (P. H. Lee et al., 2019), findings were likely to be dominated by the larger and better powered GWA studies (e.g. schizophrenia), thereby down-weighting findings for smaller GWA studies such as ADHD, as discussed previously in 6.2.3. Although by focussing on ADHD and MDD alone, the study in chapter 4 highlighted additional SNPs that might contribute to the genetic overlap of these two disorders, the ADHD GWA study is still smaller and underpowered in comparison to the MDD GWA study which may bias findings (Demontis et al., 2019; Wray et al., 2018). As GWA studies increase in sample size in the future, more variants contributing to ADHD, and indeed to MDD, will be discovered (Visscher et al., 2017). However, GWA study power also increases with higher heritability of the trait under study (Sullivan et al., 2012), which is larger for ADHD than for MDD. Moreover, in an attempt to limit findings to SNPs with evidence of association with both disorders, rather than SNPs that were genome wide significant in the meta-analysis due to a strong association with the better powered

GWA study only, a limit of $p < 5 \times 10^{-4}$ was imposed on the individual ADHD and MDD GWA studies.

Another important issue to consider is how findings might be affected by the measures used. For instance, while questionnaire symptom scales such as the hyperactivity subscale of the SDQ (Goodman, 1997) used in chapter 3 and the Short Moods and Feelings Questionnaire (Angold et al., 1995) used in chapters 2 and 3 are easy to administer to participants and useful at capturing ADHD symptoms and depression symptoms respectively across the symptom spectrum in the general population, these measures are likely to capture a broader group of individuals than a clinical diagnosis (e.g. Goodman, Ford, Simmons, Gatward, & Meltzer, 2000), thus affecting findings. For example, the work of this thesis observes more moderate, though still significant, associations between continuous symptom measures of ADHD and depression when compared to studies testing the association between ADHD and depression clinical diagnoses (e.g. Gundel et al., 2018). However, clinical measures of depression and impairment were used in chapter 5 and the measures of ADHD symptoms used in chapters 2 and 5 captured all 18 DSM-5 ADHD symptoms (American Psychiatric Association, 2013). The observed association between ADHD and depression was robust across all chapters and the respective measures used in this thesis.

The informants that reported on the symptoms or phenotypes studied in this thesis might also have impacted on results. For instance, in the school-based study presented in chapter 3, teacher-reported ADHD symptoms are used. Although teachers can give insight into ADHD symptoms in the context of school, previous studies have found that teachers might under-report ADHD symptoms in children compared to parent-reports (Antrop et al., 2002; Sollie et al., 2012), which could lead to an underestimation of ADHD and thereby potentially attenuate the observed associations in chapter 3. Indeed, a similar effect size for the association between parent-reported ADHD and depression was observed in chapter 2 with a 10-year follow-up period, to the association between teacher-reported ADHD and depression in chapter 3 with a 7-month follow-up period, even though one might expect to observe a stronger association over a shorter time period. Self-reported depression

symptoms are used in both chapters 2 and 3. Though self-reports can be a reliable measure of adolescent depression, those with ADHD have been evidenced to under-report their own depression symptoms, which might attenuate observed associations (Fraser et al., 2018). Those with ADHD may also be more likely to over-estimate their competency with peers (Ohan & Johnston, 2011), while those with depression may under report this (Whitton et al., 2008). This could affect the self-rated measures of friendship presence, quality and stability that are used in chapter 3. However, peer-rated measures of friendship were also used which would not be affected by illusory bias. In addition, the associations that were found between ADHD, friendship and depression in chapter 3 were as expected, in that they were similar to the associations observed in chapter 2 which used parent-rated peer problems as opposed to a self-rated measure.

Finally, only a finite number of potential explanatory factors of the association between ADHD and depression could be explored in this thesis. Although both mediating mechanisms and genetic factors are investigated, they are not examined in combination. The focus of this thesis is the association between ADHD and depression using a disorder-specific approach. A broader investigation of the association between neurodevelopmental traits and emotional problems could be conducted. For example, anxiety is often comorbid with depression (Angold, Costello, & Erkanli, 1999; Kessler, Chiu, Demler, Merikangas, & Walters, 2005) and thus would be of interest to investigate in future work. A more dimensional trait approach as opposed to a disorder approach could also be taken, in line with the approach encouraged by the RDoC project, for example (Cuthbert & Insel, 2013). Each of the studies of this thesis are quantitative rather than qualitative, but it is important that work is informed by the voices of young people with lived experience. The work of this thesis was informed in part by involvement in public engagement events during which children with ADHD and their parents discussed the struggles the children experienced in school (Agha, Langley, Hopkins, Bevan Jones, & Thapar, 2020), in addition to a previous review of qualitative studies of school-related experiences of children with ADHD that found children with ADHD can be a poor “fit” in a typical classroom setting (Richardson et al., 2015).

6.4. Strengths

The main strength of this thesis was the use of different samples, methodologies and informants to investigate the association of ADHD and depression. For instance, insights into the association of ADHD and depression were found in a large population sample (chapter 2), a school-based sample (chapter 3), a cohort of recurrently depressed parents (chapter 5) and in a meta-analysis of GWA studies (chapter 4). ADHD and depression were consistently found to be associated. This gives confidence that the findings are not spurious or an artefact of the specific sample under study, for example, measurement, informant or cohort effects. The use of different studies with different strengths and weakness to rigorously test an association is an important part of constructive replication of findings (Munafò & Davey Smith, 2018; Rutter et al., 2001). While findings in the cohort of depressed adults may translate more directly to the clinic by looking at severely affected individuals, large population and school samples that are more representative of the general population allow investigation of individuals with varying levels of symptoms who may or may not have been diagnosed. School-based samples also provide rich information on the academic and social lives of young people at school. The use of prospective, longitudinal designs allowed testing of associations and their mediation or moderation over time in important developmental periods. The studies of this thesis were mainly conducted in childhood and adolescence, but the impact of ADHD on depression in adulthood was also explored in chapter 5. In addition to focussing on potential social mediating mechanisms in the relationship of ADHD and depression, genetic overlap was also explored in this thesis using the most recent and well powered GWA studies of ADHD and MDD (Demontis et al., 2019; Wray et al., 2018).

