

Chronic irritability in ADHD: examining clinical and genetic links with depression

PhD 2019

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Thesis summary

Background: Attention-deficit/hyperactivity disorder (ADHD) and other neurodevelopmental disorders are often associated with depression. Irritability is common in ADHD and other neurodevelopmental disorders, and has been linked to depression in the general population. However, research into the link between irritability and depression in those with neurodevelopmental disorders is lacking. This thesis aimed to examine the association between childhood irritability and depression in young people with ADHD, and in a group with broader neurodevelopmental difficulties.

Methods: A clinical ADHD sample, the Study of ADHD Genes and Environment, was used to examine the association between childhood irritability and depression symptoms in young people with ADHD. The same sample was used to examine whether children with ADHD and irritability have an increased genetic liability for depression (indexed by depression polygenic risk scores (PRS)), compared to those with ADHD but no irritability. Finally, a longitudinal population-based cohort, the Avon Longitudinal Study of Parents and Children, was used to examine the role of irritability in the association between childhood neurodevelopmental difficulties and later depression.

Results: Childhood irritability was associated with depression symptoms cross-sectionally and longitudinally in the clinical ADHD sample. Persistent irritability across childhood and adolescence was particularly important in the longitudinal association. Childhood irritability was not associated with depression PRS in children with ADHD (although irritability was associated with ADHD PRS). Finally, irritability was important in the association between neurodevelopmental difficulties and later depression in the population-based cohort, specifically in those with ADHD and ASD difficulties.

Conclusion: Findings from this thesis suggest that childhood irritability is an important marker of depression risk in children diagnosed with ADHD, as well in children with ADHD and ASD difficulties in the general population. Assessing irritability in children with ADHD and ASD difficulties may allow early identification and treatment of depression, as well as provide an opportunity for prevention.

Statements and declarations

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Abbreviations

ADHD	Attention-Deficit/Hyperactivity Disorder
ALSPAC	Avon Longitudinal Study of Parents and Children
ASD	Autism Spectrum Disorder
CAPA	Child and Adolescent Psychiatric Assessment
CCC	Children's Communication Checklist
CD	Conduct Disorder
CIS-R	Clinical Interview Schedule- Revised
CNV	Copy Number Variant
DAWBA	Development and Well Being Assessment
DCD	Developmental Co-ordination Disorder
DMDD	Disruptive Mood Dysregulation Disorder
DSM	Diagnostic and Statistical Manual of Mental Disorders
GAD	Generalised Anxiety Disorder
GWAS	Genome Wide Association Study
HADS	Hospital Anxiety and Depression Scale
ICD	International Classification of Diseases
ID	Intellectual Disability
MABC	Movement Assessment Battery for Children
MDD	Major Depressive Disorder
MFQ	Mood and Feelings Questionnaire
ODD	Oppositional Defiant Disorder
PRS	Polygenic Risk Score
SAGE	Study of ADHD Genes and Environment
SCDC	Social Communication Disorders Checklist
SDQ	Strength and Difficulties Questionnaire
SMD	Severe Mood Dysregulation
SNP	Single Nucleotide Polymorphism
WISC	Wechsler Intelligence Scale for Children
WORD	Wechsler Objective Reading Dimension

Papers resulting from work in this thesis

Published:

Eyre, O., Langley, K., Stringaris, A., Leibenluft, E., Collishaw, S., Thapar, A. Irritability in ADHD: associations with depression liability. (2017). *Journal of Affective Disorders*, 215, 281-287.

Riglin, L., * **Eyre, O.**,* Cooper, M., Collishaw, S., Martin, J., Langley, K., Leibenluft, E., Stringaris, A., Thapar, A.K., Maughan, B., O'Donovan, M.C., Thapar, A. (2017). Investigating the genetic underpinnings of early-life irritability. *Translational Psychiatry*, 7, e1241. ***Joint first authors.**

Revised and resubmitted:

Eyre, O., Riglin, L., Leibenluft, E., Stringaris, A., Collishaw, S., Thapar, A. Irritability in ADHD: association with later depression symptoms. Revised and resubmitted to *European Child and Adolescent Psychiatry*.

Eyre, O., Hughes, R.A., Thapar, A.K., Leibenluft, E., Stringaris, A., Davey Smith, G., Stergiakouli, E., Collishaw, S., Thapar, A. Childhood neurodevelopmental difficulties and risk for adolescent depression: the role of irritability. Revised and resubmitted to *Journal of Child Psychology and Psychiatry*.

Additional related publications to which I contributed

Cooper, M., **Eyre, O.**, Doherty, J., Bevan Jones, R. (2016). Gaining approvals for mental health research in the NHS. *BJPsych Advances*, 22(1), 64-72.

Fraser, A., Cooper, M., Agha, S.S., Collishaw, S., Rice, F., Thapar, A., **Eyre, O.** (2018). The presentation of depression symptoms in attention-deficit/hyperactivity disorder: comparing child and parent reports. *Child and Adolescent Mental Health*, 23(3), 243-250.

Acknowledgements

This PhD was undertaken as part of a clinical research training fellowship awarded to me by the Wellcome Trust.

I would like to thank my PhD supervisors Professor Anita Thapar, Professor Stephan Collishaw, Professor George Davey Smith and Dr Evie Stergiakouli for all their help and encouragement. Also, I would like to thank Dr Ellen Leibenluft and Dr Argyris Stringaris, my fellowship collaborators, who provided advice and comments on the publications related to this thesis.

I would like to thank all co-authors of the papers resulting from this PhD thesis. In particular, Dr Lucy Riglin who derived polygenic risk scores for our joint paper “Investigating the genetic underpinnings of early-life irritability” (on which Chapter 5 is based), as well as Dr Joanna Martin for preparing the genetic data for this chapter. Also thanks to Dr Rachael Hughes who provided me with training and advice on how to deal with missing data (Chapter 6) and to Dr Ajay Thapar for his advice on the statistical methods used in the same chapter.

I would especially like to thank all the families who gave up their time to take part in the Study of ADHD Genes and Environment (SAGE), on which much of this thesis is based (Chapters 3, 4 and 5). I am also grateful to those who helped with data collection for the ADHD follow-up study (Chapter 4), specifically Mrs Valerie Russell, Dr Sharifah Agha, Dr Jac Airdrie, Dr Zoe Williams and Dr Annie Fraser. I would also like to thank all those involved in the Avon Longitudinal Study of Parents and Children (ALSPAC) (Chapter 6).

I am very grateful to my colleagues in the Child and Adolescent Psychiatry Section at Cardiff University for their help and support, in particular Dr Sharifah Agha and Dr Rhys Bevan Jones, as well as Dr Joanne Doherty, Dr Miriam Cooper, Dr Lucy Riglin, Dr Joanna Martin, Dr Naomi Warne and Dr Ruth Sellers.

Finally, I want to thank my family. Thanks to my mum and dad, to Liam, and also to my daughters Oli and Grace.

Chapter 1: Introduction

The overall aim of this thesis is to examine the association between irritability and depression in those with attention-deficit/hyperactivity disorder (ADHD) and a broader group of neurodevelopmental difficulties. This introductory chapter provides an overview of what is known about ADHD and its overlap with other neurodevelopmental disorders. It then goes on to discuss links between ADHD, neurodevelopmental disorders and depression. Next, irritability is defined, before discussing irritability in the context of ADHD and neurodevelopmental disorders. Current findings on the association between irritability and depression, both in the general population and in those with ADHD and other neurodevelopmental disorders are then discussed. Literature on the genetic links between depression and irritability are also considered. The chapter concludes with a summary of the key points and the specific aims of the thesis.

1.1 Attention-deficit/hyperactivity disorder (ADHD)

1.1.1 Diagnosis

High levels of inattention and motor activity have been documented in children as far back as the 18th Century (Lange, Reichl, Lange, Tucha, & Tucha, 2010). However, what we now know as ADHD was first introduced in the 2nd edition of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 1968) as hyperkinetic reaction of childhood, “a disorder characterised by overactivity, restlessness, distractibility, and short attention span” (Lange et al., 2010). The diagnosis was changed to attention deficit disorder (with or without hyperactivity) with the introduction of DSM-III (American Psychiatric Association, 1980), before the introduction of attention-deficit/hyperactivity disorder (ADHD) in DSM-III-R in 1987 (American Psychiatric Association, 1987). Since then, DSM-IV (American Psychiatric

Association, 1994) and most recently DSM-5 (American Psychiatric Association, 2013) have been published.

DSM-5 includes ADHD as a neurodevelopmental disorder (American Psychiatric Association, 2013). The core features of ADHD include inattention, hyperactivity and impulsivity. In order to meet DSM-5 diagnostic criteria for ADHD, a pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development is required. Six or more of 9 listed inattention symptoms and/or 6 or more of 9 listed hyperactive-impulsive symptoms are required for diagnosis (with 5 in either domain required for diagnosis in older adolescents or adults). Symptoms must be present before the age of 12 years, occur in 2 or more settings and be present for at least 6 months. There should also be evidence that symptoms interfere with functioning. The DSM-5 diagnostic criteria for ADHD are described in table 1.1.

Table 1.1: DSM-5 diagnostic criteria for attention deficit hyperactivity disorder
(American Psychiatric Association, 2013)

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There are minor differences in the DSM-5 diagnostic criteria for ADHD, when compared to the previous version, DSM-IV. The core symptom domains of inattention and hyperactivity/impulsivity are the same, as are the symptoms included in each domain. The main differences are in the age of onset of symptoms (changed from prior to age 7 years in DSM-IV, to prior to age 12 years in DSM-5) and the symptom threshold for diagnosis in older adolescents and adults (changed from 6 symptoms in DSM-IV to 5 symptoms in DSM-5). In addition to this, subtypes of ADHD that were included in DSM-IV (predominantly inattentive, predominantly hyperactive-impulsive and combined) were downgraded to “presentations” in DSM-5 due to their poor stability over time (Willcutt et al., 2012). Finally, where the presence of autism spectrum disorder (ASD) was an exclusion criterion for the diagnosis of ADHD in DSM-IV, DSM-5 allows both to be diagnosed concurrently.

The other widely used diagnostic classification system is the WHO International Classification of Diseases, currently in its 10th edition (World Health Organisation, 1992), with the 11th edition soon to be introduced. In ICD-10, the equivalent diagnosis to ADHD is Hyperkinetic Disorder. The core symptoms are the same across both ADHD and Hyperkinetic Disorder; however, symptoms need to be present across every domain (inattention, hyperactivity and impulsivity) for a diagnosis using ICD-10. This results in a more stringent set of criteria, reflected by lower prevalence rates when ICD-10 Hyperkinetic Disorder is compared to DSM-IV ADHD (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007).

It is also worth noting that although ADHD is a categorical diagnosis, its symptoms are continuously distributed in the general population (Rodriguez et al., 2007), and there is no clear cut point which predicts impairment and longitudinal outcomes (Bussing,

Mason, Bell, Porter, & Garvan, 2010). Therefore, subthreshold symptoms are still of relevance.

In recent years, the possibility of an “adult onset” ADHD has been suggested. A number of longitudinal studies examining persistence of ADHD into adulthood identified individuals who met criteria for ADHD in adulthood, but not in childhood (Agnew-Blais et al., 2016; Caye et al., 2016; Moffitt et al., 2015). Further research into this group is needed, but evidence to date suggests these individuals do not show the neurodevelopmental impairment typical of ADHD (e.g. autistic symptoms, deficits in language skills, executive functioning or IQ) (Cooper et al., 2018).

1.1.2 Associated clinical features

ADHD is a clinically heterogeneous condition. Although the core diagnostic features are inattention, hyperactivity and impulsivity, there are a number of associated clinical features that are also often present. These occur frequently in those diagnosed with ADHD and impact on clinical presentation, but may not be specific enough to be included in the diagnostic criteria for ADHD. For example, DSM-5 includes low frustration tolerance, irritability and mood lability as well as cognitive difficulties (e.g. problems with executive function and memory) as “associated features supporting the diagnosis of ADHD”.

ADHD is often also associated with other comorbid psychiatric disorders. More than 50% with ADHD will have at least one other psychiatric disorder (Jensen & Steinhausen, 2015; Spencer, Biederman, & Wilens, 1999), with over a quarter having 2 or more comorbid disorders (Jensen & Steinhausen, 2015). The most common comorbid disorders include other neurodevelopmental disorders such as autism spectrum disorder (ASD), developmental co-ordination disorder (DCD) and specific learning difficulties (Ghirardi et al., 2018; Jensen & Steinhausen, 2015; Kadesjö & Gillberg, 2001).

Behavioural disorders such as oppositional defiant disorder (ODD) and conduct disorder (CD) are also often present in young people with ADHD (Jensen & Steinhausen, 2015; Pliszka, 2000), and anxiety and depressive disorders occur more commonly in ADHD than in the general population (Angold, Costello, & Erkanli, 1999). Children with subthreshold ADHD also have high rates of comorbidity (Kadesjö & Gillberg, 2001).

1.1.3 Prevalence

The prevalence of ADHD varies significantly across studies. However, in a recent meta-analysis of worldwide prevalence of mental disorders, ADHD was found to be present in 3.4% of children and adolescents (Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015). In this study, variations in prevalence were related to the source of information (e.g. parent vs teacher), whether impairment was required for diagnosis, and the instrument used for diagnosis. Geographical location did not significantly impact on prevalence estimates. Prevalence of ADHD in adults is lower, with a meta-analysis finding a pooled prevalence of 2.5% (Simon, Czobor, Bálint, Mészáros, & Bitter, 2009).

Prevalence of ADHD varies according to gender. ADHD is more common in males. The male to female ratio is 3-4:1 in population samples, with the ratio more like 7-8:1 in clinical samples (Thapar & Cooper, 2016). It is not clear why males are more likely to have ADHD than females, but the higher ratio of males in clinical samples may be related to referral bias (Biederman et al., 2005). This gender difference becomes less prominent once adulthood is reached (Kessler et al., 2006).

It has been suggested that ADHD prevalence is increasing. In the US, ADHD diagnosis was found to increase by 42% between 2003 and 2011 (Visser et al., 2014). Alongside this, there has been an increase in prescription of ADHD medication (Dalsgaard, Nielsen, & Simonsen, 2013; McCarthy et al., 2012; Raman et al., 2018). However,

studies of non-referred population cohorts show that symptoms of hyperactivity and inattention have remained stable over late 20th and early 21st century (Collishaw, 2015; Polanczyk, Willcutt, Salum, Kieling, & Rohde, 2014). Therefore, it may not be an increase in prevalence of ADHD that is being observed, rather, an increase in recognition of symptoms, leading to increase in diagnosis and treatment.

1.1.4 Aetiology

ADHD is a complex, multifactorial disorder. No single risk factor has been found to cause ADHD. Research in recent years has examined the contribution of both genetic and environmental risk factors, with both likely to contribute.

In terms of genetic risk, family studies have shown that first degree relatives of those with ADHD are 2-8 times more likely to be affected than relatives of those without ADHD (Faraone, 2005). In support of a genetic aetiology, adoption studies have found ADHD symptom scores in adoptive children to be more similar to their biological than adopted parents (Sprich, Biederman, Crawford, Mundy, & Faraone, 2000). Twin studies show that ADHD is highly heritable, with genetic factors accounting for 70-80% of variation in the population (Nikolas & Burt, 2010).

Molecular genetic studies have attempted to identify specific genetic risk factors for ADHD. Initial investigations were in the form of candidate gene studies where particular genes were selected *a priori* due to their possible involvement in the pathophysiology of ADHD. This approach identified specific dopaminergic, serotonergic, and noradrenergic candidate genes significantly associated with ADHD in meta-analyses (Gizer, Ficks, & Waldman, 2009).

In recent years investigations have moved on to genome-wide approaches. The role of both common and rare genetic variants in ADHD has been examined. Genome-wide association studies (GWAS) have investigated the role of common genetic variants

(Single Nucleotide Polymorphisms (SNPs) with >5% frequency in the population). GWAS involve comparing individuals with ADHD to controls, allowing the genetic variants associated with ADHD to be identified. This approach has been limited by the large sample sizes required to provide the power necessary to detect genome-wide significant associations. However, the latest GWAS of 20,183 cases and 35,191 controls has led to the identification of 12 genome-wide significant associations (Demontis et al., 2018).

GWAS have also been used to generate composite genetic risk scores for ADHD, known as polygenic risk scores. This method allows multiple common genetic variants which individually do not meet the threshold for statistically significant association with ADHD, to be combined to make a single risk score. In order to generate these risk scores, GWAS is undertaken in a large discovery sample, identifying common genetic variants associated with ADHD below a particular statistical significance threshold (e.g. $p < 0.5$). Using this information, a risk score is then derived in an independent sample (target sample) based on the number of genetic variants associated with ADHD in the discovery sample, weighted by the effect size. Polygenic risk scores for ADHD have been found to predict ADHD cases (Hamshere et al., 2013) and ADHD traits in the general population (Martin, Hamshere, Stergiakouli, O'Donovan, & Thapar, 2014).

The role of rare genetic variants (Copy Number Variants (CNVs) with frequency <1% of population) in ADHD have also been examined. CNVs are subtle chromosomal structural abnormalities that result in segments of the DNA being absent or repeated several times (deletions and duplications). An increase in large, rare CNVs in ADHD cases compared to controls has been found (Elia et al., 2012; Lionel et al., 2011; Williams et al., 2010, 2012).

Studies also suggest genetic overlap of ADHD with other psychiatric disorders. Findings from family and twin studies suggest that ADHD shares genetic risk with autism spectrum disorder (ASD) (Lichtenstein, Carlström, Råstam, Gillberg, & Anckarsäter, 2010; Reiersen, Constantino, Grimmer, Martin, & Todd, 2008; Ronald, Simonoff, Kuntsi, Asherson, & Plomin, 2008), anxiety (Micheline, Eley, Gregory, & McAdams, 2015), major depressive disorder (MDD) (Cole, Ball, Martin, Scourfield, & McGuffin, 2009), schizophrenia, and bipolar disorder (Larsson et al., 2013). Molecular genetic studies have also shown significant genetic correlations between ADHD and MDD, and between ADHD and bipolar disorder (Demontis et al., 2018; van Hulzen et al., 2017; Cross-disorder group of the Psychiatric Genomics Consortium, 2013). With regards to rare genetic variants, CNVs found in ADHD have been found to implicate the same genomic regions as those involved with ASD and schizophrenia (Lionel et al., 2011; Williams et al., 2010).