6.5. Implications

The prospective association of childhood ADHD and later depression is supported in the studies of chapters 2 and 3 in this thesis. This association was observed over a shorter period of 7 months in chapter 3 and over a longer period of 10 years in chapter 2. This highlights the importance of monitoring children and

adolescents with ADHD for depression. Such monitoring might allow early identification and thus treatment of depression in this group. Chapters 2 and 3 together highlight difficulties with academic attainment and with friendships, in particular friendship quality in chapter 3, as mediators of the link between ADHD and depression. The implications of this are that interventions targeting these areas (e.g. Piffner et al., 2014) may also be beneficial in reducing depression risk in those with ADHD. While interventions have largely focussed on peer acceptance and social skills thus far and have shown limited success in children with ADHD (Mikami, 2010), interventions focused instead on building good quality friendships (e.g. Gardner et al., 2019) may perhaps be more effective. In chapter 3, there was also suggestive evidence of a moderating effect by parent-child relationship quality on mediated effects by friendship quality, suggesting that programs aiming to improve friendship that incorporate a parental component (e.g. Gardner et al., 2019) might be helpful for children with ADHD. Existing interventions focussed solely on improving the quality of the parent-child relationship might also have promise in reducing depression risk in this group (Abikoff et al., 2015).

In addition to the findings in children and adolescents in chapters 2 and 3, the findings of this thesis also have important implications for the association of ADHD and depression in adulthood. In the study of recurrently depressed adults presented in chapter 5, findings suggested that ADHD symptoms seem to index a worse depression clinical presentation, including an earlier age at onset, increased recurrence, increased suicide risk and use of non-standard antidepressant medication. This highlights that the possibility of underlying and undetected ADHD may need to be considered in women with an early-onset, recurrent depression presentation. This group may require more frequent monitoring for depression management and may benefit from treatment of ADHD, in addition to depression, in improving depression impairment and associated outcomes.

In addition to potential mediating mechanisms and phenotype effects explored in chapters 2, 3 and 5, the genetic overlap of ADHD and depression was also investigated in chapter 4. This study demonstrated the genetic overlap of ADHD

and depression at specific regions of the genome that were not highlighted by previous GWA studies, highlighting genomic regions of interest for future research.

6.6. Future Directions

As ADHD typically onsets in childhood and depression prevalence increases rapidly in adolescence (Avenevoli et al., 2015; Thapar & Cooper, 2016), and there is strong evidence that ADHD is related to increased subsequent depression risk as opposed to other way around (Riglin et al., 2020), I focussed on testing this direction of effect in this thesis. However, there is a possibility that reverse causation may contribute to observed results. In order to try to address this, I conducted multiple sensitivity checks in chapter 1, including adjusting the association between ADHD and later depression for baseline emotional problems. All sensitivity checks showed that the results remained very similar, suggesting that results were not affected by reverse causation. In addition, the association between ADHD and subsequent depression was robust across chapters 2 and 3, which used different samples and informants and tested the association over a different length of time. Nevertheless, I cannot be certain of the causal pathway that exists between ADHD and depression. Study designs that could be used to investigate this further in future work include MR (e.g. Bowden et al., 2016) and other genetically informed designs that can disentangle environmental from genetic effects such as twin, adoption, control sibling and IVF studies (Rice, Langley, Woodford, Davey Smith, & Thapar, 2018; Thapar & Rutter, 2015). This would also help to investigate whether the mediators observed in this thesis of school attainment and friendships are in fact a part of the causal pathway from ADHD to depression. Similarly, whether the genetic variants associated in the ADHD and depression GWA study meta-analysis in chapter 4 are in fact causal variants in the disorders' genetic overlap could be explored using MR-based techniques. This could also help to inform the type of pleiotropy (e.g. horizontal or vertical) that is behind the observed associations of SNPs with ADHD and MDD GWA studies in addition to GWA studies of related traits such as education. Future investigation of the genetic overlap of ADHD and MDD could also be expanded with in-depth functional analysis of the genomic regions identified in the current study to further investigate their biological mechanisms, particularly for

regions in protein coding deserts such as rs12658032. The contribution of rare genetic variants in addition to common variants in the overlap of ADHD and MDD could also be examined.

As discussed in the implications (section 6.5), the work of chapters 2 and 3 in particular give rise to questions of whether interventions targeting academic attainment, peer problems including friendship quality, and parent-child relationship quality would be successful in reducing depression risk in young people with ADHD. Thus, future work could focus on how one would best test and implement such interventions. For instance, one promising direction is the development of interventions that incorporate parents and aim to help children to build good quality friendships (Gardner et al., 2019).