Therefore, overall, there is clear evidence to suggest that the aetiology of ADHD has a genetic component, with both common and rare genetic variants contributing. There is also evidence for genetic overlap between ADHD and other psychiatric disorders.

Environment is also likely to be important in the aetiology of ADHD. Observational studies have examined numerous possible risk factors for ADHD, with some found to be associated. For example, ADHD has been associated with pre and perinatal risk factors such as poor maternal diet, maternal obesity, smoking during pregnancy, low birth weight, prematurity and early maternal depression (Thapar, Cooper, Eyre, & Langley, 2013). ADHD has also been linked with extreme early deprivation, low income, parental stress, inter-parental conflict, parent-child conflict and environmental toxins such as lead exposure (Larsson, Sariaslan, Langström, D'Onofrio, &

Lichtenstein, 2014; Thapar et al., 2013). However, it is important to note that observation of these associations does not mean these risk factors cause ADHD.

It is also important to consider that genetic and environmental factors do not occur in isolation. There is likely to be interplay between genetic and environmental risk factors. One example of this is gene-environment correlation. This occurs when an environmental risk is present as a consequence of genetic risk. This may be a factor in the association observed between smoking in pregnancy and ADHD. Mothers at genetic risk for ADHD are more likely to smoke. They are also more likely to have a child with ADHD. Genetically sensitive study designs suggest it may be the mother's genetic risk for ADHD rather than her smoking that is important in increasing the child's risk for ADHD (Rice, Langley, Woodford, Davey Smith, & Thapar, 2018; Thapar et al., 2009). Another example is gene-environment interaction. Here environmental influence varies by genetic risk. Also, a child's genetically influenced characteristics may evoke response from the environment e.g. child behaviour may influence parenting (Harold et al., 2013). Therefore, a child's ADHD symptoms may increase mother-child hostility, rather than the hostility causing ADHD (Lifford, Harold, & Thapar, 2009). Finally, another example of interaction between genetic and environmental risk factors is epigenetics, where the environment can influence how genes are expressed (Meaney & O'Donnell, 2015). Although further research in this field is needed, some suggest an epigenetic hypothesis for ADHD does seem plausible (Nigg, 2018).

1.1.5 Management

The treatment approach for ADHD depends on the age of the individual, the severity of ADHD symptoms and any co-morbidity experienced. Both non-pharmacological and pharmacological treatments exist. A meta-analysis of non-pharmacological

interventions was undertaken by Sonuga-Barke et al (2013). This included evaluation of behavioural treatments such as parent training (increasing positive behaviours and reducing negative behaviours), cognitive training (e.g. attention and working memory training), as well as neurofeedback (visualisation of brain activity in order to increase attention and impulse control). The results did not find enough improvement in core ADHD symptoms to recommend any of these as treatments (Sonuga-Barke et al., 2013). However, behavioural interventions may help with behavioural problems associated with ADHD, such as conduct disorder (Daley et al., 2014), as well as improve outcomes in those with comorbid anxiety disorders (Hinshaw, 2007).

In terms of pharmacological interventions, evidence suggests that stimulant medication such as methylphenidate is effective in treating symptoms of ADHD in children and adolescents (Faraone & Buitelaar, 2010). Atomoxetine (a noradrenaline reuptake inhibitor), has also been found to be effective (Bushe & Savill, 2014), as has lisdexamfetamine (a prodrug of d-amphetamine) (Najib, 2012) and guanfacine (an α 2-adrenergic agonist) (Biederman et al., 2008; Faraone, McBurnett, Sallee, Steeber, & López, 2013). A recent meta-analysis found methylphenidate to be the treatment of choice in children and adolescents with ADHD in terms of both efficacy and safety (Cortese et al., 2018). There is also evidence to suggest stimulants are effective in the treatment of adults (Moriyama, Polanczyk, Terzi, Faria, & Rohde, 2013), with amphetamines suggested as first-choice when both efficacy and tolerability are taken into account (Cortese et al., 2018).

In the UK, the National Institute for Health and Care Excellence (NICE) provide guidelines for the management of ADHD. According to the guidelines published in 2018 (NICE, 2018), children under 5 years should be offered ADHD-focused group parent training programmes as first line treatment. For children over the age of 5 years,

information about ADHD should be provided, additional support to parents offered, and for those with co-occurring symptoms of ODD or CD, a parent training program and group-based ADHD-focused support offered. Medication should be offered if ADHD symptoms cause persistent significant impairment after baseline assessment, provision of information about ADHD and environmental modifications (changes to the physical environment to minimise impact of ADHD) have been made. NICE recommends first line medication is methylphenidate, with lisdexamfetamine as second line for those who have not responded to a 6 week trial of methylphenidate at an adequate dose.

Dexamfetamine, atomoxetine or guanfacine are also included as treatment options. For young people with ADHD who have benefited from medication but whose symptoms are still causing a significant impairment consideration of cognitive behavioural therapy (CBT) is suggested.

In adults with ADHD, NICE guidelines suggest that medication should be offered if ADHD symptoms cause significant impairment after environmental modifications have been made (NICE, 2018). Non-pharmacological treatment should be considered for those who do not want to take medication, have difficulty adhering to it or have found it ineffective. It can also be considered in combination with medication where symptoms continue to cause impairment.

1.1.6 Prognosis

Although ADHD is a childhood-onset disorder, and symptoms have been found to decline with age (Biederman, Mick, & Faraone, 2000), a significant proportion continue to meet criteria for ADHD into adulthood. Agnew-Blais et al (2016) reported 21.9% of those with childhood ADHD persisted at age 18 years, and Caye et al (2016) found persistence rates of 17.2% at 19 years (Agnew-Blais et al., 2016; Caye et al., 2016).

Other longitudinal studies conducting longer follow ups, found ADHD persistence rates

of 29.3% at 30 years (Barbaresi et al., 2013) and of 4.9% at age 38 years (Moffitt et al., 2015). A meta-analysis of longitudinal studies found the proportion with ADHD that persists into adulthood is about 15%, with partial remission in 40-60% (Faraone, Biederman, & Mick, 2006). More recently, around 40% with childhood ADHD were found to have symptom persistence and impairment into adulthood (Sibley et al., 2017). Predictors of ADHD persistence include ADHD symptom severity, familiarity of ADHD, psychosocial adversity and comorbidity with conduct, mood and anxiety disorders (Biederman et al., 1996; Biederman, Petty, Clarke, Lomedico, & Faraone, 2011; Lara et al., 2009). Rates of ADHD persistence have been shown to vary depending on whether self-report or parent-report is utilised (Barkley, Fischer, Smallish, & Fletcher, 2002), with self-reports providing lower rates in adulthood. However, overall, studies suggest that ADHD continues to be a problem into adulthood with many continuing to have symptoms, if not a full diagnosis.

Children with ADHD have high levels of impairment in social, academic and family functioning (Hoza et al., 2005; Johnston & Mash, 2001; Nijmeijer et al., 2008). For many, these impairments continue into adult life. Those with ADHD often go on to have poorer educational, occupational, economic and social outcomes (Klein et al., 2012). They are more likely than controls to have one or more comorbid psychiatric disorder, as well as having increased risk for death from suicide (Barbaresi et al., 2013). A Danish registry-based study also found increased early mortality, mainly as a result of accidents, in those with ADHD, especially in those with comorbid oppositional defiant disorder, conduct disorder, and substance misuse (Dalsgaard, Ostergaard, Leckman, Mortensen, & Pedersen, 2015). Treating ADHD can improve outcomes, but it does not seem to improve functioning to normal levels (Shaw et al., 2012).

1.2 Neurodevelopmental disorders and their overlap

Neurodevelopmental disorders can be described as “a broad group of disabilities involving some form of disruption to brain development” (Thapar, Cooper, & Rutter, 2017). DSM-5 describes neurodevelopmental disorders as “a group of conditions that typically manifest early in development and are characterised by developmental deficits that produce impairments of personal, social, academic, or occupational functioning” (American Psychiatric Association, 2013). In addition to the early onset and developmental deficits described here, neurodevelopmental disorders also tend to show a steady course, they strongly overlap with each other, and more commonly affect males than females (Thapar et al., 2017). The neurodevelopmental disorders described in DSM-5 include intellectual disability (ID), communication disorders, autism spectrum disorder (ASD), specific learning disorders and motor disorders, as well as ADHD.

1.2.1 DSM-5 neurodevelopmental disorders

The key features of the diagnostic criteria for each of the DSM-5 neurodevelopmental disorders are described in table 1.2.

Table 1.2: DSM-5 diagnostic criteria for neurodevelopmental disorders (American Psychiatric Association, 2013)

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When considering neurodevelopmental disorders together, around 5-15% of the population would meet criteria for at least one disorder. Anckarsäter et al (2008) used a validated screening tool to identify prevalence rates of ASD, tic disorders, ADHD and learning disorder in a population-based study, finding 12.2% screened positive for one or more of these disorders (Anckarsäter et al., 2008). Gillberg (2010) estimated 5-7% of children under age 6 years would meet criteria for a broad group of neurodevelopmental difficulties (Gillberg, 2010). A US study used a broader definition of “developmental disabilities”, including children aged 3-17 with ADHD, ID, autism, cerebral palsy, seizures, stuttering or stammering, moderate to profound hearing loss, blindness, learning disorders and/or other developmental delays. The authors observed a prevalence of 15% (Boyle et al., 2011).

It is also important to note that, as for ADHD, despite the categorical nature of these diagnoses, neurodevelopmental disorders such as ASD have also been shown to lie at extremes of dimensions (Thapar et al., 2017). There is not a clear cut-point at which impairment from symptoms begins, with impairment occurring in the presence of subthreshold symptoms (Kanne, Christ, & Reiersen, 2009).

1.2.2 Overlap of neurodevelopmental disorders

As has been discussed, ADHD often co-occurs with other neurodevelopmental disorders. Although the core features of the neurodevelopmental disorders differ, clinical overlap between them is high. The prevalence of comorbidity depends on whether it is measured in clinical or population samples, with clinical samples tending to show higher rates of comorbidity, likely due to referral bias.

Jensen et al (2015) examined a range of comorbidities in children and adolescents with a clinical diagnosis of ADHD, finding that language, learning disorders and motor disorders were amongst the most prevalent (Jensen & Steinhausen, 2015). These

findings are supported in a number of other clinical and population-based studies. A review by Mueller et al (2012), which mainly included clinical samples, found that as many as 50-90% of children with ADHD have co-existing language problems (Mueller & Tomblin, 2012). Another review found that 45% of those with ADHD have a learning disability in reading, writing or maths (DuPaul, Gormley, & Laracy, 2013).

Developmental co-ordination disorder (DCD) was found to be present in nearly half of those with ADHD, in a general population sample of school aged children (Kadesjö & Gillberg, 2001). ASD has also been shown to be particularly common in ADHD, with 20-50% meeting diagnostic criteria across a number of clinical and population studies (Rommelse, Franke, Geurts, Hartman, & Buitelaar, 2010).

In addition to the overlap with ADHD, other neurodevelopmental disorders also overlap with each other. For example, up to 70% of children with ASD have some intellectual disability (Fombonne, 2003; Matson & Nebel-Schwalm, 2007), and children with DCD have been found to be at increased risk of ASD type symptoms and difficulties in reading and spelling (Lingam et al., 2010). Tourette's syndrome and tics are also more commonly found in ASD than would be expected by chance (Baron-Cohen, Scahill, Izaguirre, Hornsey, & Robertson, 1999).

This clinical overlap across neurodevelopmental disorders seems to occur both across diagnoses, as well as at a symptom level. For example, both ADHD and ASD symptoms have been reported to overlap (Rommelse et al., 2010) and children with high ASD traits often have learning problems (Posserud, Hysing, Helland, Gillberg, & Lundervold, 2018). This idea that neurodevelopmental difficulties overlap, often in early childhood, has been described by Gillberg (2010). Due to this overlap, Gillberg suggests grouping together early neurodevelopmental problems, defined as ESSENCE (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations)

(Gillberg, 2010). Included in this grouping are young children who present with problems of general development, communication and language, social interrelatedness, motor coordination, attention, activity, behaviour, mood, and/or sleep (Gillberg, 2010).

As well as evidence for clinical overlap in neurodevelopmental disorders, there is also evidence for genetic overlap. Genetic overlap between ADHD and ASD has been found across a number of studies. Family studies suggest that individuals with ASD and their relatives are at increased risk for ADHD (Ghirardi et al., 2018), and twin studies find shared inherited factors contribute to the comorbidity between ADHD and ASD (Lichtenstein et al., 2010; Rommelse et al., 2010; Ronald et al., 2008). In addition to this, rare genetic risk variants (CNVs) associated with ADHD have been shown to overlap with rare genetic variants associated with autism (Williams et al., 2010).

Genetic overlap between ADHD and intellectual disability has also been reported. A large register-based family study found most of the correlation between ADHD and intellectual disability to be explained by genetic factors (Faraone, Ghirardi, Kuja-Halkola, Lichtenstein, & Larsson, 2017), and a twin study has also shown strong genetic correlation between lower IQ and ADHD (Kuntsi et al., 2004). Others have also found that ADHD polygenic risk scores are associated with lower cognitive abilities in the general population (Martin, Hamshere, Stergiakouli, O'Donovan, & Thapar, 2015; Evie Stergiakouli et al., 2017).

Another pair of neurodevelopmental disorders where the genetic overlap has been investigated is ADHD and reading difficulties. Family members of those with reading difficulties or ADHD are more likely to meet criteria for the other disorder than family members of those without the disorder (Friedman, Chhabildas, Budhiraja, Willcutt, & Pennington, 2003). This finding is supported by twin studies which suggest genetic

overlap between ADHD and reading difficulties, with overlap particularly prominent in those with symptoms of inattention (Greven, Harlaar, Dale, & Plomin, 2011).

Finally, in addition to genetic overlap between individual disorders, Pettersson et al. (2013) found that one general genetic factor was responsible for the overlap of 53 neurodevelopmental symptoms (Pettersson, Anckarsäter, Gillberg, & Lichtenstein, 2013). This suggests that a broad genetic liability could be contributing to different neurodevelopmental diagnoses.

1.2.3 Grouping neurodevelopmental disorders together

Due to the high levels of clinical and genetic overlap described above, it has been suggested that grouping neurodevelopmental disorders together may be useful (Thapar et al., 2017). Although the different neurodevelopmental disorders have their own distinct clinical features with their own treatment approaches, there is clinical rationale for grouping them together. Considering them completely separately may lead to difficulties, as co-occurring problems may go unrecognised (Gillberg, 2010).

Identifying the overlapping difficulties is important as the treatment of one disorder may be different in the presence of another. For example, ADHD medication is less well tolerated in those with ID (Aman, Buican, & Arnold, 2004). Also, the outcomes for children with more than one neurodevelopmental disorder are worse than if one neurodevelopmental disorder presents alone (Leitner, 2014), so identifying and treating co-occurring difficulties is important.

1.3 ADHD, neurodevelopmental disorders and depression

As discussed, children and young people with ADHD often meet diagnostic criteria for another psychiatric disorder. Depression is one comorbid disorder that is of particular interest. This is because depression often co-occurs in those with ADHD (Daviss, 2008), and leads to significant impairment (Blackman, Ostrander, & Herman, 2005), yet

is amenable to treatment. Young people with both ADHD and depression have poorer outcomes than those with either condition alone. They have poorer outcomes in terms of social and academic functioning (Blackman et al., 2005), higher rates of psychiatric hospital admission, suicidality (Biederman et al., 2008) and completed suicide (James, Lai, & Dahl, 2004). Therefore, understanding more about depression in ADHD, in particular identifying which individuals are at greatest risk of developing it, could help with early identification and treatment of those affected. In addition to this, the onset of ADHD predates the onset of depression. Therefore, if those with ADHD at particular risk of developing depression could be identified, there is the potential for early intervention and prevention of depression in this group. This rationale further extends to young people with other neurodevelopmental disorders, who also often experience comorbid depression (Gadow, Guttman-Steinmetz, Rieffe, & DeVincent, 2012; Kim, Szatmari, Bryson, Streiner, & Wilson, 2000; Mammarella et al., 2016) leading to significant impairment.

In the next section, I will briefly describe depression, including the diagnostic criteria, prevalence and aetiology, before moving on to consider depression in the context of ADHD and other neurodevelopmental disorders.

1.3.1 Depression

Depression is a mood disorder characterised by core symptoms of low mood (in children and adolescents it can be irritable mood) and loss of interest or pleasure, with associated symptoms of altered appetite and sleep, psychomotor agitation/retardation, lack of energy, feelings of worthlessness/guilt, difficulty concentrating and thoughts of death/suicide. In order to meet diagnostic criteria for DSM-5 major depressive disorder (MDD), five or more of these symptoms should be present in the same 2 week period (with at least 1 being depressed mood or loss of interest), and they should represent a

change from previous functioning (American Psychiatric Association, 2013). The full DSM-5 diagnostic criteria for MDD are listed in table 1.3.

Table 1.3: DSM-5 diagnostic criteria for major depressive disorder (American Psychiatric Association, 2013)

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The ICD-10 criteria (World Health Organisation, 1992) for depression does differ slightly compared to DSM-5. ICD-10 categorises depression diagnosis according to severity (into mild, moderate or severe depressive episodes). In order to meet criteria for ICD-10 diagnosis, at least two core symptoms from depressed mood, loss of interest or pleasure and decreased energy must be present, with a further 2 symptoms required for a diagnosis of mild depressive episode, a further 4 for a moderate depressive episode, and a total of at least 8 (including all 3 of the core symptoms) for severe depressive episode. Symptoms must be present for at least 2 weeks. Irritable mood is not included as a core symptom for children and adolescents in ICD-10 as it is in DSM-5.

This thesis primarily examines depression in adolescence. Therefore, from here on, when discussing depression, the focus will be on child and adolescent depression unless otherwise stated.

1.3.1.1 Prevalence and aetiology of depression in childhood and adolescence

The prevalence of depression differs across childhood and adolescence. Depression in childhood is relatively rare, with prevalence of around 1-2% (Egger & Angold, 2006). The 12 month prevalence increases to around 5% in mid to late adolescence (Costello, Erkanli, & Angold, 2006), with a lifetime prevalence of adolescent depression up to 20% by age 18 (Thapar, Collishaw, Pine, & Thapar, 2012). Gender differences in depression, similar to those in adults, also become apparent in adolescence with the female to male ratio reaching 2:1 (Thapar et al., 2012).

Depression is a complex disorder, with multiple risk factors involved in its aetiology. As with other complex disorders, it is likely that both environmental and genetic factors contribute. Depression is less heritable than other psychiatric disorders such as ADHD. However, there is evidence of a genetic contribution to depression in young people.

Family studies show children of parents with depression have up to 4 fold increased risk

of developing depression compared to children of parents without depression (Rice, Harold, & Thapar, 2002), and twin studies estimate depression heritability at around 30-50% in adolescence (Thapar & Rice, 2006). Molecular genetic studies have looked for genetic risk variants associated with depression, initially with little success. However, due to increased sample sizes, a recent genome-wide association study (GWAS) identified 44 independent loci meeting genome-wide significance criteria (Wray et al., 2018), supporting the idea that common genetic variants contribute to depression risk. Research into the association between rare genetic variants (e.g. Copy Number Variants) and depression has provided less insight. However, Kendall et al (2018) found four neurodevelopmental CNVs to be associated with depression, suggesting rare genetic variants may also have a role to play in the aetiology of depression (Kendall et al., 2018).

There is also evidence of genetic overlap between depression and other psychiatric disorders. As discussed earlier, a genetic overlap between depression and ADHD has been observed both in twin studies (Cole et al., 2009) and molecular genetic studies (Cross-disorder group of the Psychiatric Genomics Consortium, 2013). In addition to this, twin studies provide evidence of genetic overlap between depression and anxiety disorders (Middeldorp, Cath, Van Dyck, & Boomsma, 2005; Roy, Neale, Pedersen, Mathe, & Kendler, 1995) and between depression and bipolar disorder (Song et al., 2015). There is also molecular genetic evidence for overlap between depression and schizophrenia, and between depression and bipolar disorder (Cross-disorder group of the Psychiatric Genomics Consortium, 2013)). Of relevance to this thesis, a twin study conducted by Stringaris et al (2012) suggested a genetic overlap between depression and irritability (Stringaris, Zavos, Leibenluft, Maughan, & Eley, 2012). The genetic overlap between depression and irritability will be further discussed later in this chapter.

Overall, the evidence suggests there is a genetic component to the aetiology of depression, with common genetic variants in particular playing a role. However, environmental factors are also likely to be important.

Environmental risk factors that have been associated with depression in childhood and adolescence include stressful life events, adverse family environments, negative parental and peer relationships, and family conflict (Arseneault, 2017; Birmaher et al., 1996; Daviss, 2008; Maughan, Collishaw, & Stringaris, 2013; Thapar et al., 2012). It is not easy to establish to what extent these risk factors are causal, although genetically informative studies suggest some psychosocial stressors likely have causal effects on depression (Thapar et al, 2012).

Interplay between genes and environment should also be considered here. For example, for the association between stressful life events and depression, a number of studies have shown gene-environment interaction and gene-environment correlation to be relevant (Kendler et al., 1995; Lau & Eley, 2008; Silberg, Rutter, Neale, & Eaves, 2001). Silberg et al (2001) found that life events only increase risk for depression in the presence of parental emotional disorder, and Kendler et al (1995) found the impact of stressful life events was higher for those at higher genetic risk for depression. The study by Lau et al (2008) showed that adolescents at genetic risk for depression were more likely to experience negative life events, as well as being more susceptible to developing depression symptoms in response to those negative life events. These examples support the idea that genes and environment do not act in isolation in the aetiology of depression. Overall, literature to date suggests that multiple risk factors contribute to the aetiology of depression, with both genetic and environmental factors playing a part.

1.3.1.2 Management of child and adolescent depression

The management of depression in children and adolescents involves both psychological and pharmacological approaches, although the benefits of antidepressant medication are less clear in young people than adults. Only fluoxetine, a selective serotonin reuptake inhibitor (SSRI), has been shown to be more effective than placebo in children and adolescents with depression (Cipriani et al., 2016). With regards to psychological treatment, most of the evidence in children and young people is for cognitive behavioural therapy (CBT) (Klein, Jacobs, & Reinecke, 2007) and interpersonal therapy (IPT) (Mufson et al., 2004). The National Institute for Health and Care Excellence (NICE) in the UK provide clear guidelines on the management of depression in children and adolescents, reflecting these research findings.

Some research has also been done into the prevention of depression, with a meta-analysis finding that depression can be reduced if adolescents at high risk of depression are targeted (Horowitz & Garber, 2006). A group cognitive behavioural prevention program has since been found to be effective in offspring of parents with a history of depressive disorders, who themselves also have a history of depression or current sub-threshold depressive symptoms (Garber et al., 2009). However, little is known about prevention of depression in those with ADHD or other neurodevelopmental difficulties, although there is some evidence to suggest treating ADHD with stimulants may protect against later depression (Chang, D'Onofrio, Quinn, Lichtenstein, & Larsson, 2016).

1.3.1.3 Prognosis of child and adolescent depression

Depression in adolescence is often recurrent. Although most with adolescent depression will remit within 1 year (Dunn & Goodyer, 2006), around half will go on to have an adult episode of depressive disorder (Costello & Maughan, 2015). Depression in adolescence is also associated with later anxiety disorder (Fergusson & Woodward,

2002), bipolar disorder (Rao et al., 1995) and predicts attempted suicide in adulthood (Harrington et al., 1994). In addition to poor mental health outcomes, adolescent depression also has an impact on general health, social and occupational outcomes (Thapar et al., 2012). Those with depression in late adolescence were found to have poor self-rated health and low levels of social support after 10 years of follow-up (Naicker, Galambos, Zeng, Senthilselvan, & Colman, 2013). Even subthreshold levels of depression in late adolescence have been found to have increased risk of later depression and suicidal behaviour (Fergusson, Horwood, Ridder, & Beautrais, 2005).

1.3.2 ADHD and depression

As discussed, depression is commonly seen in those with ADHD (Daviss, 2008). ADHD has been observed to be associated with depression in both community and clinical samples (Biederman et al., 2006; Chronis-Tuscano et al., 2010; Fischer, Barkley, Smallish, & Fletcher, 2002; Smalley et al., 2007). These results are backed up by a meta-analysis of general population studies which found rates of MDD to be more than 5 times higher in those with ADHD than in those without (Angold et al., 1999), with a more recent meta-analysis of the co-occurrence of ADHD and depression finding a medium sized association between ADHD and depression (sample size weighted mean correlation coefficient (\bar{r})=0.22) (Meinzer, Pettit, & Viswesvaran, 2014). Children with subthreshold ADHD have also been shown to have higher rates of depression diagnosis than those without (Roy, Oldehinkel, Verhulst, Ormel, & Hartman, 2014).

However, it should be noted that not all studies find an association between ADHD and depression. For example, a prospective longitudinal study following up hyperactive children over 33 years did not find any association between ADHD and depression (Klein et al., 2012), and the recent meta-analysis by Meinzer et al (2014) did not find an

association across all studies (only 7 of the 12 longitudinal studies). However, there are possible explanations for these findings. In the majority of studies where there was no association, females were excluded. Although the effect of gender on association between ADHD and depression is not clear, excluding females may have impacted on the results, as depression is more common in females from adolescence onwards (Thapar et al., 2012). In the study by Klein et al (2012), those with evidence of aggressive or other antisocial behaviour were also excluded. These may well be the most severely affected children, who may also be those at highest risk for depression. In the meta-analysis by Meinzer et al (2014), 3 of the 5 longitudinal studies that did not find an association between ADHD and depression defined ADHD using DSM-II (as hyperkinetic reaction of childhood) (Meinzer et al., 2014). Hyperkinetic reaction of childhood includes predominantly hyperactive symptoms, yet those at highest risk for depression may have predominantly inattentive symptoms or combined inattentive and hyperactive/impulsive symptoms (Chronis-Tuscano et al., 2010; Willcutt, Pennington, Chhabildas, Friedman, & Alexander, 1999). It is also worth noting that in some of the studies, depression was measured at a single time point. Depression is episodic, so assessing depression in this way may lead to many cases being missed. There is also evidence to suggest that it may be younger onset depression that is associated with ADHD (Bird, Gould, & Staghezza, 1993), so the association may be less prominent as the follow-up time increases. This may provide another possible explanation for lack of association in some studies. Finally, there is evidence to suggest that the rater is important when examining depression in those with ADHD (Fraser et al., 2017). Bird et al (1993) found that ADHD and depression occurred more frequently than expected by chance when parent ratings of symptoms were used, but not when child ratings were used (Bird et al., 1993). Some studies that do not find an association between ADHD

and depression were based on child rated symptoms of depression (Klein et al., 2012; Meinzer et al., 2014). Therefore, despite some inconsistencies in the findings, overall the large meta-analyses suggest that depression occurs in those with ADHD at a higher rate than in those without ADHD.

There are a number of possible explanations for the co-occurrence of two disorders (Caron & Rutter, 1991), many of which are relevant when considering the association between ADHD and depression. Firstly, it is possible that artificially high levels of comorbidity may be seen due to overlapping diagnostic criteria between two disorders. In ADHD and depression, some symptoms do overlap. Restlessness and concentration difficulties are listed as diagnostic criteria for both disorders (American Psychiatric Association, 2013). In addition to this, symptoms of depression such as appetite loss and sleep disturbance are common side effects of stimulant medication used to treat ADHD. However, associations between ADHD and depression have been found even after overlapping criteria have been removed (Biederman, Faraone, Mick, & Lelon, 1995). Therefore, it seems unlikely that this would fully explain the link between ADHD and depression.

It is also possible that two disorders may co-occur due to shared risk factors. This is possible in the case of ADHD and depression. As has already been discussed, there is evidence of shared genetic risk between these two disorders. Family members of those with ADHD are more likely to have depression than those without (Biederman et al., 1992), twin studies have found a genetic overlap between ADHD and depression (Cole et al., 2009), and molecular genetic findings suggest significant genetic overlap between ADHD and depression (Demontis et al., 2018; Cross-disorder group of the Psychiatric Genomics Consortium, 2013).

Having one disorder may also create risk for another. For example, ADHD itself may increase risk for depression. ADHD precedes onset of depression, so this is feasible. One suggestion is that depression may result from ADHD-related demoralisation (Biederman, Mick, & Faraone, 1998). Symptoms of ADHD impact on peer relationships e.g. bullying, family relationships as well as academic achievement (Harold et al., 2013). These factors may contribute to increasing risk for depression (Thapar et al., 2012). Humphreys et al (2013) did find that peer problems mediated relationship between ADHD and depression (Humphreys et al., 2013). However, Biederman et al (1998) did not find an association between ADHD related impairment and depression (Biederman et al., 1998). Pharmacoepidemiological studies do, however, seem to support the idea that ADHD may play a role in the onset of depression, as treating ADHD with medication seems to protect against the onset of later depression (Chang et al., 2016).

Finally, it is also possible that the association between 2 disorders is as a result of a third disorder (epiphenomenal co-morbidity) (Angold et al., 1999). This is a plausible explanation for the association between ADHD and depression. For example, both anxiety and conduct disorder are common in ADHD and are also associated with depression. Therefore, the association between ADHD and depression could be a result of one of these disorders (Angold et al., 1999). However, studies have shown the association between ADHD and depression to remain when controlling for anxiety (Biederman et al., 2008; Meinzer et al., 2013) and conduct problems (Blackman et al., 2005). Irritability is also relevant here, as it is associated with both ADHD and depression (Shaw, Stringaris, Nigg, & Leibenluft, 2014; Vidal-Ribas, Brotman, Valdivieso, Leibenluft, & Stringaris, 2016). However, research into the role of

irritability in the association between ADHD and depression is limited. This will be discussed in detail in section 1.5 of this introductory chapter.

1.3.3 Neurodevelopmental disorders and depression

As discussed, ADHD is one of a group of overlapping neurodevelopmental disorders. High rates of MDD as well as elevated levels of depressive symptoms are also seen across the different categories of neurodevelopmental disorders including ASD, reading disorder and tic disorders (Gadow et al., 2012; Kim et al., 2000; Mammarella et al., 2016; Maughan, Rowe, Loeber, & Stouthamer-Loeber, 2003). Ghaziuddin (2002) described depression as “probably the most common psychiatric disorder seen in persons with autism”, suggesting it is an important problem in this group (Ghaziuddin, Ghaziuddin, & Greden, 2002). Those with language impairment are also more likely to develop “internalising problems” than children with typical language development (Yew & O’Kearney, 2013), and children with dyslexia have been found to be at increased risk of emotional difficulties (Snowling, Muter, & Carroll, 2007), as have children with intellectual disability (ID) (Simonoff, 2015). This association with depression also extends to those with sub-threshold neurodevelopmental problems. For example, those with relatively high autistic traits reported more depressive symptoms than those with minimal autistic traits (Kanne et al., 2009).

As has been discussed for ADHD, identifying those at risk of depression is important. Co-occurring depression in disorders such as ASD can put individuals at risk of withdrawal, non-compliance, aggression and suicide (Matson & Nebel-Schwalm, 2007) as well as impacting on long term outcomes.

1.4 Irritability

1.4.1 Defining irritability

A number of related definitions of irritability have been described in the literature.

Stringaris and Goodman (2009) describe irritability as “a propensity to react with anger, grouchiness, or tantrums disproportionate to the situation” (Stringaris, Cohen, Pine, & Leibenluft, 2009). Brotman et al (2017) described it as “an increased proneness to anger relative to peers at the same developmental level” (Brotman, Kircanski, Stringaris, Pine, & Leibenluft, 2017), and Vidal-Ribas et al (2016) as “inter-individual differences in proneness to anger that might reach a pathological extent” (Vidal-Ribas et al., 2016).

As these definitions suggest, anger is the emotion that characterises irritability.

However, a number of broader terms have been used interchangeably to refer to irritability in the past. These include: emotion dysregulation, emotional lability, emotional impulsivity, deficient emotional self-regulation, affective instability. These are broader constructs than irritability as they include difficulties regulating all emotions, rather than being specific to anger.

Irritability and aggression are also sometimes considered together. Aggression can be seen as the behavioural component of irritability (Leibenluft & Stoddard, 2013).

However, not all with irritability will manifest aggression. A recent review suggested that 12% with temper outbursts in the general population show aggressive behaviour (Stringaris, Vidal-Ribas, Brotman, & Leibenluft, 2018).

It is worth noting that for irritability to be considered as pathological, it should be at a level that is inconsistent with a child’s developmental level. In young children, irritability is common and can be seen as a normal part of development. Wakschlag et al (2012) reported that more than 80% of preschool children had tantrums in the last month (Wakschlag et al., 2012). However, irritability typically decreases with age

(Copeland, Brotman, & Costello, 2015), and by adolescence, high levels of irritability become less common and more predictive of difficulties (Copeland et al., 2015). This developmental difference in normative levels of irritability needs to be taken into account when defining pathological irritability in children and young people.

It is also important to note that irritability is a symptom or group of symptoms that occurs across a number of DSM-5 disorders including oppositional defiant disorder (ODD), anxiety, major depressive disorder (MDD) and bipolar disorder (American Psychiatric Association, 2013). It is not clear whether the irritability seen across these different disorders is the same; for example whether it has the same underlying aetiology or is explained by the same mechanisms.

In recent years there has been an increased interest in childhood irritability, which has led to clearer operationalised definitions. These have been utilised for research, and contributed to new clinical diagnoses. Both dimensional and categorical definitions of irritability now exist (American Psychiatric Association, 2013; Leibenluft, Charney, Towbin, Bhangoo, & Pine, 2003; Stringaris & Goodman, 2009a). The reasons for an increased interest in childhood irritability, and the definitions that have resulted from that interest, are described below.

1.4.1.1 Recent research into childhood irritability: the paediatric bipolar debate

From the 1990s to 2000s, the United States saw a large increase in the diagnosis of paediatric bipolar disorder (Blader & Carlson, 2007; Moreno et al., 2007). This was likely to be due to a change in the way it was diagnosed (Leibenluft, 2011). It was suggested by some that, instead of having an episodic course, mania in childhood could present as chronic, persistent irritability without elevated mood (Wozniak et al., 1995). However, there was some debate over whether this approach was correct. In order to try and further understand this group of children with chronic persistent irritability,

Leibenluft et al (2003) described a number of phenotypes of paediatric bipolar disorder, ranging from a narrow DSM-IV definition (where episodic symptoms are necessary to meet diagnostic criteria), to a broad definition including those with chronic irritability. This broad definition of irritability was labelled as Severe Mood Dysregulation (SMD) and characterised by severe rages, hyperarousal, and abnormal mood between rages (sadness or anger) (Leibenluft et al., 2003).

With these operationalised definitions, research was conducted to establish whether children with chronic, impairing irritability differed from those with classic DSM-IV episodic bipolar disorder (Leibenluft & Rich, 2008). Findings from the research suggested that the two groups did differ in clinical presentation (Dickstein et al., 2005), in family history of bipolar disorder (Brotman et al., 2007) and in terms of behavioural deficits and neuroimaging signatures (Deveney et al., 2012; Thomas et al., 2012). In addition to this, it became clear that at follow-up, children with SMD were found to be at elevated risk of anxiety disorders and unipolar depression compared to controls, rather than bipolar disorder (Brotman et al., 2006). This provided evidence that children with chronic, persistent irritability did not have paediatric bipolar disorder. Interestingly though, they were found to be as impaired as those who did (Leibenluft, 2011). The research into SMD had identified a group of severely impaired children without bipolar disorder, who did not neatly fit into any existing diagnostic category. There was a need for better diagnostic classification for these children, along with the need to reduce over diagnosis of bipolar disorder, at least in the United States. This was the basis for the introduction of the diagnostic category of disruptive mood dysregulation disorder (DMDD) in DSM-5.