6.7. Conclusions

There is increasing evidence in the literature that ADHD is associated with depression and that the two disorders are genetically correlated, but the mechanisms behind the association are unclear. There is some evidence mainly from samples of young people to suggest that those with ADHD might be at risk of worse depression-related outcomes than those with depression alone. This thesis extends the literature firstly by confirming a prospective association between ADHD and depression and finding that this is mediated by difficulties with academic attainment and peers in a longitudinal population cohort. Secondly, this thesis investigates the role of friendships in the association of ADHD and depression in more detail, finding that quality of friendships is particularly important and that this effect may be moderated by quality of the parent-child relationship. Thirdly, the genetic correlation of ADHD and depression is investigated using a GWA study meta-analysis, which identifies several potentially shared genomic regions of interest that might explain, in part, the genetic correlation of the two disorders. Finally, this thesis finds that the rate of ADHD is high in a sample of adults with recurrent depression and these ADHD symptoms are associated with an earlier onset, more recurrent and impairing depression phenotype, in addition to increased odds of suicide or self-harm attempt, hospitalisation and non-standard depression medication use.

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Appendices

Appendix 2.1. Mediation of the Association between Childhood ADHD and Late Adolescent Depression Adjusted for Depression at 14 Years Old

Mediator	Pure Natural Direct Effect b (95% CI)	Total Natural Indirect Effect b (95% CI)	Proportion of Total Effect Mediated % (95% CI)
(Measured at 16 years)			
Peer problems	0.47 (0.22-0.71)	0.09 (0.02-0.17)	16.35 (11.44-29.36)
GCSE results	0.44 (0.19-0.70)	0.11 (0.01-0.21)	19.04 (13.46-36.62)

Two individual potential outcomes causal mediation analyses each adjusted for sex, maternal age at birth and socioeconomic status were repeated with adjustment for the additional covariate of depressive symptoms at 14 years old. This was to account for the effect of depression prior to the measurement of the mediators which could affect peer relationships and GCSE results. The exposure levels being compared in these analyses are mean ADHD symptoms and 1 Standard Deviation above this. The mediation allowed for an interaction between exposure and mediator and was conducted on complete cases for exposure, mediators, outcome and confounders (n=2161). Interpretation of results remained the same. Significant mediators are indicated by confidence intervals of 'Total Natural Indirect Effect' not containing zero. *ADHD* attention-deficit hyperactivity disorder, *GCSE* general certificate of secondary education, *b* unstandardized beta, *CI* confidence interval

Appendix 2.2. Mediation of the Association between ADHD at 7.5 years and Depression at 13 Years Old by Peer Problems at 9.5 Years Old

Mediator (Measured at 9.5 years)	Pure Natural Direct Effect b (95% CI)	Total Natural Indirect Effect b (95% CI)	Proportion of Total Effect Mediated % (95% CI)
Peer problems	0.22 (0.19-0.25)	0.07 (0.05-0.08)	22.83 (20.16-26.04)

The peer problems individual potential outcomes causal mediation analyses adjusted for sex, maternal age at birth and socioeconomic status was repeated using data collected at earlier time points. This was done to check whether peer problems still mediated the association between ADHD and depression when it was measured at a time point prior to the typical age of onset of depression. The exposure levels being compared in these analyses are mean ADHD symptoms and 1 Standard Deviation above this. The mediation allowed for an interaction between exposure and mediator and was conducted on complete cases for exposure, mediators, outcome and confounders (n=4330). Interpretation of results remained the same. Significant mediators are indicated by confidence intervals of 'Total Natural Indirect Effect' not containing zero. *ADHD* attention-deficit hyperactivity disorder, *b* unstandardized beta, *CI* confidence interval

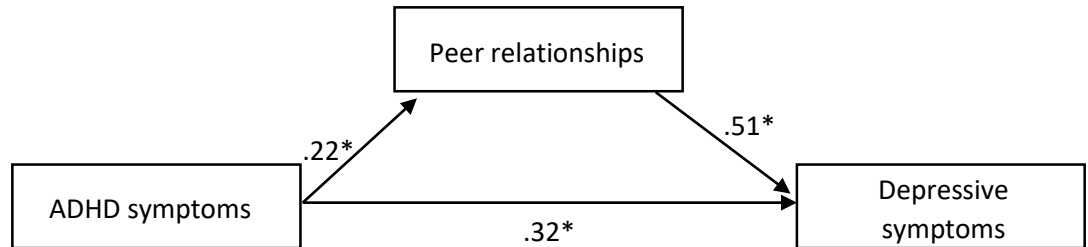
Appendix 2.3. Prediction of Missingness from Analysis Sample

Predictor Variable	OR	95% CI	P-value
ADHD symptoms at 7 years 7 months	1.22	1.16, 1.29	<0.001
Sex (1=male, 2=female)***	0.66	0.60, 0.73	<0.001
Month of birth**	1.00	0.99, 1.02	0.65
Socioeconomic status based on occupation of mother is 'unskilled'***	1.19	1.03, 1.37	0.02
Maternal age at delivery of child***	0.95	0.94, 0.96	<0.001
Number of children mother had before study child***	1.11	1.05, 1.17	<0.001
Mother's highest educational qualification is a degree***	0.63	0.55, 0.71	<0.001
Mother owns a home during pregnancy***	0.42	0.36, 0.49	<0.001
Mother had financial problems during pregnancy***	1.50	1.25, 1.79	<0.001
Mother smoked during pregnancy***	1.77	1.51, 2.08	<0.001
Mother's social support score during pregnancy***	0.97	0.96, 0.99	<0.001
Mother has a partner when child is 8 months old*	0.54	0.39, 0.75	<0.001
Mother ever had severe depression (reported during pregnancy)***	1.44	1.17, 1.78	0.001
Child's mood score at 24 months old (from the Carey Toddler Temperament Scale)*	1.01	1.00, 1.02	0.22