Interestingly, there has been some debate over this diagnostic category (discussed later), and has not been included in the new ICD-11. Instead, it has been suggested that ICD-

11 should take the approach of including irritability as a subtype of ODD (ODD with chronic irritability/anger) rather than adopting the DSM-5 approach of using a categorical measure of DMDD (Evans et al., 2017).

1.4.1.2 Irritability as a category in DSM-5: disruptive mood dysregulation disorder

Disruptive mood dysregulation disorder (DMDD) was first introduced as a diagnosis with the publication of the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) (American Psychiatric Association, 2013). It is defined as a childhood-onset disorder that is characterised by severe temper outbursts that are grossly out of proportion in intensity or duration to the situation. Alongside these temper outbursts, the child experiences a persistently irritable or angry mood most of the day, nearly every day. The temper outbursts and irritable mood must be present for at least 12 months, across settings, and have an onset before the age of 10 years (see table 1.4 for DSM-5 diagnostic criteria).

Table 1.4: DSM-5 diagnostic criteria for disruptive mood dysregulation disorder
(American Psychiatric Association, 2013)

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DMDD diagnosis differs from that of SMD, as SMD also includes hyperarousal symptoms requiring at least 3 of: insomnia, agitation, distractibility, racing thoughts, pressured speech, and intrusiveness. These symptoms were excluded from DMDD due to their overlap with ADHD symptoms (Krieger, Leibenluft, Stringaris, & Polanczyk, 2013). This diagnostic category of DMDD provides a clear, operationalised way of

measuring severe, chronic, impairing irritability in children. However, there have been a number of criticisms of this newly introduced diagnosis.

Firstly, it was suggested that not enough research into DMDD had been carried out to warrant its inclusion as a new DSM-5 diagnostic category, with others suggesting it may be pathologising normal childhood behaviour (Evans et al., 2017). Another major criticism of DMDD is that it is not a distinct disorder. Those with DMDD almost always present with another disorder, the overlap with ODD being particularly high. In fact, a number of studies have found it difficult to differentiate DMDD and ODD (Axelson et al., 2012; Freeman AJ et al., 2016), with Axelson et al (2012) finding that 96% of those with DMDD also had ODD or conduct disorder (CD). In addition to this, those who have examined DMDD longitudinally have found its stability to be low, with not many meeting full criteria across time (Axelson et al., 2012).

However, despite these criticisms, it seems unlikely that DMDD is pathologising normal behaviour. DMDD diagnosis is rare and associated with high levels of impairment. In epidemiological studies the 3 month prevalence has been found to be between 0.8% and 3.3% (Copeland, Angold, Costello, & Egger, 2013). Also, despite the clear overlap between DMDD and ODD, there are differences between the two (see table 1.5 for symptoms ODD). Although symptoms overlap, the diagnostic criteria for DMDD require a higher frequency of temper outbursts (3 times per week versus once per week), a longer duration of symptoms (12 months vs 6 months) and more evidence of impairment, making DMDD the more severe of the two disorders. This leads to a higher proportion with DMDD also having ODD, than vice versa (Copeland et al., 2013). Also, although the temporal stability of DMDD is low, many with DMDD diagnosis at one time point do continue to have later subthreshold irritability (Stringaris et al., 2018). Although there is still research to be done to fully understand this new

diagnostic category, DMDD does provide a clear operationalised way of measuring chronic, severe irritability for the purposes of research.

1.4.1.3 Irritability as a component of Oppositional Defiant Disorder and a dimension

As well as being conceptualised as the DSM-5 diagnosis of DMDD, irritability is also included as a dimension of ODD in DSM-5, as well as in the new ICD-11. Symptoms of ODD, including three items making up the irritable dimension are listed in table 1.5.

Table 1.5: DSM-5 diagnostic criteria for oppositional defiant disorder
(American Psychiatric Association, 2013)

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The inclusion of an ODD dimension into DSM-5 and ICD-11 was based on findings from a number of studies which undertook factor analysis of the symptoms of ODD. These studies found up to 3 dimensions make up the single diagnostic category of ODD – an irritable dimension, a headstrong dimension and a hurtful dimension (Aebi et al.,

2010; Burke et al., 2014; Krieger, Polanczyk, et al., 2013; Rowe, Costello, Angold, Copeland, & Maughan, 2010; Argyris Stringaris & Goodman, 2009a; Whelan, Stringaris, Maughan, & Barker, 2013). Although there have been some subtle differences in study findings, the irritable dimension has been identified across all studies. The irritable dimension is made up of 3 ODD symptoms: often loses temper/has temper tantrums, is often touchy or easily annoyed, and is often angry and resentful. This irritable dimension of ODD has consistently been found to be associated with anxiety and depression cross-sectionally and longitudinally (Aebi et al., 2010; Burke et al., 2014; Krieger et al., 2013; Stringaris & Goodman, 2009a). This is in contrast to the headstrong dimension which is associated with ADHD and conduct problems, but not emotional disorders (Stringaris & Goodman, 2009a; Whelan et al., 2013). This ODD dimension of irritability, in contrast to DMDD, has been shown to be moderately stable over time (Leadbeater & Homel, 2015; Roberson-Nay et al., 2015; Whelan et al., 2013).

Viewing irritability as a dimension fits with the Research Domain Criteria (R-DoC) developed by the National Institute of Mental Health (NIMH) in the United States. R-DoC aims to gain better understanding of mental disorders by examining dimensional constructs that cross diagnostic boundaries, rather than using existing diagnostic classification. Irritability cuts across diagnoses (e.g. it can present in those with ADHD, ODD, depression, anxiety and bipolar disorder), so is well suited to this approach.

1.4.2 Irritability, comorbidity and impairment

Research to date suggests that children who have DMDD have high rates of comorbidity. A diagnosis of DMDD rarely occurs in isolation. In community samples, DMDD has been found to co-occur with another disorder in at least 60% (Copeland et al., 2013; Dougherty et al., 2014), most commonly with ODD, ADHD, anxiety and depression. High levels of comorbidity with DMDD have also been found in clinical

samples, with ADHD, ODD and CD co-occurring most frequently (Axelson et al., 2012; Freeman AJ et al., 2016).

Children with irritability are also significantly impaired. This was clear from the initial research into Severe Mood Dysregulation (SMD), where those with SMD were found to be as impaired as those with bipolar disorder (Leibenluft, 2011). DMDD has also been found to be associated with significant impairment. Higher rates of social impairment (Copeland et al., 2013), lower peer functioning (Dougherty et al., 2014) and higher rates of school suspension (Copeland et al., 2013) have been described in children with DMDD compared to those without DMDD. This impairment may not just be as a result of the high levels of comorbidity. Dougherty et al. (2014) found that impairment associated with DMDD remained even when controlling for comorbid disorders. Also, it may not only be those with severe, chronic irritability that are impaired. Almost any level of irritability was found to have an impact on functioning in a community sample aged 9-16 years (Copeland et al., 2015).

1.4.3 Prevalence and aetiology of irritability

Irritability is one of the most common reasons for referral to Child and Adolescent Mental Health Services (Mikita & Stringaris, 2013). The reported prevalence of irritability in children and adolescents varies according to the definition of irritability used, the age at which it is measured, and whether it was measured in a clinical or population sample.

In the general population, elevated symptoms of DMDD (measured as irritable-angry outbursts and temper tantrums) have been found in 3% (Mayes et al., 2015), with the prevalence of DMDD diagnosis estimated at around 1-3% (Copeland et al., 2013).

Irritability is more common in young children and declines with age (Copeland et al., 2015; Leibenluft, 2017). The prevalence of DMDD reflects this; Dougherty et al (2014)

found 8% met criteria for DMDD at age 6, but only 1% had DMDD by age 9 (Dougherty et al., 2016). The prevalence of DMDD diagnosis is much higher in clinical samples of children at around 26-31% (Axelson et al., 2012; Freeman AJ et al., 2016; Margulies, Weintraub, Basile, Grover, & Carlson, 2012).

It is not clear whether the prevalence of irritability differs by gender, with some studies finding no difference in rates of DMDD between males and females (Copeland et al., 2013; Dougherty et al., 2014), but others finding higher prevalence in males (Mulraney et al., 2016). Pagliaccio et al (2008) examined irritability trajectories across childhood in a sample of children enriched for early depression symptoms. They found that children with consistently elevated irritability were much more likely to be male (Pagliaccio, Pine, Barch, Luby, & Leibenluft, 2018). However, the age at which irritability is measured may affect whether it is more common in males or females (Leadbeater & Homel, 2015).

Although research into the aetiology of irritability is limited, it is likely that both genetic and environmental risk factors are important. Irritability has been found to have a heritability estimate of around 30% in adolescence (Stringaris et al., 2012), similar to the level seen for anxiety and depression (Thapar & Rice, 2006). There has been little research into the molecular genetics of irritability, however, a recent genome-wide association study of mood instability (a broader construct than irritability) found four independently associated loci (Ward et al., 2017). In the same study, this measure of mood instability was found to have strong genetic correlation with MDD, as well as smaller but significant correlations with schizophrenia and anxiety disorders (Ward et al., 2017), although no genetic correlation with ADHD or Bipolar Disorder. Despite this, there is some evidence for a genetic overlap between irritability (as part of emotional lability/emotion dysregulation) and ADHD. Family studies suggest that

emotional lability is elevated in family members of individuals with ADHD (Epstein et al., 2000; Surman et al., 2011) and one twin study observed significant genetic overlap between emotional dysregulation and ADHD symptoms (Merwood et al., 2014). The genetic overlap between mood instability and MDD is supported by family and twin studies which suggest there may be an overlap between irritability and depression (Krieger et al., 2013; Stringaris et al., 2012). Therefore, there is evidence of a genetic aetiology of irritability, and that there may be some genetic overlap with other disorders. This is discussed further, later in the chapter.

In terms of environmental risk factors for irritability, Munhoz et al (2017) examined possible pre/perinatal and postnatal risk factors for DMDD utilising a longitudinal birth cohort. They found early risk factors for development of DMDD included maternal mood symptoms during pregnancy, maternal depression in the first years after childbirth and low maternal level of education (Munhoz et al., 2017). DMDD has also been associated with lower parental support and poverty cross-sectionally (Copeland et al., 2013; Dougherty et al., 2014). However, observed associations do not mean causation as unmeasured confounding can be a problem. As with other psychiatric disorders it is likely that both genetic and environmental factors play a part in aetiology.

1.4.4 Irritability in ADHD and other neurodevelopmental disorders

Irritability is common in those with ADHD and other neurodevelopmental disorders (Shaw et al., 2014; Simonoff et al., 2012). As discussed earlier, irritability has been included in DSM-5 as an “associated feature supporting the diagnosis of ADHD” (American Psychiatric Association, 2013). However, much of the research in ADHD has examined emotional dysregulation or emotional lability rather than irritability specifically. Stringaris and Goodman (2009) utilised a population survey to estimate the prevalence of emotional lability in those with ADHD, finding that 38% had marked

emotional lability (Stringaris & Goodman, 2009b). Clinically referred samples have also found high rates of emotional lability in ADHD (Sobanski et al., 2010). A review of clinical and epidemiological studies of emotional dysregulation in ADHD, found that 24-50% of young people with ADHD experience emotional dysregulation (Shaw et al., 2014).

More specifically, with regards to irritability, Mick et al (2005) found that ODD-type irritability symptoms (losing temper, angry/resentful, easily annoyed) were common in ADHD, with 76% experiencing at least one symptom (Mick, Spencer, Wozniak, & Biederman, 2005). DMDD symptoms and diagnosis are also found more commonly in those with ADHD than in those without. Mayes et al. (2015) found that 39% of children with ADHD combined type had symptoms of DMDD (measured as irritable-angry outbursts and temper tantrums), compared to 3% of typically developing children (Mayes et al., 2015). In a community sample with ADHD, Mulraney et al. (2016) found that 21.8% met diagnostic criteria for DMDD (Mulraney et al., 2016). The data available from population cohorts suggest that 4.3-23.5% of those with ADHD meet diagnostic criteria for DMDD (Copeland et al., 2013).

Studies suggest that those with ADHD and emotional dysregulation go on to experience more psychiatric comorbidity, greater impairment and poorer academic and occupational attainment than young people with ADHD who do not have problems with emotional dysregulation. Peer relationships and family life are also affected (Althoff, Verhulst, Rettew, Hudziak, & Van Der Ende, 2010; Shaw et al., 2014).

With regards to other neurodevelopmental disorders, severe irritability is also common in those with ASD (Simonoff et al., 2012). In community cases of ASD, severe irritability is present in about 20% (Stringaris et al., 2018). Data are not available on rates of DMDD in ASD but, according to DSM-5, DMDD cannot be diagnosed in the

presence of ASD (American Psychiatric Association, 2013). Severe irritability in ASD is also associated with high comorbidity and impairment (Stringaris et al., 2018).

Irritability is also a problem for those with intellectual disability (ID), where behavioural difficulties related to irritability are common. For example, temper tantrums have been found to present in 36% of adults with ID (Deb, Thomas, & Bright, 2001), and anger is described as an important part of the challenging behaviour often seen in those with ID (Willner et al., 2011).

1.5 Irritability and its links with depression

1.5.1 Clinical association between irritability and depression

As has been mentioned, recent research into irritability has involved examining the association between childhood irritability and later depression in the general population. This has been done as part of the research differentiating severe mood dysregulation (SMD) from paediatric bipolar disorder (Brotman et al., 2006), but also through identifying a separate irritable dimension of oppositional defiant disorder (ODD). Overall, results suggest that irritability is associated with depression in the general population. The irritable dimension of ODD has been found to be associated with emotional problems such as anxiety and depression, both cross-sectionally and longitudinally (Krieger et al., 2013; Stringaris & Goodman, 2009c; Whelan et al., 2013). SMD in childhood also has been found to be associated with depression in young adulthood (Brotman et al., 2006), and depression diagnosis was found to occur more commonly in children and young people with DMDD than in those without (Copeland et al., 2013; Dougherty et al., 2014). There is also emerging evidence suggesting that persistent irritability (rather than remitted irritability) may be particularly important in the link with depression (Pagliaccio et al., 2018; Wiggins, Mitchell, Stringaris, & Leibenluft, 2014). Studies that have examined irritability trajectories across childhood

suggest that children with consistently elevated levels of irritability are more likely to develop depression or have higher internalising symptoms than those whose levels of irritability started high but decreased over time (Pagliaccio et al., 2018; Wiggins et al., 2014).

However, not every study finds an association between childhood irritability and depression. Axelson et al (2012) examined the association between DMDD and depression in a clinical outpatient sample and did not find an association with depression cross-sectionally or longitudinally (Axelson et al., 2012). However, these results may have been related to the age of the participants who were prepubertal (age 6-12 years) so had not reached the age of risk for depression onset. In addition to this, although depression diagnosis was no more common in those with DMDD compared to those without in this study, depression symptom levels were higher in those with DMDD. Freeman AJ et al (2016) also failed to find an association between DMDD and depressive disorders in a clinical outpatient sample (Freeman AJ et al., 2016), although the mean age of the sample was also prepubertal (10.6 years).

Despite these findings, overall there is evidence of an association between irritability and depression in the general population. Results from a meta-analysis by Vidal-Ribas et al (2016) found a significant longitudinal association between irritability and depression (OR=1.80, 95% CI=1.42-2.27, $p<0.001$) (Vidal-Ribas et al., 2016).

1.5.2 Genetic association between irritability and depression

Due to the clinical association between irritability and depression, a genetic overlap has also been considered. Studies have examined the link between childhood irritability and family history of depression, with mixed results. Krieger et al (2013) found the irritable dimension of ODD to be associated with a family history of maternal depression (Krieger et al., 2013). Wiggins et al. (2014) examined irritability trajectories in

childhood, finding that children with higher levels of irritability were more likely to have mothers with recurrent depression (Wiggins et al., 2014). In this same study, paternal depression was also associated with more severe offspring irritability trajectories. However, Axelson et al (2012) and Dougherty et al (2014) did not find any association between childhood diagnosis of DMDD and family history of depression. Evidence from twin studies do, however, suggest presence of a genetic overlap between irritability and depression. Stringaris et al (2012) found that the longitudinal association between irritability and depression may be best explained by overlapping genetic factors. Savage et al (2015) also found shared genetic factors to play a role in the link between irritability and anxiety/depression (although they also found evidence supporting the possibility that irritability may have a causal role in later anxiety/depression) (Savage et al., 2015).

Molecular genetic studies examining the genetic overlap between irritability and depression are yet to be carried out. However, as discussed, a genome-wide association study of mood instability (a broader construct than irritability) has recently been undertaken in the UK Biobank (Ward et al., 2017), finding a strong correlation with MDD. Therefore, there is some evidence to suggest a genetic overlap between irritability (and related constructs) and depression, but further research is needed to explore this more fully.

1.5.3 Irritability in ADHD and neurodevelopmental disorders: a link to depression

The association between irritability and depression may be particularly relevant in those with ADHD and other neurodevelopmental disorders. As has been discussed, not only do children with ADHD have high levels of irritability (Shaw et al., 2014), they are also at increased risk of depression (Angold et al., 1999; Meinzer et al., 2014). Thus it is plausible that high levels of irritability are the mechanism by which children with

ADHD become depressed. Despite this, little work has been done investigating the association between irritability and depression in those with ADHD.

Ambrosini et al (2013) utilised a cross-sectional clinical ADHD sample to examine the association between irritability and depression, finding that irritability symptoms were associated with depression symptoms (Ambrosini, Bennett, & Elia, 2013). Mulraney et al (2016) did not find an association between DMDD diagnosis and depression in a community based ADHD sample (Mulraney et al., 2016). However, this sample had a mean age of 7.3 years and had not yet reached the age of risk for depression onset, and they did find an association with anxiety, an antecedent of depression (Pine & Fox, 2015).

The association between irritability and depression in a clinical ADHD sample is yet to be examined longitudinally. Seymour et al (2014) utilised a population sample to examine the role of emotion regulation in the link between ADHD and depression symptoms, finding evidence that emotion regulation mediated the relationship (Seymour, Chronis-Tuscano, Iwamoto, Kurdziel, & MacPherson, 2014). However, longitudinal investigation in a clinical ADHD sample, specifically examining irritability is needed.

Even less research into the link between irritability and depression has been undertaken in those with other neurodevelopmental disorders. One cross-sectional study has examined the association between irritability and depression in a clinical sample with autism spectrum disorder (ASD) (Mandy, Roughan, & Skuse, 2014). This study found that the irritable dimension of ODD was associated with emotional problems in this group. However, little more is known about the association between irritability and depression in ASD or other neurodevelopmental disorders, despite the clinical importance of this possible association.

1.6 Summary and rationale

There are a number of key points which have been discussed throughout this introductory chapter providing rationale for the thesis aims. These are summarised here before the main aims of the thesis are listed.

ADHD is a relatively common, impairing neurodevelopmental disorder which shows high overlap with other neurodevelopmental disorders. It is associated with later depression, and when both ADHD and depression are present, outcomes are worse than for either disorder alone. Therefore, identifying those with ADHD who are at increased risk of developing depression may allow early intervention and prevention, with the aim of improving outcomes.

Irritability is a potential risk factor for depression in this group. It is associated with depression in the general population and is particularly common in those with ADHD. It is possible that irritability could explain high rates of depression in individuals with ADHD. However, findings from the general population cannot be generalised to those with ADHD. Children with ADHD are predominantly male, and it is unclear if irritability in ADHD is the same as irritability seen in those without ADHD. Despite this, there has been little research into the association between irritability and depression in young people with ADHD. Evidence from twin studies also suggests presence of genetic overlap between irritability and depression, and molecular genetic studies examining the overlap between irritability and depression in those with ADHD are yet to be undertaken.

Finally, as ADHD shows high clinical and genetic overlap with other neurodevelopmental difficulties, which are also associated with high rates of irritability and depression, the association between irritability and depression across a broader group of neurodevelopmental difficulties is also important to consider.

1.7 Thesis aims

The overall aims of this thesis are to utilise existing cross-sectional data and new follow-up data on a clinical outpatient sample of children with ADHD to test whether:

1. Irritability is associated with concurrent and future depressive symptoms (Chapters 3 and 4).
2. Irritability is associated with a higher genetic liability to depression as indexed by increased polygenic risk score for depression (Chapter 5).

Utilise a longitudinal population sample to examine those with a broader group of neurodevelopmental difficulties, testing whether:

3. Irritability contributes to the longitudinal association between childhood neurodevelopmental difficulties and later adolescent depression (Chapter 6).

Chapter 2: Methods

This chapter describes the two samples used to address the aims of this thesis. Firstly, a clinical ADHD sample (Study of ADHD, Genes and Environment (SAGE)), and secondly, a longitudinal, population-based, birth cohort (Avon Longitudinal Study of Parents and Children (ALSPAC)). For each sample, information is provided on the sample recruitment and study procedures, the relevant measures completed/data collected, and the characteristics of the participants. Where relevant, information on the genetic data available for the sample is also described. The analytic methods used to address each thesis aim are described in the individual results chapters that follow.

2.1 Study of ADHD, Genes and Environment (SAGE): a clinical ADHD sample

The Study of ADHD, Genes and Environment (SAGE) is a large cross sectional study of children with ADHD that was initially set up at Cardiff University in 2007 with the aim of understanding more about genetic and environmental influences on ADHD. To address the aims of this thesis, further longitudinal data from a subsample of SAGE participants were collected between 2014 and 2016. The initial SAGE study is described below as the “baseline sample”, and the data collected subsequently are described as the “follow-up sample”.

2.1.1 Baseline Sample

2.1.1.1 Sample recruitment and procedures

A clinical sample of children with ADHD was recruited from UK child psychiatry and paediatric clinics between 2007 and 2011. Clinicians completed referral forms with the parents of children attending their clinics, providing family contact details and information on the child’s diagnoses. Once a referral form was received by the study team, parents were contacted by telephone for further explanation of the study and to confirm eligibility. To be included in the study, children were required to have a clinical

diagnosis of ADHD, to be aged between 6-18 years, to be of British Caucasian origin (at that time genetic studies required a homogeneous ethnic group, so the most common ethnic group was selected), and to live with at least one biological parent at the time of the study. Exclusion criteria were any major comorbid neurological disorder or genetic syndrome (including fragile X syndrome, tuberous sclerosis, epilepsy, psychosis, Tourette's syndrome and any known diagnosis of autism or other pervasive developmental disorder), in keeping with ICD and DSM recommendations at that time. Once verbally enrolled in the study, information sheets and questionnaires were posted to families, and a time was arranged for researchers to visit them at home. Families were visited at home by trained research psychologists, who conducted semi-structured psychiatric interviews, cognitive tasks, and ensured previously posted questionnaires had been completed. Blood or saliva samples were also collected from parents and children for DNA extraction and genotyping. Teachers were contacted by telephone and/or sent postal questionnaires to obtain information about the child's ADHD symptoms in the school setting.

Written informed consent from parents, and assent from children (or consent for those aged 16 years and older) were obtained for all individuals. Ethical approval for the study was obtained from the Wales Multicentre Research Ethics Committee (reference number: 06/MRE08/75).

2.1.1.2 Measures

Questionnaire measures

Parent-completed questionnaires included demographic items covering annual household income and highest maternal and paternal educational level. Current parental depression and anxiety symptoms were measured using the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983). This is a 14 item rating scale

widely used and validated as a measure of depression and anxiety symptoms in adults in the last 1 week (Bjelland, Dahl, Haug, & Neckelmann, 2002). Mothers and fathers were asked to complete this measure.

Teacher-completed questionnaires included the DuPaul ADHD rating scale, a 28 item rating scale (DuPaul, 1981), and Conner's rating scale, a 28 item rating scale (Conners, 1969), both validated measures of ADHD symptoms in childhood (Collett, Ohan, & Myers, 2003), providing information about the child's ADHD symptoms in the school setting.

Interview measures

Child and Adolescent Psychiatric Assessment (CAPA): Mothers were interviewed about their child using the Child and Adolescent Psychiatric Assessment (CAPA) (Angold & Costello, 2000). The CAPA is a semi-structured diagnostic interview that involves trained interviewers asking about symptoms of a range of psychiatric disorders present in the preceding 3 months. When a parent reports the presence of any symptom, they are asked about how severe it is, specifically whether it interferes in different areas of their child's life. To be coded as present, a symptom must occur uncontrollably and interfere with at least 2 activities. Research diagnoses (e.g. ICD-10 or DSM-5) can be made based upon the presence of symptoms and impairment. In this study, all interviewers were trained to a high level of reliability ($\kappa=1.00$ for agreement on ADHD diagnosis) (Langley et al., 2011), all interviews were recorded, and interviewers were supervised weekly by an experienced child and adolescent psychiatrist.

The parent-reported CAPA was used to establish the presence of a number of DSM-5 defined psychiatric disorders, including ADHD, major depressive disorder (MDD), common childhood anxiety disorders (generalised anxiety disorder and separation

anxiety disorder), oppositional defiant disorder (ODD), conduct disorder (CD) and disruptive mood dysregulation disorder (DMDD). Although the CAPA predates the addition of DMDD to DSM-5, the symptoms required for generating a DMDD diagnosis are included in the interview and have been used previously to establish DMDD diagnosis (Copeland et al., 2013). Therefore, for the purpose of this work, DMDD diagnosis was derived using the CAPA as per Copeland et al (2013). This is described in detail in table 2.1.

Table 2.1: Defining DMDD using Child and Adolescent Psychiatric Assessment

DSM-5 DMDD diagnostic criteria	CAPA items used (ODD and depression sections)
Severe temper outbursts	Fulfilled if “losing temper” or “temper tantrum” items present in the ODD section.
Temper outbursts inconsistent with development	Fulfilled if either “losing temper” or “temper tantrum” items present in the ODD section.
Frequency of temper outbursts ≥ 3 x/week	Fulfilled if “losing temper” frequency total ≥ 36 , or “temper tantrum” frequency total ≥ 36 (equivalent to the symptom being present on average at least 3 x per week over the 3 month period that the CAPA asks about).
Irritable or angry mood (mood between outbursts is persistently irritable or angry most of the day, nearly every day and is observable by others)	Fulfilled if any of the following items from the depression section of the CAPA have a frequency >45 : <ul style="list-style-type: none"> • “touchy or easily annoyed”, • “angry or resentful”, • “depressed mood” • “irritable” (equivalent to the symptom being present on more days than not over the 3 month period the CAPA asks about).
Temper outbursts and irritable mood present for >12 months	Fulfilled if “losing temper” or “temper tantrum” present ≥ 3 x/week for >12 months, AND “touchy or easily annoyed” or “angry or resentful” or “depressed mood” or “irritable” symptom present ≥ 3 x/week for >12 months.
Symptoms present in at least 2 settings	Fulfilled if “losing temper” or “temper tantrums” were present in at least 2 of the 3 settings asked about in the CAPA i.e. school, home or elsewhere.
Diagnosis not to be made before age 6 or after age 18	No children in this sample were <6 years or >18 years.
Temper outbursts and irritable mood onset <10 yrs	Fulfilled if date of onset of required symptoms was before the child was aged 10 yrs.

CAPA=child and adolescent psychiatric assessment; DMDD=disruptive mood dysregulation disorder; ODD=oppositional defiant disorder.

CAPA parent-reports were also used to derive continuous total symptom scores for ADHD, MDD, anxiety disorders, ODD and CD. In addition to these symptom scores, the parent-reported CAPA was used to derive an irritable symptom score for each child based upon symptoms previously defined as making up an irritable dimension of ODD (Stringaris & Goodman, 2009a). The irritable score was derived using 3 items from the ODD section of the CAPA: “temper tantrums”, “touchy/easily annoyed” and “angry or resentful”. For these items to be counted as present, they had to occur frequently over the past three months (at least four times per week for touchy/easily annoyed or angry/resentful, or three times per week for temper tantrums), be rated as uncontrollable, and interfere with at least two activities. A total score of 0-3 was generated based on the presence or absence of these items.

An overall impairment score was also generated using the CAPA. If a parent reported any symptoms as present for the child, they were asked if the symptoms interfered in different areas of their child’s life (at home, in social interactions, in activities in the community, at school, in sports/clubs, in taking care of themselves, in play/leisure activities and in handling daily chores/responsibilities). If the symptoms interfered “sometimes” or “often”, then impairment was counted as present in that area of the child’s life. The number of areas of the child’s life where impairment was present (using information from all sections of the CAPA) was added up to make a total. This information allowed an overall child impairment score of 0-8 to be calculated.

Child Attention Deficit Hyperactivity Disorder Teacher Telephone Interview: Research psychologists contacted a teacher who knew the child well by telephone, and asked them to complete the Child Attention Deficit Hyperactivity Disorder Teacher Telephone Interview (CHATTI) (Holmes et al., 2004) about the study child. The CHATTI is a reliable structured interview designed to assess ADHD symptoms in the school setting

(Holmes et al., 2004), asking about the presence of ADHD symptoms in the preceding 3 months. In this study any ADHD symptom plus impairment in the school setting were used to confirm pervasiveness across settings. These are criteria for DSM-IV/DSM-5 ADHD and ICD-10 hyperkinetic disorder.

Other information: As part of the interview, parents also answered questions about family history of mental illness, including any psychiatric disorder in first or second degree relatives of the child.

Cognitive measures

Wechsler Intelligence Scale for Children (WISC-IV): All children completed the Wechsler Intelligence Scale for Children (WISC-IV) (Wechsler, 2003). The WISC-IV provides a measure of cognitive ability. It includes 10 subscales assessing verbal comprehension, perceptual reasoning, working memory and processing speed, and provides a full scale IQ for each child.

Blood/saliva sample

A biological sample in the form of blood/saliva was collected from each child and, where possible, both biological parents, from which DNA was extracted.

2.1.1.3 Characteristics of sample

The sample consisted of 696 participants aged 6-18 years (mean age=10.9 years, SD=2.99) with a clinical diagnosis of ADHD. At the time of recruitment DSM-5 was not published, so DSM-IV and DSM-III-R research diagnostic criteria were used to confirm clinical ADHD diagnosis and study eligibility using the parent-reported CAPA and teacher reports (ChATTI, DuPaul ADHD rating scale or Conner's Teacher Rating Scale). However, all research diagnoses derived for the current study were based on DSM-5 diagnostic criteria.

A total of 84% of the sample were male (n=583) and they had a mean IQ of 83 (Range=41-119, SD=13.4). In addition to having an ADHD diagnosis, the majority of the sample had one or more additional DSM-5 disorder, with 52.1% (n=357) having ODD, 18.3% (n=125) CD, 6.1% (n=40) anxiety disorder (GAD and/or separation anxiety disorder), and 4.5% (n=30) any depressive disorder (MDD=1.9% (n=13), persistent depressive disorder=3.0% (n=20), both=0.4% (n=3)). The majority of the sample was taking stimulant medication as a treatment for their ADHD (80.6%, n=554). A total of 63% (n=358) of the sample came from low income families with an income of <£20,000 per year. The characteristics of the sample are summarized in table 2.2.

Table 2.2: Baseline characteristics of SAGE sample (n=696)

Gender, % male (n)	84% (583)
Age, mean in years (range, SD)	10.9 (6-18, SD=2.99)
IQ, mean (range, SD)	83 (41-119, SD=13.4)
Income, % < £20,000/year (n)	63% (358)
ADHD medication, % (n)	80.6% (554)
ODD, % (n)	52.1% (357)
CD, % (n)	18.3% (125)
Anxiety disorder, % (n)	6.1% (40)
Any depressive disorder, % (n)	4.5% (30)

ADHD=attention/deficit-hyperactivity disorder; CD=conduct disorder; ODD=oppositional defiant disorder; SAGE=Study of ADHD, Genes and Environment. Anxiety disorder includes generalised anxiety disorder and separation anxiety disorder. Any depressive disorder includes major depressive disorder and persistent depressive disorder.

2.1.1.4 Genetic data

All children and parents who took part in the Study of ADHD, Genes and Environment (SAGE) provided blood or saliva samples from which DNA was extracted. For the purpose of this study, 674 children were genotyped, of whom 569 passed quality control.

Genotyping of the SAGE sample was carried out at two different time points using two different genotyping chips. The two genotyping chips used were the Illumina (San Diego) Human660W-Quad BeadChip (Stergiakouli et al., 2012) (batch 1), and the custom Institute of Psychological Medicine and Clinical Neurosciences chip (IPMCN, Cardiff University) on the Illumina Infinium platform (Caseras, Tansey, Foley, & Linden, 2015) (batch 2). Quality control was done separately for each batch in order to filter out poorly genotyped single nucleotide polymorphisms (SNPs) as well as samples with poor quality data. Only common autosomal variants with Minor Allele Frequency (MAF) >0.01, call rate >0.99 that did not deviate from Hardy-Weinberg equilibrium at $p < 1 \times 10^{-5}$ were included. Quality control involved excluding individuals based on minimal/excess heterozygosity, incorrect gender assignment, cryptic relatedness (where

one of each pair of individuals related at least at the level of second cousins was excluded), duplicate entries and being of non-European ancestry (assessed using principal components analysis). Of those who passed quality control, 354 had been genotyped as part of batch 1 and 215 as part of batch 2.

The 2 batches were then merged. This was done by, firstly, converting the batch 1 dataset to be on the same genome build as batch 2, making it possible for the SNPs to be matched up correctly across the 2 batches. Next, asymmetric/ambiguous SNPs were identified and removed from both batches. For the SNPs that were available in both batches following quality control, the match between alleles was checked, and SNPs where the alleles could not be matched were excluded. Finally, the datasets were merged using the genetics analysis software PLINK.

2.1.2. Follow-up sample

2.1.2.1 Sample recruitment and procedures

A subsample of those who took part in the Study of ADHD, Genes and Environment (SAGE) between 2007 and 2011 were invited to take part in the follow-up study (Fraser et al., 2018). Follow-up was on average 5.4 years after initial participation (range 2-9 years, SD=1.42). All participants who were aged ≤ 12 years at baseline and whose family had consented to be contacted for future research were invited to take part in the follow-up. The age criterion for inclusion was chosen to minimize the number of children with depression at baseline. A total of 434 participants were sent follow-up postal questionnaires. In addition to questionnaires, the questionnaire pack included a letter explaining the study, information leaflets for parent and child/adolescent and a “reply card” asking whether families agreed to being contacted about undertaking an interview as part of the research. If questionnaires had not been returned within 2 weeks, families were contacted by telephone to ensure they had received them, and to

offer help with completing them. If they could not be contacted by telephone, a reminder card was sent by post.

Once questionnaires were returned, those who had also agreed to undertake interviews by completing the “reply card” were contacted and a time arranged for these to take place. Interviews took place in the participant’s own home or at Cardiff University.

A total of 201 of 434 families returned completed questionnaires; a further 48 eligible families had completed pilot questionnaires. Therefore, follow-up data were available for 57% (n=249) of the eligible sample. Of those completing questionnaires, 124 also completed structured diagnostic interviews at follow-up. Figure 2.1 provides a flow chart detailing the numbers of participants taking part at each stage of the study from baseline through to follow-up. Ethical approval for this study was obtained from the Wales Multicentre Research Ethics Committee (reference number: 14/WA/0157).