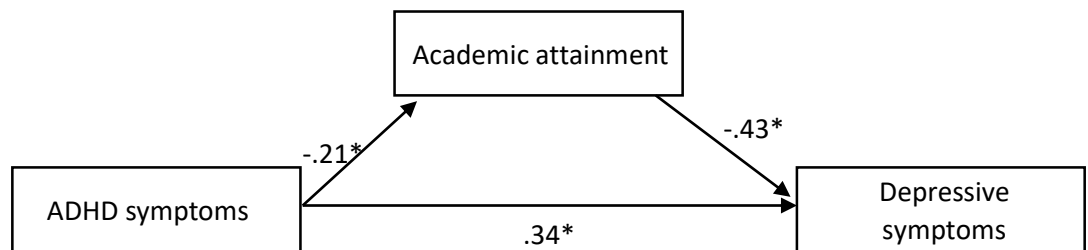
Within those with ADHD symptom data at 7 years and 7 months (n=8182), logistic regressions between numerous predictor variables and being missing from the regression or mediation analysis sample were conducted to establish predictors of attrition in this study. Results shown here use missingness from mediation analysis as the outcome. * indicates this variable was used as a predictor in the missingness model used to generate Inverse Probability Weights (IPWs) for regression analyses. ** indicates this variable was used to generate IPWs for mediation analyses. *** indicates this variable was used for both. *ADHD* attention-deficit hyperactivity disorder, *OR* odds ratio, *CI* confidence interval

Appendix 2.4. Testing Mediators Simultaneously in Multiple Mediator Structural Equation Model

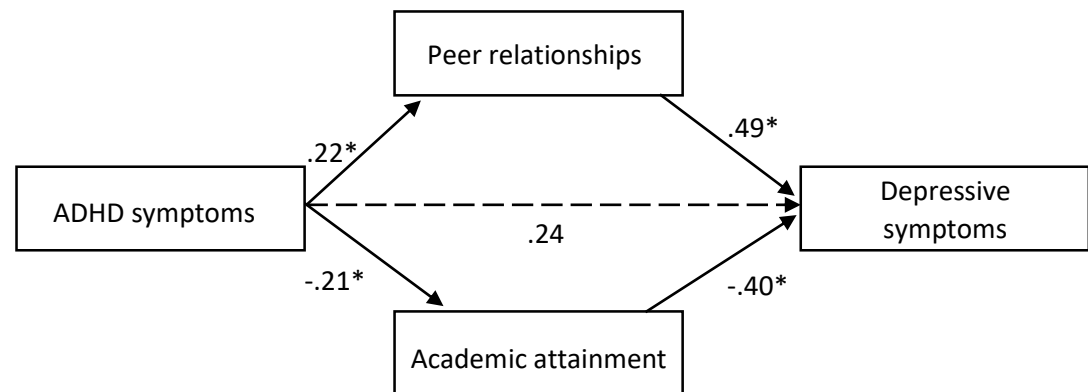
A



B



C



A sensitivity analysis to check that peer relationships and academic attainment still mediated the association of ADHD and depressive symptoms when tested simultaneously (Figure C) as opposed to individually (Figures A and B) was conducted using Structural Equation Modelling (SEM). This test was conducted on complete cases for exposure, mediators, outcome and confounders (n=2161). When both mediators were entered simultaneously, the direct association between ADHD and depressive symptoms became non-significant (p=0.06). Both mediated pathways via peer relationships and academic attainment remained significant at p<0.007. Beta coefficients are shown on the path arrows. *ADHD* attention-deficit hyperactivity disorder

Appendix 2.5. Sensitivity Analysis of Mediators of the Association between ADHD and Depression

Mediator	Rho at which ACME = 0	$R^2_{M \sim R^2_{Y \sim}}$ at which ACME = 0	$R^2_M * R^2_{Y^*}$ at which ACME = 0
Peer problems at 16 years	0.09 or greater	0.008	0.009
GCSE results at 16 years	-0.07 or lower	0.005	0.006

Sensitivity analysis to check for the effect of confounding of the association between mediator and outcome for each mediation analysis was conducted on complete cases for exposure, mediators, outcome and confounders (n=2161) using the 'medsens' package. ACME is the Average Causal Mediation Effect. 'Rho at which ACME = 0' is the correlation between residuals of mediator and outcome variable (as an indication of confounding of the mediator-confounder association) that would be needed for an observed mediation effect to disappear. ' $R^2_{M \sim R^2_{Y \sim}}$ at which ACME=0' is the product of how much of the observed variance in the mediator and in the outcome would need be explained by unobserved confounders for an observed mediation effect to disappear. ' $R^2_M * R^2_{Y^*}$ at which ACME = 0' is the product of how much previously unexplained variance in the mediator and in the outcome would need to be explained by unobserved confounders for the mediation effect to disappear. For example, for the observed mediation of the association between ADHD and depression via peer problems to disappear, unobserved confounders would need to explain 9% of observed variance in mediator and 9% of observed variance in the outcome (the product of which is 0.008), with a Rho of 0.09 or greater for mediator-outcome confounding. As long as Rho is lower than 0.09, the mediation effect will still be observed. *ADHD* attention-deficit hyperactivity disorder, *GCSE* general certificate of secondary education

Appendix 2.6. Mediators of the Association between Childhood ADHD and Adolescent Depression with Inverse Probability Weights Applied

Mediator (Measured at 16 years)	Pure Natural Direct Effect b (95% CI)	Total Natural Indirect Effect b (95% CI)	Proportion of Total Effect Mediated % (95% CI)
Peer problems	0.58 (0.29-0.87)	0.09 (0.02-0.18)	13.62 (9.59-23.92)
GCSE results	0.54 (0.24-0.83)	0.13 (-0.002-0.27)	19.00 (13.62-34.35)