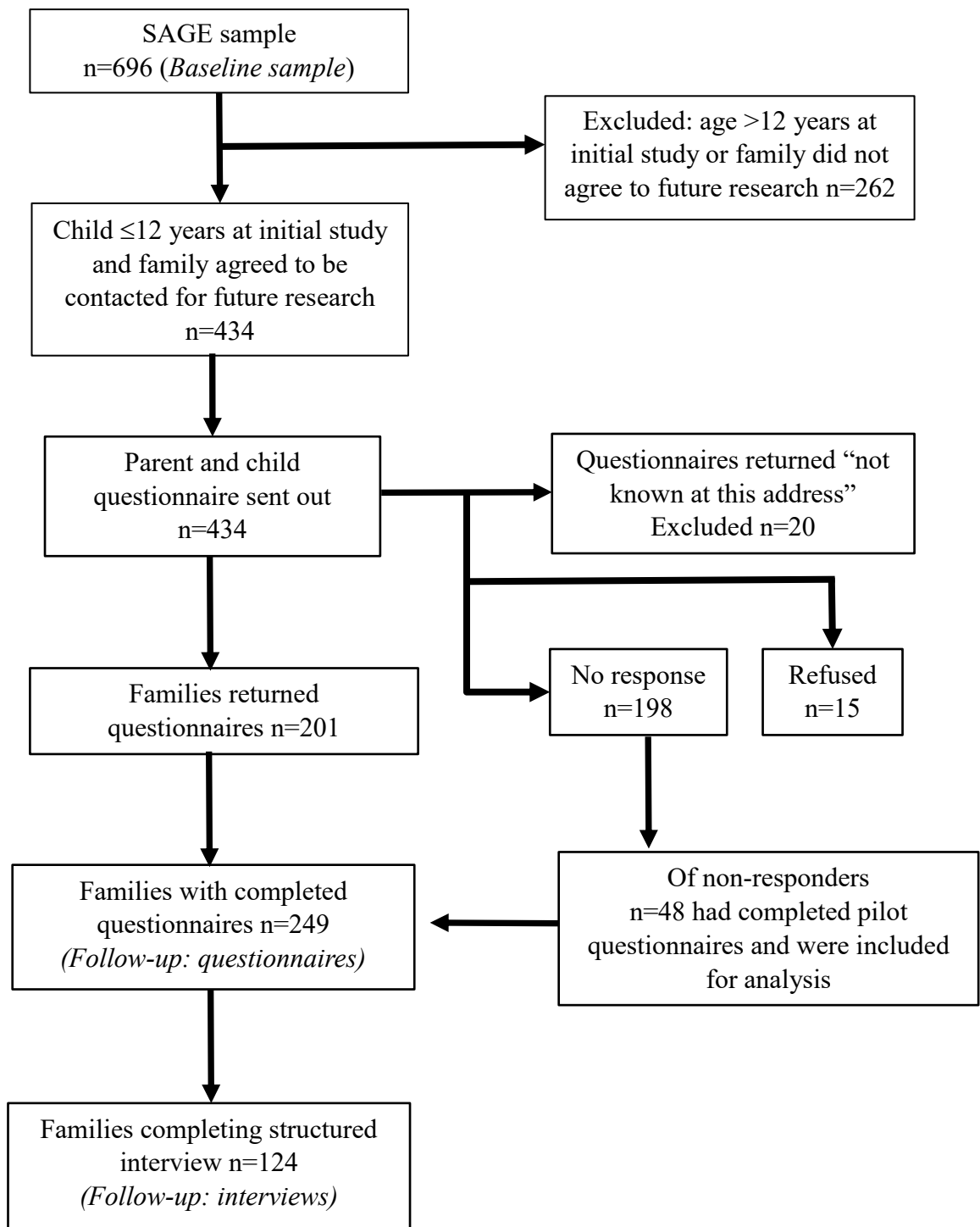


Figure 2.1: Flow chart showing numbers completing follow-up questionnaires and interviews in the SAGE sample.

2.1.2.2 Measures

Questionnaire measures

The parent-rated Mood and Feelings Questionnaire (MFQ) (Angold & Costello, 1987) was used to assess depression symptoms in the child at follow-up. The MFQ is a widely used depression screening instrument (Wood, Kroll, Moore, & Harrington, 1995). It is made up of 34 items, each scored from 0 to 2, with 0 being 'not true', 1 being 'sometimes true' and 2 being 'true'. These scores were used to derive a total parent-rated MFQ score, with a possible range of 0 to 68. A score of ≥ 21 on the parent-rated MFQ is an accepted cut off when screening for possible depression (Wood et al., 1995). This cut off point was used to make a binary MFQ outcome measure. Where >3 MFQ items ($>10\%$) were missing for an individual, the total score was counted as missing. Where ≤ 3 ($<10\%$) MFQ items were missing, a mean score of the completed items was imputed. Parent-rated questionnaires also provided data on ADHD medication use for their children at follow-up.

Interview measures

The Development and Well Being Assessment (DAWBA) was completed by parents on their children at follow-up. The interview was administered by a trained psychiatrist or psychologist. The DAWBA is a structured interview covering common emotional, behavioral and hyperactivity disorders (Goodman, Ford, Richards, Gatward, & Meltzer, 2000). For each diagnostic category, DAWBA algorithms can be used to generate six probability bands, ranging from a probability of having the relevant diagnosis of less than 0.1% to 70%+. The 2 highest probability bands (50% and 70%+) have been described as equivalent to clinician rated diagnosis (Goodman, Heiervang, Collishaw, & Goodman, 2011). These DAWBA bands were used to establish the presence of DSM-5

ADHD, MDD and anxiety disorders (generalised anxiety disorder and separation anxiety disorder), at follow-up.

Irritability at follow-up was also measured using the DAWBA, both as a symptom score and as a categorical measure. An irritable score was generated using 3 items from the ODD section including “temper outbursts”, “easily annoyed” and “angry and resentful”. These were the same items used to make the irritable score from the CAPA at baseline. If the item was rated as being present “rarely or never” or “at least once per week” then a score of 0 was assigned for that item. If it was rated as being present “most days” or “every day” then a score of 1 was assigned, providing a possible total irritable score of 0-3. A categorical diagnosis of DMDD was derived based on the symptoms reported in the DMDD section of the DAWBA. Although a DMDD section has been developed for use in the DAWBA, the algorithms generating probability bands are not yet available for this diagnosis. Therefore, the available items were used to generate a DMDD diagnosis according to DSM-5 diagnostic criteria. See table 2.3 for details on how DMDD diagnosis was made using DAWBA items.

Table 2.3: Defining DMDD using the Development and Well Being Assessment at follow-up

DMDD diagnostic criteria	DAWBA items used (DMDD section)
Severe temper outbursts	Fulfilled if “temper outburst” triggered very easily compared to others.
Temper outbursts inconsistent with development	Fulfilled if “temper outburst” triggered very easily compared to others.
Frequency of temper outbursts ≥ 3 x/week	Fulfilled if “temper outburst” occurs ≥ 3 times per week over last 12 months.
Irritable or angry mood (mood between outbursts is persistently irritable or angry most of the day, nearly every day and is observable by others)	Fulfilled if <ul style="list-style-type: none"> • “easily get annoyed, or become irritable or angry”, AND • “get into seriously irritable or angry moods that are stronger and more intense than is usual for others of their age”, AND • when irritable or angry they stay that way “most or all of the day” OR they experience “angry” weeks where they are “irritable or angry for most of the day, nearly every day” AND • “irritable or angry mood” is obvious to most other people.
Temper outbursts and irritable mood present for > 12 months	Fulfilled if the longest period without a “temper outburst” in last 12 months is <3 months, AND the longest period without an “angry week” in the last 12 months is <3 months.
Symptoms present in at least 2 settings	Fulfilled if “temper outburst” AND “irritable or angry mood” present in at least 2 of the 3 settings asked about in the DAWBA i.e. home, classroom, with friends.
Diagnosis not to be made before age 6 or after age 18	No children with available follow-up DAWBA data in this sample were <6 years or >18 years.
Temper outbursts and irritable mood onset <10 years	Fulfilled if irritability or temper outbursts began before age 10 years.

DAWBA=Development and Well Being Assessment; DMDD=disruptive mood dysregulation disorder; ODD=oppositional defiant disorder.

Using the interview measures across both baseline and follow-up, it was possible to identify those with persistent irritability and persistent ADHD. Irritability persistence was defined as an irritable score of ≥ 1 at baseline (using CAPA) and of ≥ 1 at follow-up (using DAWBA). ADHD persistence was defined as presence of DSM-5 ADHD diagnosis at follow-up (using DAWBA), as all the sample had ADHD at baseline.

2.1.2.3 Characteristics of sample

Of the 434 participants who were invited to follow-up, questionnaire data were available for 249 participants and interview data for 124. For those with any follow-up data, the mean age was 14.4 years (range=8-19 years, SD=2.38), with 82% (n=358) being male. For those with follow-up interview data, 66.7% (n=82) still met full criteria for ADHD diagnosis, 22.8% (n=26) for anxiety disorder, and 4.9% (n=6) for MDD diagnosis. 63% (n=71) of those with irritability at baseline continued to have irritability at follow-up. A total of 69.6 % (n=126) of the total follow-up sample continued to take ADHD medication. Table 2.4 describes the baseline characteristics of those taking part at each stage of the study, and table 2.5 provides characteristics of those completing follow-up questionnaires and interviews.

Table 2.4: Baseline characteristics of (i) the full sample taking part at baseline, (ii) those invited to follow-up, (iii) those completing follow-up questionnaires, and (iv) those completing follow-up interviews

	(i) SAGE sample n=696^a	(ii)Invited to follow-up n=434^b	(iii) Completed follow- up: questionnaire n=249^c	(iv) Completed follow-up: interview n=124^d
Gender, % male (n)	84% (583)	82% (358)	82% (204)	80% (99)
Age, in years (range, SD)	10.9 (6-18, SD=2.99)	9.2 (6-12, SD=1.95)	9.0 (6-12, SD=1.90)	8.5 (6-12, SD=1.80)
IQ (range, SD)	83 (41-119, SD=13.4)	84 (46-119, SD=12.4)	85 (50-119, SD=12.5)	84 (58-118, SD=12.0)
Income, % < £20,000/yr (n)	63% (358)	66% (239)	62% (133)	68% (74)
ADHD medication, % (n)	80.6% (554)	77.3% (333)	77.9% (194)	79.0% (98)
Irritable score, mean (range, SD)	2.19 (0-3, SD=1.0)	2.24 (0-3, SD=0.95)	2.22 (0-3, SD=0.94)	2.38 (0-3, SD=0.79)
DMDD diagnosis, % (n)	31% (207)	37.2% (152)	39% (93)	45.8% (55)
Anxiety disorder, % (n)	6.1% (40)	7.3% (30)	7.9% (19)	10.7% (13)
MDD diagnosis, % (n)	1.9% (13)	1.4% (6)	1.6% (4)	0.8% (1)

^aNumber available for each variable ranged from 565-696; ^bNumber available for each variable ranged from 364-434; ^cNumber available for each variable ranged from 214-249; ^dNumber available for each variable ranged from 109-124. ADHD=attention/deficit-hyperactivity disorder; DMDD=disruptive mood dysregulation disorder; MDD=major depressive disorder; anxiety disorder includes generalised anxiety disorder or separation anxiety disorder. DMDD, anxiety disorder and MDD diagnoses were made using the CAPA, based on DSM-5 diagnostic criteria.

Table 2.5: Characteristics of respondents at follow-up

	Follow-up: questionnaires n=249^a	Follow-up: interviews n=124^b
Gender, % male (n)	82% (204)	81% (99)
Age, in years (range, SD)	14.4 (8-19, SD=2.38)	14.7 (11-20, SD=2.10)
ADHD medication, % (n)	69.6% (126)	69.8% (81)
MFQ total score (range, SD)	24.4 (0-68, SD=15.4)	23.7 (0-68, SD=15.13)
ADHD diagnosis, % (n)	-	66.7% (82)
Irritable score, mean (range, SD)	-	1.46 (0-3, SD=1.29)
DMDD diagnosis, % (n)	-	22.6% (26)
MDD diagnosis, % (n)	-	4.9% (6)
Anxiety disorder, % (n)	-	22.8% (25)

^aNumber available for each variable ranged from 181-249; ^bNumber available for each variable ranged from 113-124; ADHD=attention/deficit-hyperactivity disorder, DMDD=disruptive mood dysregulation disorder, MDD=major depressive disorder, anxiety disorder=generalised anxiety disorder or separation anxiety disorder. Diagnoses were made using the DAWBA, based on DSM-5 diagnostic criteria.

Those who took part at follow-up were younger than those who were eligible but did not take part (9.0 vs 9.5 years, $t(432)=2.45$, $p=0.01$). However, there were no significant differences between responders and non-responders in terms of gender, IQ, parental income, ADHD medication or baseline child psychopathology (see table 2.6).

Table 2.6: Comparing baseline characteristics of eligible participants who did not take part in follow-up compared to those who did

	Did not take part at follow-up n=185^a	Did take part at follow-up n=249^b	Test statistic, p value
Gender, % male (n)	83% (154)	82% (204)	$\text{Chi}^2=0.13$, $p=0.721$
Age, in years (range, SD)	9.5 (6-12, SD=1.99)	9.0 (249)	$t(432)=2.45$, $p=0.015$
IQ (range, SD)	83 (46-110, SD=12.12)	85 (50-119, SD=12.50)	$t(394)=-1.57$, $p=0.12$
Income, % < £20,000/yr (n)	71% (106)	62% (133)	$\text{Chi}^2=2.84$, $p=0.092$
ADHD medication, % (n)	76.4% (139)	77.9% (194)	$\text{Chi}^2=0.14$, $p=0.707$
Irritable score, mean (Range, SD)	2.26 (0-3, SD=0.96)	2.22 (0-3, SD=0.94)	$t(423)=0.43$, $p=0.670$
DMDD diagnosis, % (n)	34.3% (59)	39% (93)	$\text{Chi}^2=1.04$, $p=0.308$
Anxiety disorder, % (n)	6.5% (11)	7.9% (19)	$\text{Chi}^2=0.31$, $p=0.580$
MDD diagnosis, % (n)	1.2% (2)	1.6 % (4)	-

^aNumber for analysis ranged from 150-185; ^bNumber for analysis ranged from 214-249. ADHD=attention-deficit/hyperactivity disorder; DMDD=disruptive mood dysregulation disorder. MDD=major depressive disorder. Anxiety disorder includes generalised anxiety disorder or separation anxiety disorder. DMDD, anxiety disorder and MDD diagnoses were made using the CAPA, based on DSM-5 diagnostic criteria.

2.2 Avon Longitudinal Study of Parents and Children (ALSPAC)

2.2.1 Sample recruitment and procedures

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a longitudinal, population-based, birth cohort that recruited pregnant women resident in Avon, UK with expected delivery dates between 1st April 1991 and 31st December 1992 (Boyd et al., 2013; Fraser et al., 2013). Pregnant women were recruited as early in pregnancy as possible, both opportunistically through the media as well as at routine antenatal appointments where “expression of interest” cards were distributed. If women completed and returned these cards requesting further study information, they were sent an information booklet followed by an initial study questionnaire. The majority (82.6%) eligible for the study were known to have been invited to take part, with a total of 14,541 pregnant women (71.8% of those eligible) being recruited into the study between 1990 and 1992. Of these initial pregnancies, 13,988 children were alive at 1 year.

A further attempt to recruit children who fit the original eligibility criteria was made when participants were age 7 years. This resulted in 456 children from 452 pregnancies being recruited. In addition, another 257 children from 254 pregnancies were also recruited opportunistically between ages 8-18 years (e.g. through eligible families seeking enrolment or through ALSPAC community outreach and promotion services). This resulted in a total of 15,247 pregnancies (75.3% of those eligible), of which 14,701 were alive at 1 year. For the purpose of the current work, data were available for 13,975 participants, all of whom were recruited during pregnancy (1990-1992).

The children from these pregnancies have been followed up at multiple time points since recruitment using a range of questionnaire and clinic-based measures. Between birth and age 18 years there have been 68 data collection time-points, with 59 questionnaires and 9 clinic assessment visits completed (Boyd et al., 2013). Ethical approval for the ALSPAC study was

obtained from the ALSPAC Ethics and Law Committee and Local Research Ethics Committees.

2.2.2 Measures

As discussed, the ALSPAC study collected multiple questionnaire and clinic-based measures, at multiple time points from pregnancy onwards. Only the measures relevant to this thesis are described here. However, the study website contains details of all the data that are available through a fully searchable data dictionary (<http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/>).

The measures relevant to this thesis include those used to define childhood neurodevelopmental difficulties, childhood irritability, adolescent depression, as well as measures providing demographic information. A number of additional measures were also used when undertaking methods to deal with missing data. Figure 2.2 provides a timeline for the key measures relevant to this thesis.

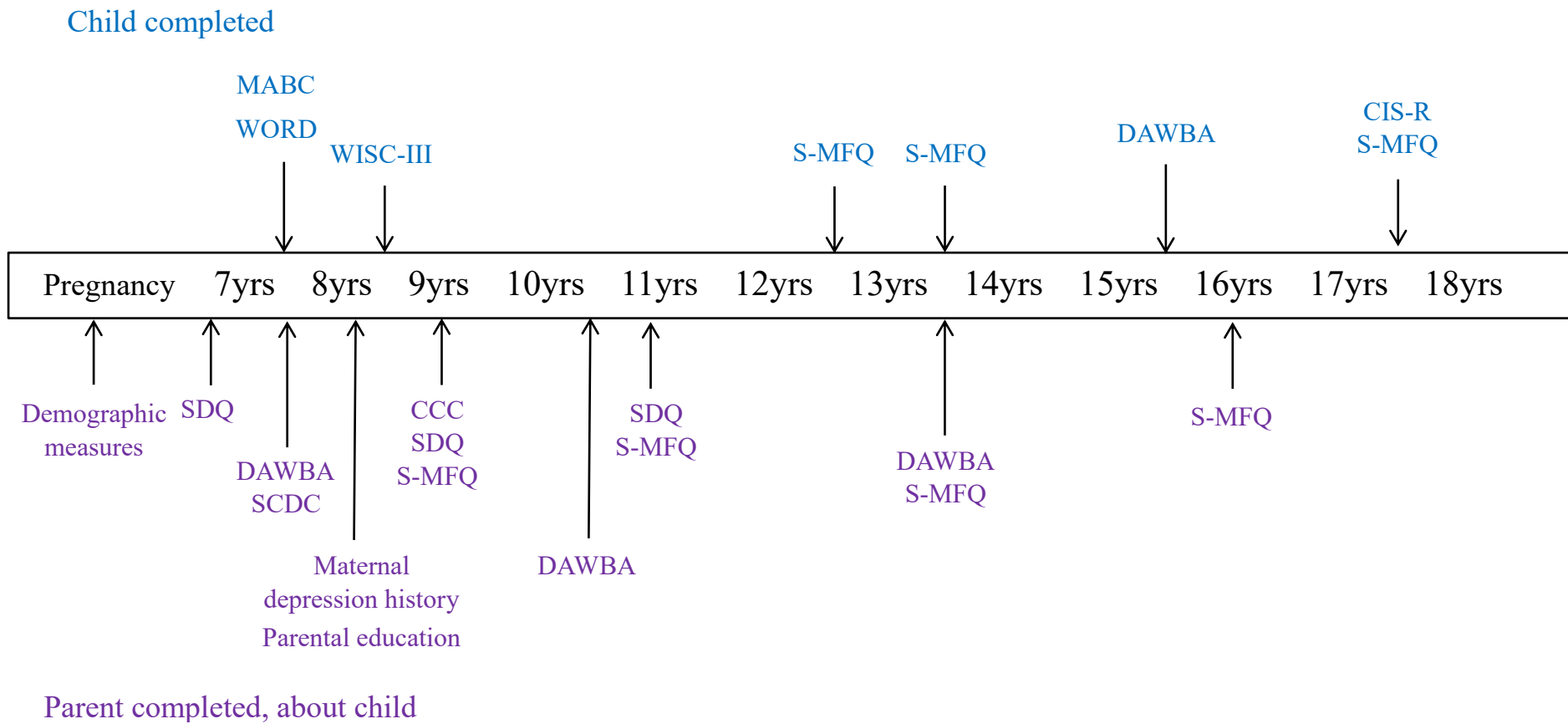


Figure 2.2: Timeline of key ALSPAC measures collected. MABC=Movement Assessment Battery for Children, WORD=Wechsler Objective Reading Dimension, DAWBA=Development and Well Being Assessment, SCDC=Social Communication Disorders Checklist, WISC=Wechsler Intelligence Scale for Children, CCC=Children’s Communication Checklist. SDQ=Strength and Difficulties Questionnaire. S-MFQ=Short Mood and Feelings Questionnaire. CIS-R=Clinical Interview Schedule- Revised.

Childhood neurodevelopmental difficulties

To identify those in the ALSPAC sample with a broad group of neurodevelopmental difficulties, an attempt was made to identify measures that covered each of the six DSM-5 neurodevelopmental disorder categories (intellectual disability, communication disorders, ASD, ADHD, specific learning disorders and motor disorders). Seven scales from six validated parent-reported measures, covering symptoms in each of these diagnostic categories, were identified. These measures were all collected between ages 7 and 9 years and included both questionnaire and clinic-based measures. They included the Wechsler Intelligence Scale for Children (WISC-III) (Wechsler, 1991), the Children's Communication Checklist (CCC) (Bishop, 1998), the Social Communication Disorders Checklist (SCDC) (Skuse, Mandy, & Scourfield, 2005), the Development and Well Being Assessment (DAWBA) (Goodman et al., 2000), the Wechsler Objective Reading Dimension (WORD) (Rust, Golombock, Trickey, & Wechsler, 2003) and the Movement Assessment Battery for Children (MABC) (Henderson & Sugden, 1992). These measures allowed a broad range of neurodevelopmental difficulties to be identified. Individuals who scored in the bottom 5% of the ALSPAC sample (i.e. the 5% with most difficulties) on at least one of these neurodevelopmental measures were classified as having neurodevelopmental difficulties. Identifying the bottom 5% on each measure allowed a consistent method of identifying difficulties across measures (not all of which have validated cut points), and meant that each neurodevelopmental difficulty could be equally represented within the neurodevelopmental difficulties group. Using this selection method it is estimated that around 17% of the sample have any neurodevelopmental difficulty (see chapter 6). This is an appropriate proportion, as around 5-15% of the population are likely to meet criteria for one neurodevelopmental disorder (Anckarsäter et al., 2008; Gilberg et al., 2010; Boyle et al., 2011). These measures and the neurodevelopmental difficulty they assess are described in table 2.7.

Table 2.7: Measures used to identify neurodevelopmental (ND) difficulties

Measure	Description of measure used to identify ND difficulties	ND difficulty assessed	Age at completion (N with data)	N with ND difficulties based on this measure
WISC-III	Test measuring cognitive ability in children. Provides full scale IQ (range 45-151).	Intellectual Disability	8 years, 6 months (7037)	321
CCC	70 item questionnaire assessing children's communication. (a) Speech and syntax subscales total identifying structural language difficulties (range 45-70). (b) Pragmatic composite score identifying pragmatic language difficulties (range 96-162).	Communication Disorders	9 years (7544) (7085)	(a) 408 (b) 355
SCDC	12 item questionnaire assessing social cognition (range 0-24).	Autistic Spectrum Disorder	7 years, 7 months (7886)	373
DAWBA	Structured diagnostic interview based on DSM-IV diagnoses. ADHD section used to generate ADHD symptom count (range 0-18).	ADHD	7 years, 7 months (8158)	372
WORD	Series of tests assessing literacy skills in children. Basic reading subtest used to identify reading impairment (range 0-50).	Specific Learning Disorder: impairment in reading	7 years, 6 months (7606)	401
MABC	Series of tests assessing motor ability. Subtests used: heel to toe walking (balance), placing pegs (manual dexterity), throwing bean bag into a box (ball skills). Standardised scores were available for each subtest (Lingam, Hunt, Golding, Jongmans, & Emond, 2009), allowing a total score to be calculated (range 0-15).	Motor Disorder: Developmental Co-ordination Disorder	7 years, 6 months (6682)	305

WISC-III (Wechsler Intelligence Scale for Children); CCC (Children's Communication Checklist); SCDC (Social Communication Disorders Checklist); DAWBA (Development and Well Being Assessment); WORD (Wechsler Objective Reading Dimension); MABC (Movement Assessment Battery for Children). ND=neurodevelopmental. ADHD=attention-deficit/hyperactivity disorder. All questionnaire/interview measures were completed by parents, all tests were completed by children.

The *WISC-III* (Wechsler, 1991) is a widely used measure of cognitive function. It was administered at age 8 years and 6 months in the ALSPAC sample providing a full scale IQ for each participant, allowing identification of those with cognitive difficulties/intellectual disability.

The *CCC* (Bishop, 1998) is a checklist that assesses children's communication across nine subscales. The first two subscales- speech and syntax subscales- identify possible deficits in structural language skills. The next five subscales measure pragmatic language difficulties, and can be combined to make a pragmatic composite score. The final two subscales measure social interaction and interests. In the ALSPAC sample, the *CCC* was completed by parents when children were age 9 years. For the purpose of this study, a combined speech and syntax subscale score (range 45-70), as well as the pragmatic composite score (range 96-162) were used to identify children with communication difficulties.

The *SCDC* (Skuse et al., 2005) is a 12 item scale asking about social cognition (score range 0-24). In the ALSPAC sample, this questionnaire was completed by parents when children were age 7 years and 7 months. The *SCDC* has been found to be an effective screening questionnaire for autistic traits (Skuse et al., 2005) and was used to identify children with autistic traits in the current study.

The *DAWBA* (Goodman et al., 2000) is a structured diagnostic interview which asks about a range of psychiatric symptoms based on DSM diagnosis. It can be used to examine the presence of symptoms as well as probability of diagnosis. The *DAWBA* was completed a number of times during the course of the ALSPAC study (age 7 years 7 months, 10 years 8 months, 13 years 10 months and 15 years 7 months). The parent completed *DAWBA* at age 7 years 7 months was used to generate a total ADHD symptom score (range 0-18).

The *WORD* (Rust et al., 2003) is a series of tests designed to assess literacy skills in children aged 6 to 16 years. It is made up of 3 subtests assessing basic reading, spelling and reading comprehension. The *WORD* was administered in ALSPAC when the child was age 7 years, 6 months. For the purpose of this study, the basic reading subtest of *WORD* was used to identify children with impairment in reading (score range 0-50). The *MABC* (Henderson & Sugden, 1992) is used to assess motor ability. It is made up of three sections which assess balance, manual dexterity and ball skills. Each section has a number of subtests. In the ALSPAC study, subtests were administered when the children were age 7 years, 6 months. These included heel to toe walking (balance), placing pegs task (manual dexterity) and throwing a bean bag into a box (ball skills). Scores for each of the subtests were standardised and a score of 0-5 for each subscale allocated (Lingam et al., 2009). The higher the score, the more difficulties present. For the purpose of this study, a total score (sum of the 3 subscales) was used as a measure to identify children with co-ordination difficulties (score range 0-15).

As discussed, individuals who scored in the bottom 5% of the ALSPAC sample on at least one of these neurodevelopmental measures were classified as having neurodevelopmental difficulties. However, as age at completion was associated with the score on a number of the neurodevelopmental measures (CCC-speech and syntax score, DAWBA-ADHD symptom score and *WORD*-basic reading score), participant age was taken into account before identifying the bottom 5% of the sample for each measure. For the *WISC-III* and the *MABC*, age standardised scores were already available, therefore, the bottom 5% for these measures was readily identified using frequency tables (the bottom 5% on the *WISC-III* were those with a score of ≤ 77 , the bottom 5% on the *MABC* were those with a score of > 5). For the other measures, residual scores were derived by regressing the measure of interest on the age of participant. These

residual scores demonstrate how far a score is from its predicted value, given the age of the participant. The bottom 5% of the sample on these residual scores was identified for each measure. To be classified as having a neurodevelopmental difficulty, it was necessary to have data available on at least one of the neurodevelopmental measures (e.g. if the individual scored in the bottom 5% on one measure they would be included as having a neurodevelopmental difficulty, even if data from the other measures was missing). A comparison group was then selected including those in the sample without any neurodevelopmental difficulty. Participants classified as having no neurodevelopmental difficulties were required to have data on all 7 neurodevelopmental measures to ensure they did not have any neurodevelopmental difficulty. A total of 1697 were classified as having neurodevelopmental difficulties, and 3177 without neurodevelopmental difficulties, so the total sample size for analysis was 4874. Figure 2.3 provides details on the numbers in the neurodevelopmental difficulties and comparison group.

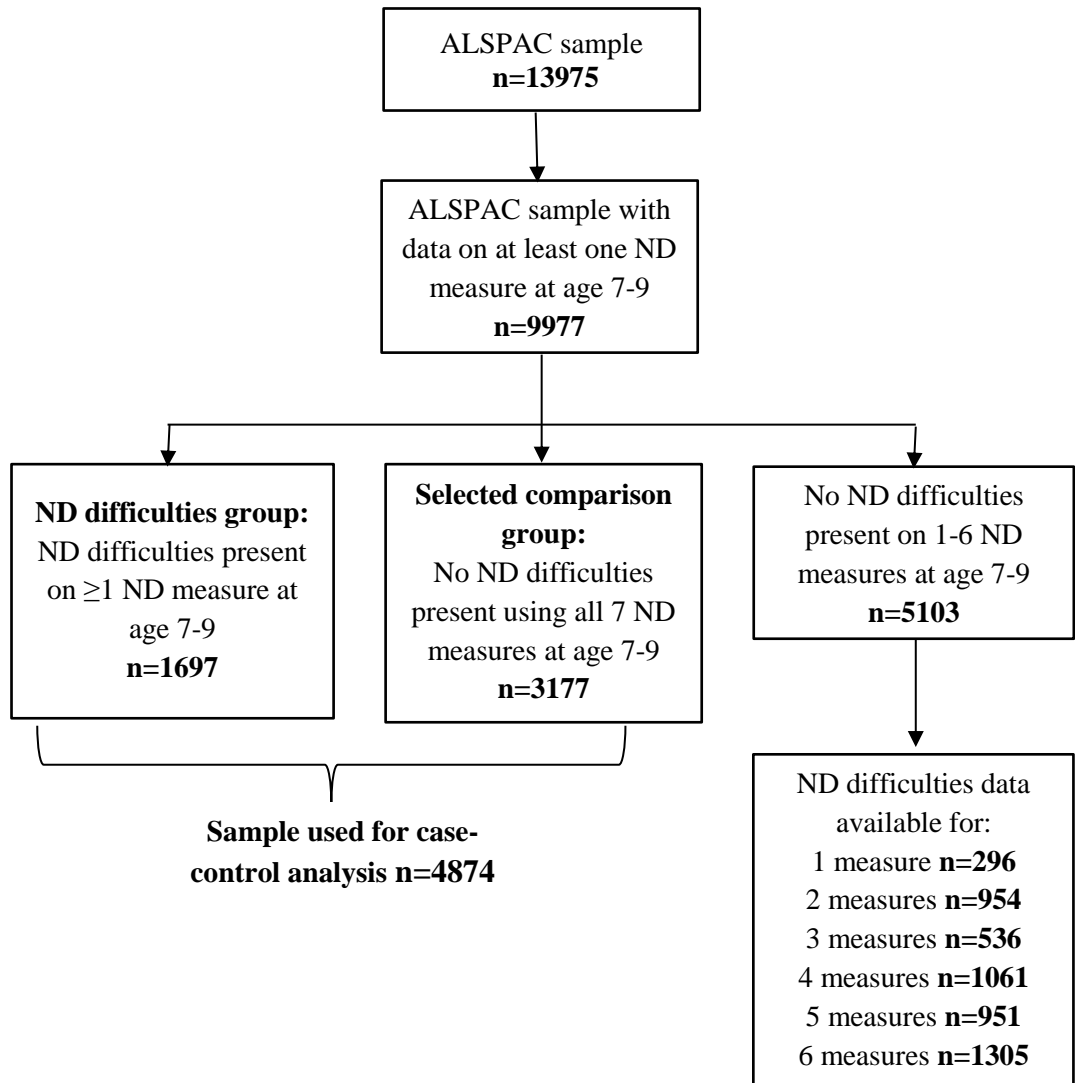


Figure 2.3: Flow chart showing how the ALSPAC sample for analysis was selected

Childhood irritability

Irritability was assessed using the parent-completed DAWBA at age 7 years, 7 months. As discussed, the DAWBA is a structured diagnostic measure that covers a range of common emotional, behavioral and hyperactivity disorders (Goodman et al., 2000). In the ALSPAC study, the DAWBA at age 7 years 7 months was completed in the form of a postal questionnaire.

Irritability was measured using symptoms previously defined as making up an irritable dimension of ODD (Stringaris & Goodman, 2009a). Three items from the ODD section of the DAWBA were used: having temper outbursts, being touchy or easily annoyed and being angry and resentful. Parents were asked whether their child had experienced these symptoms over the last 6 months “no more than others” (score 0), “a little more than others” (score 1) and “a lot more than others” (score 2). A total irritable score ranging from 0-6 was derived for each participant.

Adolescent depression

Depression was assessed using the parent-completed DAWBA at ages 10 years 8 months and 13 years 10 months, and the self-completed DAWBA at age 15 years 7 months. The DAWBA at ages 10 and 13 years were completed in the form of postal questionnaires, and age 15 years the DAWBA was completed in clinic. The depression section of the DAWBA asks about the presence of depression symptoms in the previous 4 weeks. As discussed, the DAWBA can be used to generate six probability bands (Goodman et al., 2011), ranging from a probability of having the relevant diagnosis of less than 0.1% to a probability of 70%+, with the 2 highest probability bands equivalent to clinician rated diagnosis (Goodman et al., 2011). These DAWBA bands were used to establish the presence of DSM-IV major depressive disorder (MDD) at age 10, 13 and 15 years. DSM-IV diagnostic criteria were used in the ALSPAC sample as DSM-IV

was the current edition available at the time of the data collection. This information was then combined to provide the outcome measure: a DSM-IV diagnosis of MDD at any assessment point between ages 10 and 15.

Other study measures

Demographic information about the ALSPAC sample included a measure of social class based on mother's occupation, maternal and paternal age at birth of child, and maternal and paternal education (each split into those with at least A-levels vs those without).

The DAWBA at age 7 years 7 months provided information about baseline MDD (diagnosis and symptoms), anxiety disorder, oppositional defiant disorder (ODD) and conduct disorder (CD) all based on DSM-IV diagnostic criteria.

Additional ALSPAC measures were used when undertaking methods to deal with missing data (described in Chapter 6). These included the parent-rated short Mood and Feelings Questionnaire (MFQ) (Angold et al., 1995) at ages 9, 11, 13 and 16 years, the child-rated short MFQ at 12, 13 and 17 years, the parent-rated Strengths and Difficulties Questionnaire (SDQ) (Goodman, 2001) at age 7, 9 and 11 years, and the Clinical Interview Schedule-Revised (CIS-R) (Lewis, Pelosi, Araya, & Dunn, 1992) at age 18 years. Mothers were also asked about their own history of depression at the age 8 assessment for the child (see figure 2.2).

2.2.3 Characteristics of sample

The sample used for the purpose of this thesis included those with evidence of neurodevelopmental difficulties, plus a comparison group without any neurodevelopmental difficulties. This provided a total sample size of 4874. These children differed on a number of demographic factors when compared to the rest of the ALSPAC sample (see table 2.8). They were more likely to be male, from a higher social

class, with a higher maternal age at birth and higher levels of maternal and paternal education.

Table 2.8: Demographics of ALSPAC study sample compared to the rest of ALSPAC

	Study sample (n≤4874)	Rest of ALSPAC (n≤9101)	Test statistic
Gender % male (n)	52.8% (2574)	51.0% (4645)	$\chi^2= 3.99, p=0.046$
Social Class based on occupation, % I/II (n)	36.6% (1560)	28.5% (1910)	$\chi^2=79.1, p<0.001$
Maternal age, mean in years (range, SD)	29.2 (15-44, SD=4.6)	27.3 (15-44, SD=5.0)	$t=-22.0, p<0.001$
Maternal Education, % with A-levels (n)	41.8 (1707)	35.6 (1115)	$\chi^2=28.8, p<0.001$
Paternal Education, % with A-levels (n)	44.3 (1574)	40.8 (1074)	$\chi^2=8.0, p=0.005$

Social class based on occupation (formerly the Registrar General’s Social Classes) was split into social classes I/II or II/IV/V and percentage in social classes I/II calculated

Within the overall study sample that was used (n=4874), 52.8% (n=2574) were male, with a mean IQ of 104. A total of 36.6% (n=1560) had a social class of I or II. Based on the parent-rated DAWBA at age 7 years, 3.5% (n=159) of the sample had diagnosis of ADHD, 5.4% (n=248) ODD, 1% (n=44) CD, 2.3% (n=104) an anxiety disorder and 0.9% (n=41) a diagnosis of MDD. The mean irritable score for the sample was 0.61.