Two individual potential outcomes causal mediation analyses each adjusted for sex, maternal age at birth and socioeconomic status were repeated with Inverse Probability Weights (IPW) applied to examine potential bias due to missing data on results of whether peer problems and GCSE results mediated the association between ADHD and depression. The exposure levels being compared in these analyses are mean ADHD symptoms and 1 Standard Deviation above this. Each mediation allowed for an interaction between exposure and mediator and was conducted on complete cases for exposure, mediators, outcome and confounders (n=2161). Interpretation of results remained the same with IPW weights applied. Significant mediators are indicated by confidence intervals of 'Total Natural Indirect Effect' not containing zero. *ADHD* attention-deficit hyperactivity disorder, *GCSE* general certificate of secondary education, *b* unstandardized beta, *CI* confidence interval

Appendix 3.1. Guess Who and “Who Hangs Around Together in your Class?”

Measures

Guess Who?

Read the following description of someone who **cooperates**. Look down the names of the people in your class. Tick the name of anyone you think fits the description. You can tick as many or as few people as you think there are. You can tick your own name if you think you cooperate. If you think nobody in your class fits that description, then you wouldn't have any ticks.

Cooperates - *this person is really good to have as part of your group because they are agreeable and cooperate. They join in, share and give everyone a turn.*

NAME	CO-OPERATES
Andi	
Dylan	
Ezri	
Faith	
Jennifer	
Joseph	
Kabeerat	
Kamil	
Keelan	
Maria	
Mohammed Fahim A	
Muhammed Mahdi R	
Nicola	
Sabrina	
Sajid	
Sami	
Sanzida	
Shaun	
Sophie	
Zainab	

Guess Who?

Read the following description of someone who **disrupts**. Look down the names of the people in your class. Tick the name of anyone you think fits the description. You can tick as many or as few people as you think there are. You can tick your own name. If you think nobody in your class fits that description, then just go to the next description.

Disrupts - *this person has a way of upsetting everything when he or she gets in a group. They don't share and try to get everyone to do things their way.*

NAME	DISRUPTS
Andi	
Dylan	
Ezri	
Faith	
Jennifer	
Joseph	
Kabeerat	
Kamil	
Keelan	
Maria	
Mohammed Fahim A	
Muhammed Mahdi R	
Nicola	
Sabrina	
Sajid	
Sami	
Sanzida	
Shaun	
Sophie	
Zainab	

Who hangs around together in your class?

Are there some people in your class who hang around together a lot? Who are they?

Write their names together on this piece of paper. Show as many groups as you can think of in your class.

Some groups can have just 2 people. Some people might be in more than one group.

You can use the list of people in your class to help you.

Don't forget to put your name on the map.

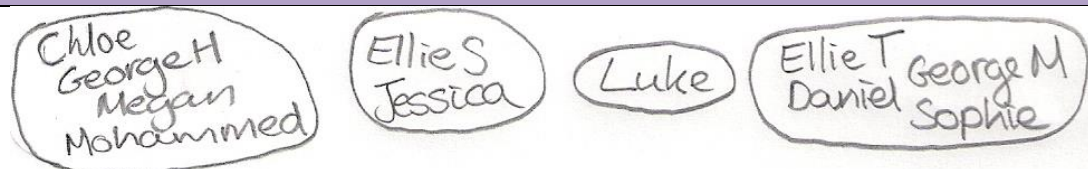
Draw a circle around each group of people who hang around together a lot.

Maybe some people don't hang around in a group – you can put them in a circle on their own.

Write each person's name clearly. If there are 2 people with the same first name put the first letter of their second name also.

To help you do this, the top box has an example of what this might look like once you are finished.

This is a pretend example using made-up characters but you should do it for your class.



Appendix 3.2. Prediction of Missingness from Analysis Sample (Pre-Imputation)

Predictor Variable (Baseline)	OR	95% CI	P-value
Sex (1=male, 2=female)	0.78	0.64, 0.95	0.014
English as first language	0.40	0.31, 0.51	<0.001
Black Minority Ethnic	2.60	2.09, 3.24	<0.001
Free School Meals	1.47	1.10, 1.96	0.009
Special Education Needs	1.61	1.23, 2.12	0.001
Academic performance in English (Key Stage 2 test result)	0.63	0.53, 0.76	<0.001
Academic performance in Maths (Key Stage 2 test result)	0.70	0.61, 0.80	<0.001
Unauthorised school absences	1.001	0.92, 1.08	0.976
Authorised school absences	1.03	1.004, 1.05	0.018

Within the children who participated at baseline (n=1712), logistic regressions between numerous predictor variables and being missing from the pre-imputation analysis sample (n=752) were conducted to establish predictors of missingness in this study. All the variables shown were included in the final missingness model for Multiple Imputation. *OR* odds ratio, *CI* confidence interval

Appendix 3.3. Results for Subscales of the Friendship Qualities Scale (FQS)

FQS subscale score	ADHD symptoms association with subscale (<i>b</i> (95% CI) <i>p</i>)	Subscale association with depressive symptoms (<i>b</i> (95% CI) <i>p</i>)	Indirect effect via subscale between ADHD and depressive symptoms (<i>b</i> (95% CI) <i>p</i>)	Percentage of total effect mediated
Companionship	-0.05 (-0.21, 0.12) 0.568	-0.53 (-0.77, -0.28) <0.001	0.01 (-0.02, 0.04) 0.539	2.12%
Conflict	0.17 (0.02, 0.33) 0.027	0.54 (0.30, 0.79) <0.001	0.04 (0.001, 0.07) 0.046	7.48%
Closeness	-0.17 (-0.31, -0.03) 0.014	-0.24 (-0.51, 0.03) 0.086	0.02 (-0.01, 0.04) 0.197	3.59%
Help	-0.13 (-0.29, 0.02) 0.084	-0.62 (-0.87, -0.37) <0.001	0.04 (-0.01, 0.08) 0.087	7.29%
Security	-0.23 (-0.40, -0.06) 0.008	-0.54 (-0.79, -0.29) <0.001	0.05 (0.01, 0.08) 0.018	9.75%

n=1712. ADHD attention deficit/hyperactivity disorder, *b* unstandardized beta, *CI* confidence interval

Appendix 3.4. Moderation by Mother Warmth of the Indirect Effect via Top Three Friendships Quality – Comparing Alternative Models

Model	Indirect effect (<i>b</i> (95% CI) <i>p</i>) at mean -1SD level of moderator	Indirect effect (<i>b</i> (95% CI) <i>p</i>) at mean level of moderator	Indirect effect (<i>b</i> (95% CI) <i>p</i>) at mean+1SD level of moderator	Z-test of difference in indirect effect at mean level of moderator versus mean+1SD
Moderation of both paths of indirect effect	0.06 (0.004, 0.12) 0.038	0.02 (-0.005, 0.05) 0.103	0.004 (-0.01, 0.02) 0.640	$z=2.05, p=0.040$
Moderation of ADHD to friendship path only	0.04 (-0.0004, 0.09) 0.052	0.03 (-0.004, 0.06) 0.086	0.01 (-0.02, 0.05) 0.509	$z=1.27, p=0.203$
Moderation of friendship to depression path only	0.06 (0.01, 0.11) 0.023	0.04 (0.0005, 0.07) 0.047	0.01 (-0.03, 0.06) 0.494	$z=1.49, p=0.136$

Indirect effects between ADHD and depressive symptoms via top three friendships quality at mean level of moderator (mother warmth) $\pm 1SD$ ($n=1712$). The models specified included a model with moderation effects on the path between ADHD symptoms and friendship quality and on the path between friendship quality and depressive symptoms (preferred model), a model with an interaction effect on the path between ADHD symptoms and friendship quality only, and a model with an interaction effect on the path between friendship quality and depressive symptoms only. *ADHD* attention deficit/hyperactivity disorder, *b* unstandardized beta, *CI* confidence interval, *SD* standard deviation

Appendix 3.5. Results in Pre-Imputation Sample

Friendship variable	ADHD symptoms association with variable (<i>b</i> (95% CI) <i>p</i>)	Variable association with depressive symptoms (<i>b</i> (95% CI) <i>p</i>)	Indirect effect via variable between ADHD and depressive symptoms (<i>b</i> (95% CI) <i>p</i>)
Presence of friends	-0.05 (-0.08, -0.02) 0.004	-0.21 (-0.60, 0.18) 0.291	0.02 (-0.03, 0.06) 0.470
Stability: best friend	OR=0.95 (0.80, 1.14) 0.595	-0.58 (-1.30, 0.14) 0.116	0.01 (-0.02, 0.03) 0.574
Stability: top three friends	OR=0.99 (0.83, 1.17) 0.870	-0.39 (-1.13, 0.35) 0.305	0.002 (-0.01, 0.02) 0.841
Quality: best friend	-0.77 (-1.43, -0.12) 0.021	-0.87 (-1.23, -0.50) <0.001	0.08 (0.004, 0.15) 0.040
Quality: top three friends	-0.10 (-0.21, 0.01) 0.071	-1.00 (-1.37, -0.62) <0.001	0.07 (-0.01, 0.14) 0.089
Classroom friendship group: total difficulties	0.21 (-0.15, 0.56) 0.248	-0.07 (-0.31, 0.46) 0.707	0.003 (-0.03, 0.03) 0.855
Classroom friendship group: cooperativeness	-0.02 (-0.03, -0.01) 0.001	-0.26 (-0.65, 0.13) 0.196	0.03 (-0.04, 0.11) 0.396
Classroom friendship group: disruptiveness	0.02 (0.01, 0.03) <0.001	0.36 (-0.10, 0.83) 0.123	0.04 (-0.04, 0.13) 0.298

All results in pre-imputation sample (n=752) except for the association of ADHD and depressive symptoms (*b*=0.61 (95% CI 0.21, 1.00) *p*=0.002) are shown. *ADHD* attention deficit/hyperactivity disorder, *b* unstandardized beta, *CI* confidence interval, *OR* odds ratio

Appendix 4.1. Results of meta-analysis using z-score thresholds, description of the 37 reference GWA studies, regions of overlapping signal with individual ADHD and MDD GWA studies, associations of index SNP regions with 37 reference GWA studies and eQTL results

Please refer to electronic appendix file.

Appendix 4.2. Association of index SNPs with the 37 reference GWA studies

Please refer to the electronic appendix file.

Appendix 4.3. Descriptions of the Protein-Coding Genes within LD Range of Index

SNPs

Chromosome 3 – 49193081 to 49890967 bp

AMIGO3. Encodes a member of a family of interacting transmembrane proteins located on the cell surface. This family's predicted function is in cell adhesion.

AMT. Encodes one of four proteins of the glycine cleavage system within mitochondria. Mutations in these proteins have been associated with cases of glycine encephalopathy (GCE). Ubiquitously expressed.

APEH. Encodes the enzyme acylpeptide hydrolase, which catalyses terminal acetylated amino acid hydrolysis from small acetylated peptides. Deletions at this locus are associated with decreased activity of this enzyme. It can be important in destroying proteins damaged by oxidation in cells. Deletions of APEH are found in a variety of cancers. Ubiquitously expressed.

BSN. Encodes part of a network of pre-synaptic proteins involved in events at the nerve terminal. It is thought to be a scaffolding protein that contributes to the organisation of the pre-synaptic cytoskeleton. Expressed primarily in neurones of the brain.

C3orf62. Ubiquitously expressed.

C3orf84. Restricted expression in testes.

CCDC36. Biased expression in testes.

CCDC71. Ubiquitously expressed.

CDHR4. Biased expression in lung and testes.

DAG1. Encodes dystroglycan – part of the dystrophin-glycoprotein complex linking the extracellular matrix and the cytoskeleton in skeletal muscle. Certain DAG1 mutations are known to cause forms of muscular dystrophy. Ubiquitously expressed.

FAM212A. Broadly expressed.

GMPPB. Encodes a subunit of the enzyme GDP-mannose pyrophosphorylase, which catalyses the conversion of mannose-1-phosphate and GTP to inorganic diphosphate and GDP-mannose. GDP-mannose is required in glycosylation pathways. Mutations in GMPPB have been identified in patients with muscular dystrophy, in some cases with additional brain abnormalities or mental retardation. Ubiquitously expressed.

GPX1. Ubiquitously expressed. Encodes member of glutathione peroxidase family. These enzymes catalyse the reduction of organic hydroperoxides and hydrogen peroxide by glutathione, thus protecting cells from oxidative damage. Studies have indicated that hydrogen peroxide is also involved in other processes including growth-factor mediated signal transduction and mitochondrial function and thus glutathione peroxidases could also affect these functions. Ubiquitously expressed.

IP6K1. Encodes inositol triphosphate – a messenger molecule that releases calcium from intracellular stores. Ubiquitously expressed but more so in the brain than other tissues.

KLHDC8B. Encodes a protein with a beta-propeller structure of kelch domains, which allows protein-protein interactions to take place. Mutations in this gene have been found in patients with Hodgkin lymphoma. Ubiquitously expressed.

MST1. Encodes a protein with a structure similar to hepatic growth factor. The receptor for this protein is RON tyrosine kinase, which stimulates ciliary motility in ciliated epithelial cells of the lung when activated. Biased expression in liver. Ubiquitously expressed.

NICN1. Encodes a protein which localises to the nucleus. Ubiquitously expressed but more so in the brain than other tissues.

RHOA. Encodes a member of the Rho family of small GTP-ases. These cycle between active and inactive states and function as molecular switches in signal transduction cascades. They are also involved in reorganising the actin cytoskeleton for cell morphology and motility. Overexpression of this gene is associated with proliferation of cancerous cells and metastasis. Ubiquitously expressed.

RNF123. Encodes an E3 ubiquitin ligase that functions in the progression of the cell cycle. Ubiquitously expressed.

RP11-3B7.1. Encodes a component of the spliceosome complex. It is one of the retinitis pigmentosa-causing genes. Ubiquitously expressed.

TCTA. Ubiquitously expressed.

TRAIP. Encodes a protein containing an N-terminal ring finger domain. Interacts with TNFRF-associated factors (TRAFs), leading to cell apoptosis via nuclear factor kappa-B activation. Mutations in TRAIP have been found in patients presenting with intrauterine growth defects, dwarfism, microcephaly and mental retardation.

UBA7. Encodes a member of the E1 ubiquitin-activating enzyme family. It is a retinoid target that triggers cell degradation and apoptosis in acute promyelocytic leukaemia. Ubiquitously expressed.

USP4. Encodes a protease that deubiquitinates target proteins, maintaining the operations of the endoplasmic reticulum. Ubiquitously expressed.

NCKIPSD (3:48,663,813). This gene was not located in the LD window but was found to have its expression affected by rs2029591 in eQTL analysis. Encodes a protein with a nuclear localisation signal. It is involved in signal transduction and may be involved in sarcomere maintenance. It is involved in the building and maintenance of dendritic spines and modulates synaptic activity in neurones. Ubiquitously expressed.

Chromosome 5 – 44816452 to 44944054 bp

MRPS30. Encodes the 28S subunit protein of a mitochondrial ribosome. Mitochondrial ribosomes help in protein synthesis in mitochondria. Ubiquitously expressed.

Chromosome 5 – 92995013 to 92995013 bp

FAM172A. Ubiquitously expressed.

Chromosome 10 – 106544216 to 106830537 bp

SORCS3. Encodes a type-1 transmembrane receptor which is a member of the vacuolar protein sorting 10 receptor family. Mutations in this gene are thought to contribute to shared risk across psychiatric disorders. Highly expressed in the brain.

Chromosome 11 – 48234357 to 49873791 bp

FOLH1. Encodes a type II transmembrane glycoprotein which acts as a glutamate carboxypeptidase on various substrates. It is expressed in a number of tissues but expression in the brain may be involved in pathological conditions associated with glutamate excitotoxicity. An example is motor neurone death in amyotrophic lateral sclerosis. Biased expression in small intestine, prostate and brain amongst others.

OR4A47, OR4B1, OR4C3, OR4C5, OR4S1, OR4X1, OR4X2. Each encodes a member of the olfactory receptor family. Olfactory receptors detect odours in the nose to trigger a neuronal response as part of smell perception. Broadly expressed.

TRIM49B. Low observed expression biased to brain and testis.

TRIM64C. Low observed expression biased to placenta and testis.

Chromosome 12 – 89721105 to 89904596 bp

DUSP6. Encodes a member of a class of proteins that dephosphorylate MAPK (mitogen-activated protein kinase). Activation of MAPK cascades plays a role in various cellular process including proliferation and apoptosis. Ubiquitously expressed.

POC1B. Encodes a protein that localises to the centrioles and has an apparent role in centriole duplication and maintenance. Mutations in POC1B result in cone-rod dystrophy. Ubiquitously expressed.

Chromosome 15 – 47659445 to 47685378 bp

SEMA6D. Encodes a class 6 transmembrane semaphorin. Semaphorins have been implicated as having roles in axon pathfinding and branching. Transmembrane semaphorins can act as chemorepellants in axon guidance. Broadly expressed.

Chromosome 18 – 50713243 to 50746748 bp

DCC. Encodes a netrin 1 receptor and guides neuronal axon growth cones towards sources of netrin 1. Mutations of DCC have been found in patients with agenesis of the corpus callosum and patients with gaze palsy, scoliosis and intellectual disability. Biased expression in the testis, brain and lung and adrenal gland.

Appendix 5.1. Prediction of Missingness from Analysis Sample

Predictor Variable (assessment wave 1)	OR	95% CI	P-value
Approximate gross family income*	0.81	0.71, 0.92	0.001
Education (GCSEs or equivalent qualifications)*	0.50	0.27, 0.90	0.020
Number of children*	1.37	1.07, 1.76	0.013
Age at birth of index child*	0.97	0.94, 1.01	0.149
Has a partner living with them*	0.68	0.42, 1.09	0.109
Current extreme or moderate anxiety or depression* (questionnaire self-report)	1.66	1.17, 2.36	0.004
Comorbid illness*	1.47	0.78, 2.76	0.229
Previous non-pharmacological treatment for depression (e.g. talking therapies, electroconvulsive shock therapy)	0.75	0.47, 1.19	0.214
Percentage of life unwell since depression onset	0.98	0.79, 1.20	0.835

Within adults who participated at wave 1 (n=337), logistic regressions between numerous predictor variables and being missing from the analysis sample (n=148) were conducted to establish predictors of attrition in this study. * indicates variables that were included in the final missingness model for inverse probability weighting. *OR* odds ratio, *CI* confidence interval

Appendix 5.2. Association of Adult ADHD Symptoms and Clinical Features of Depression with Inverse Probability Weighting Applied

Clinical feature of depression	Association with self-reported adult ADHD symptom score		
	b or OR (95% CI)	p-value	n
Depression age of onset of 25 or before	OR=1.47 (1.05, 2.05)	0.023	148
Ever had GAF score \leq 50 (Severe impairment associated with depression)	b=1.81 (1.20, 2.75)	0.005	148
Number of MDD episodes during study	b=0.72 (0.42, 1.03)	<0.001	148
Subthreshold depression persistence	b=0.07 (-0.18, 0.32)	0.594	148
Ever hospitalised	OR=1.76 (1.14, 2.72)	0.011	148
Use of non-standard antidepressants	OR=2.04 (1.39, 2.98)	<0.001	148
Ever attempted self-harm or suicide during study	OR=2.88 (1.29, 6.44)	0.010	148
Ever had psychotic affective symptoms during study	OR=0.87 (0.48, 1.56)	0.629	148

Results in complete case women (n=148) with IPW applied are shown. IPW inverse probability weighting, ADHD attention-deficit/hyperactivity disorder, MDD major depressive disorder, GAF global assessment of functioning, b unstandardized beta, CI confidence interval

Appendix 5.3. Analysis with Fathers Included

Clinical feature of depression	Association with self-reported adult ADHD symptom score		Association with dichotomised self-reported adult ADHD symptoms (above clinical cut-point versus below)	
	b or OR (95% CI)	p-value	b or OR (95% CI)	p-value
Depression age of onset of 25 or before	OR=1.37 (0.98, 1.92)	0.068	OR=1.84 (0.68, 4.97)	0.230
Ever had GAF score \leq 50 (Severe impairment associated with depression)	OR=1.52 (0.98, 2.35)	0.061	- - - -	- - - -
Number of MDD episodes during study	b=0.75 (0.52, 0.99)	<0.001	b=1.88 (1.14, 2.62)	<0.001
Subthreshold depression persistence	b=0.24 (0.03, 0.45)	0.025	b=0.34 (-0.31, 0.98)	0.305
Ever hospitalised	OR=1.96 (1.31, 2.94)	0.001	OR=5.12 (1.82, 14.43)	0.002
Use of non-standard antidepressants	OR=1.99 (1.34, 2.97)	0.001	OR=4.66 (1.66, 13.10)	0.004
Ever attempted self-harm or suicide during study	OR=3.54 (1.48, 8.50)	0.005	- - - -	- - - -
Ever had psychotic affective symptoms during study	OR=0.86 (0.54, 1.36)	0.510	OR=0.81 (0.19, 3.52)	0.781

ADHD symptoms were dichotomised using the clinical cut point of the Adult ADHD Investigator Symptom Rating Scale AISRS (>24). All participants above the cut point for ADHD had a GAF score below 50, so the association of dichotomised ADHD and depression impairment could not be tested due to complete separation issues. The association between dichotomised ADHD and suicide or self-harm attempts could not be tested due to small cell sizes. Results in complete case women and men are shown (n=153). ADHD attention-deficit/hyperactivity disorder, MDD major depressive disorder, GAF Global Assessment of Functioning, b unstandardized beta, CI confidence interval, OR odds ratio