Chapter 3: Irritability in ADHD: associations with depression liability

The work presented in this chapter has been published in the Journal of Affective Disorders: Eyre, Langley, Stringaris, Leibenluft, Collishaw, Thapar. (2017). Irritability in ADHD: associations with depression liability. *Journal of Affective Disorders*, 215, 281-287.

The published paper has been edited for this chapter in order to include some of the paper's supplementary results, as well as to reduce the repetition with Chapter 1 (Introduction) and Chapter 2 (Methods). However, some of the relevant background literature and methods from Chapters 1 and 2 are also included in this chapter.

Chapter description

This chapter will address the first aim of the thesis- to utilise a clinical ADHD sample to test whether irritability is associated with depression symptoms. The focus here was on the cross-sectional association between irritability and depression symptoms as well as the association between irritability and other measures of depression liability (anxiety and family history of depression). This cross-sectional analysis uses the "baseline sample" described in Chapter 2.

My contribution

The data used for analysis were collected between 2007-2011 prior to the start of this thesis. However, I derived the necessary variables (including DMDD and other DSM-5 diagnoses), and undertook all analyses included in this chapter.

3.1 Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common, impairing neurodevelopmental disorder that is associated with poor adult mental health outcomes (Klein et al., 2012). Depression is a common comorbidity (Spencer et al., 1999) that usually develops post-pubertally after ADHD onset. Young people with ADHD and depression are more impaired than those with ADHD or depression alone (Blackman et al., 2005). Therefore, identifying young people with ADHD who are at risk of depression is important, in terms of facilitating early intervention or prevention.

Although depression risk factors have been identified in the general population, these may not generalise to young people with ADHD, especially as children with ADHD are predominantly male and the impact of risk factors for depression may differ by gender (Kendler & Gardner, 2014; Piccinelli & Wilkinson, 2000).

Irritability is common in ADHD, even though it is not a defining diagnostic feature. Irritability can be described as a propensity to react with anger, grouchiness, or tantrums disproportionate to the situation (Stringaris et al., 2009) and when included in the broader definition of emotional dysregulation, it is present in around 25-45% of children with ADHD (Shaw et al., 2014). In recent years an “irritable” dimension of oppositional defiant disorder (ODD) has been identified (Stringaris & Goodman, 2009a). This includes the items “often loses temper”, “is often angry and resentful”, and “is often touchy or easily annoyed by others”, all of which are common in ADHD. This irritable dimension has been associated with elevated risk of emotional disorders and depression in the general population (Krieger et al., 2013; Stringaris et al., 2009, 2012; Vidal-Ribas et al., 2016; Whelan et al., 2013), but it is not known whether high levels of these symptoms in ADHD are also an early marker of mood problems.

More recently, severely impairing childhood chronic irritability has been conceptualised as a new diagnostic category in the mood disorders section of the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) (American Psychiatric Association, 2013). This new diagnostic category, known as disruptive mood dysregulation disorder (DMDD), is characterised by severe temper outbursts that are grossly out of proportion in intensity or duration to the situation. Alongside these temper outbursts the child experiences a persistently irritable or angry mood most of the day, nearly every day. In order for diagnostic criteria to be met, the temper outbursts and irritable mood must be present for at least 12 months, across settings, and have an onset before the age of 10 years.

Early research into DMDD in the general population, where existing data have been used to derive diagnoses retrospectively, suggests that the prevalence ranges from 0.8% to 3.3% (Copeland et al., 2013). Children with DMDD have been found to be very impaired, with high rates of comorbidity including depression (Copeland et al., 2013; Dougherty et al., 2014). DMDD in the context of ADHD has not been studied widely. Results from community samples suggest that 4.3-23.5% of those with ADHD meet DMDD diagnostic criteria (Copeland et al., 2013; Mulraney et al., 2016). Therefore, the findings to date suggest that DMDD is more common in those with ADHD than in the general population. The only study that has examined the association between DMDD diagnosis and depression in an ADHD sample did not find any association with depression (Mulraney et al., 2016). However, this sample was pre-pubertal and so had not yet reached the age of risk for depression onset. Interestingly they did find an association with anxiety, an established pre-pubertal antecedent of depression (Pine & Fox, 2015).

If chronic childhood irritability is closely related to mood disorders, as conceptualised in DSM-5, then we would expect it to be associated with family history of depression and established pre-pubertal antecedents of depression in children with ADHD.

Therefore, the aims of this chapter, which was based on a large clinical sample of children with ADHD, were to: (1) examine the prevalence of irritability, defined both as a continuous measure and categorically as DMDD, and (2) test cross-sectional associations between irritability and anxiety (symptoms or diagnosis), depression (symptoms or diagnosis), and family history of depression.

3.2 Methods

3.2.1 Sample

The sample used was the Study of ADHD, Genes and Environment (SAGE) “baseline sample”, described in Chapter 2 (n=696). The recruitment procedures, eligibility and characteristics of the sample also are described in Chapter 2.

3.2.2 Measures

The measures collected as part of SAGE are described in Chapter 2. The measures used for the current analysis are briefly described again here.

3.2.2.1 Child Psychopathology

The Child and Adolescent Psychiatric Assessment (CAPA) was completed with all parents. The CAPA, along with teacher reports (Child ADHD Teacher Telephone Interview (ChATTI) (Holmes et al., 2004), and Conner’s Teacher Rating Scale (Conners, 1969)), were used to confirm the diagnosis of ADHD. The CAPA was also used to ascertain other DSM-5 comorbid psychiatric disorders, and symptoms of these disorders, including depressive disorders (major depressive disorder and persistent depressive disorder (dysthymia)), common childhood anxiety disorders (generalised

anxiety disorder and separation anxiety disorder), conduct disorder (CD), oppositional defiant disorder (ODD) and disruptive mood dysregulation disorder (DMDD) (see table 2.1 in Chapter 2 for information on how DMDD diagnosis was derived from the CAPA). For the diagnosis of DMDD, DSM-5 stipulates a number of exclusion criteria based on comorbidity. However, as comorbidity was of interest in this study, exclusions based on comorbidity were not applied.

CAPA reports were also used to derive a continuous measure of irritability, as described in Chapter 2, by counting the presence or absence of the items “touchy or easily annoyed”, “angry or resentful” and “temper tantrums” (score range: 0-3).

3.2.2.2 Parent and family history of depression

To assess current parental depression, the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) was completed by mothers and fathers. Parents were recorded as having depression if they scored at or above the suggested cut point of 11 on the depression sub-scale of the HADS (Snaith, 2003). Parents were also asked about any family history of depression. This included lifetime history of depression in the parent, as well as any history of depression in other first- and second-degree relatives of the child. A score of 1 was given for each first-degree relative (parent or sibling) and a score of 0.5 for each second-degree relative (grandparent, aunt or uncle, nephews or nieces, or half siblings). The total provided a family history score for each child weighted by relatedness (Milne et al., 2009).

3.2.2.3 Other measures

Demographic information (child gender, age and family income) was obtained through parent completed questionnaires. All children completed the Wechsler Intelligence Scale for Children (WISC-IV) (Wechsler, 2003), providing a full scale IQ for each

child. The CAPA was used to derive an impairment score of 0-8, based upon the number of areas in the child's life where impairment was present.

3.2.3 Analyses

Data were analysed using SPSS version 20. Chi squared and independent samples t-tests were used to compare children with DMDD to those without DMDD on a number of demographic (child age, gender, IQ, family income), and clinical (ODD, CD, child impairment score) factors. As the overlap between DMDD and ODD is predominantly due to irritable symptoms, the association between DMDD and non-irritable ODD symptoms was also examined. These non-irritable ODD symptoms have previously been identified as part of a headstrong/hurtful dimension of ODD (Stringaris & Goodman, 2009a). The prevalence of DSM-5 disorders in the sample was also examined according to child age and ADHD subtype.

A series of univariate regression analyses were carried out to examine the association between irritability and depression related measures. Predictor variables were irritable score or DMDD diagnosis. Outcome variables were current child anxiety symptoms or diagnosis, depression symptoms or diagnosis, current mother or father depression, and family history of depression. These analyses were also run controlling for child age, family income and child impairment, all of which were found to be associated with DMDD diagnosis. A sensitivity analysis excluding participants with IQ <70 was also conducted. As “depressed mood” and “irritable” CAPA items were used in the algorithm for DMDD diagnosis, there was a potential for associations between DMDD and depression related outcome measures to be inflated. Therefore, the regression analyses were also run with the “depressed mood” and “irritable” symptoms excluded from the DMDD algorithm. A sensitivity analysis was also carried out to test whether

the headstrong/hurtful symptoms of ODD were associated with the depression related measures.

A number of variables were skewed (child impairment, family history of depression, child depression symptom and child anxiety symptom score variables) so analyses were conducted using both transformed and untransformed variables. As the results did not differ following transformation, the untransformed scores were reported for ease of interpretation.

3.3 Results

Complete DMDD data were available for 95% of the sample (662 out of the 696).

Therefore, a final sample of 662 was used in the DMDD analyses. A total of 97% (678 out of the 696) had information recorded for all 3 of the irritable symptoms, so these were included for the irritable score analyses.

Based on parent report, symptoms of irritability were common in this sample. The mean irritability symptom score was 2.19 (SD=1.0), with 9% of the sample having reported no symptoms, 15% having one symptom, 23% having two symptoms and 53% having the maximum of three symptoms. In terms of the categorical DMDD diagnosis, the 3-month prevalence of the disorder was 31% (95% CI=27.8, 34.9). The numbers meeting each of the DMDD diagnostic criteria are reported in table 3.1.

Table 3.1: Frequency of individual DMDD criteria and diagnosis

DMDD criteria	N meeting criteria	%
Severe temper outbursts (“losing temper” or “temper tantrums” present at CAPA interview)	630	92
Frequency of temper outbursts ≥ 3 x/week	412	60
Irritable or angry mood present more days than not	388	57
Temper outbursts (≥ 3 x/week) and irritable mood (present more days than not) for >12 months	282	42
Symptoms present in at least 2 settings	328	51
Temper outbursts (≥ 3 x/week) and irritable mood (present more day than not) with an onset <10 years	258	38
Full DMDD criteria met	207	31

CAPA=Child and Adolescent Psychiatric Assessment; DMDD=disruptive mood dysregulation disorder.

Children with a diagnosis of DMDD were significantly younger than those without (mean=9.9 vs 11.3 years, $t(447)=6.04$, $p<0.001$), and were more likely to have come from low income families (71% vs 59%, $\chi^2=6.71$, $p=0.010$). There was no difference between those with and without DMDD in child gender or IQ. Those with DMDD had a higher mean impairment score (mean=7.4 vs 6.9, $t(568)=4.91$, $p<0.001$) and were more likely to have comorbid ODD (88.9% vs 33.5%, $\chi^2=174.6$, $p<0.001$) and CD (34.5% vs 11.0%, $\chi^2=51.9$, $p<0.001$) (table 3.2). The association between DMDD and non-irritable symptoms of ODD (i.e. headstrong/hurtful dimension) was significant (unstandardized $B=1.055$, 95% CI=0.83, 1.28, $p<0.001$).

Table 3.2: DMDD and associated demographic and clinical factors

	With DMDD (n≤207) ^a	Without DMDD (n≤455) ^b	Test statistic (df)	p value
Demographic factors				
Gender, % male	83.7	84.1	$\chi^2=0.01$	0.917
Age, mean, in years	9.9	11.3	t=6.04 (447)	<0.001
IQ, mean	82	83.3	t=1.13 (602)	0.261
Income, % <£20,000/year	71	59	$\chi^2=6.71$	0.010
Clinical factors				
Comorbid ODD, %	88.9	33.5	$\chi^2=174.6$	<0.001
Comorbid CD, %	34.5	11.0	$\chi^2=51.9$	<0.001
Impairment score, mean	7.4	6.9	t=4.91 (568)	<0.001

^aFor all variables n ≥183 except income where n=166; ^bfor all variables n ≥421 except income where n=372. CD=conduct disorder; DMDD=disruptive mood dysregulation disorder; ODD=oppositional defiant disorder; df=degrees of freedom.

The prevalence of DMDD and other comorbidities was explored according to ADHD subtype and age. DMDD prevalence was 35.8% in those with ADHD combined type, 13.3% in those with a predominantly hyperactive-impulsive presentation, and 10% in those with a predominantly inattentive presentation. Rates of all comorbidities were highest in the ADHD combined presentation. The pattern of a higher prevalence in a younger age group was less marked for ODD than for DMDD (table 3.3).

Table 3.3: Comorbidities according to age and ADHD subtype

	Age ≤10yrs (n=338)	Age ≥11yrs (n=358)	ADHD: combined (n=486)	ADHD: inattentive (n=41)	ADHD: hyperactive- impulsive (n=64)
Anxiety disorder	7.5%	4.7%	7.4%	0%	3.3%
Depression diagnosis	2.8%	5.5%	4.5%	2.6%	4.8%
ODD	55.1%	49.3%	57.8%	5.0%	32.8%
CD	16.9%	19.6%	21.0%	5.0%	9.4%
DMDD	39.4%	23.7%	35.8%	10%	13.3%

ADHD=attention-deficit/hyperactivity disorder; CD=conduct disorder; DMDD=disruptive mood dysregulation disorder; ODD=oppositional defiant disorder.

Results from the regression analyses found that DMDD was associated with comorbid anxiety symptoms (unstandardized B=0.49, 95% CI=0.15, 0.84, p=0.006), anxiety disorder (OR=2.59, 95% CI=1.36, 4.93, p=0.04) and depression symptoms (unstandardized B=0.38, 95% CI=0.15, 0.60, p=0.001), but not depression diagnosis (OR=0.97, 95% CI=0.41, 2.26, p=0.940).

The mothers of children with DMDD were more likely to be currently depressed than mothers of children without DMDD (27.1% v. 17.8%, OR=1.7, 95% CI=1.11, 2.65, p=0.016), but there was no difference in rates of current depression in the fathers (9.5% v. 9.6%, OR=0.99, 95% CI=0.41, 2.41, p=0.983). Children with DMDD had higher mean family history of depression score than those without (0.51 v. 0.40, unstandardized B=0.11, 95% CI=0.01, 0.22, p=0.04) (table 3.4). As only 2 participants relied solely on the “depressed mood” or “irritable” symptoms of the CAPA in order to reach the threshold for DMDD diagnosis, all results remained the same when the “depressed mood” and “irritable” items were excluded from the DMDD algorithm.

Table 3.4: Association between DMDD and child anxiety, depression and family history of depression

	With DMDD (n=207)^a	Without DMDD (n=455)^b	Test statistic (95% CI)	p value
Child anxiety or depression				
Anxiety symptoms, mean	1.23	0.78	B=0.49 (0.15, 0.84)	0.006
Anxiety disorder, %	10.5	4.3	OR=2.59 (1.36, 4.93)	0.040
Depression symptoms, mean	1.49	1.16	B=0.38 (0.15, 0.60)	0.001
Depressive disorder, %	3.9	4.0	OR=0.97 (0.41, 2.26)	0.940
Family history of depression				
Current maternal depression (% ≥11 on HADS)	27.1	17.8	OR=1.7 (1.11, 2.65)	0.016
Current paternal depression (% ≥11 on HADS)	9.5	9.6	OR=0.99 (0.41, 2.41)	0.983
Weighted family history of depression, mean	0.51	0.40	B=0.11 (0.01, 0.22)	0.040

^aFor all variables $n \geq 195$ except current maternal depression ($n=170$) and current parental depression ($n=84$); ^b for all variables $n \geq 428$ except current maternal depression ($n=348$) and current paternal depression ($n=177$). B=unstandardized B coefficient; CI=confidence interval; DMDD=disruptive mood dysregulation disorder; HADS=hospital anxiety and depression scale; OR=odds ratio. Child anxiety disorder includes generalised anxiety disorder and separation anxiety disorder; depressive disorder includes major depressive disorder and persistent depressive disorder.

The results were similar when irritable score was used as the predictor variable. Irritable score was also associated with child anxiety symptoms (unstandardized $B=0.29$, 95% CI=0.13, 0.44, $p < 0.001$), anxiety disorder (OR=1.88, 95% CI=1.2, 2.96, $p=0.006$) and depression symptoms (unstandardized $B=0.296$, 95% CI=0.196, 0.395, $p < 0.001$).

However, in addition, irritable score was associated with depression diagnosis (OR=2.8, 95% CI=1.36, 5.73, $p=0.005$). When the association was examined separately for major depressive disorder (MDD) and persistent depressive disorder, association was strongest for persistent depressive disorder (OR=4.70, 95% CI=1.3, 17.0, $p=0.018$) and association with MDD alone did not reach conventional levels of statistical significance

(OR=2.13, 95% CI=0.90, 5.04, p=0.086). Irritable score was also associated with family history of depression (unstandardized B=0.058, 95% CI=0.01, 0.11, p=0.021). Irritable score was not associated with current maternal (OR=1.12, 95% CI=0.9, 1.4, p=0.307) or paternal depression (OR=1.17, 95% CI= 0.79, 1.73, p= 0.444) (table 3.5).

Table 3.5: Association between irritable score and child anxiety, depression and family history of depression

	Test statistic (95% CI)	P value
Child anxiety or depression		
Anxiety symptoms	B=0.29 (0.13, 0.44)	<0.001
Anxiety disorder	OR=1.88 (1.2, 2.96)	0.006
Depression symptoms	B=0.296 (0.20, 0.40)	<0.001
Depressive disorder	OR=2.8 (1.36, 5.73)	0.005
Family history of depression		
Current maternal depression (≥11 on HADS)	OR=1.12 (0.9, 1.4)	0.307
Current paternal depression (≥11 on HADS)	OR=1.17 (0.79, 1.73)	0.444
Weighted family history of depression	B=0.058 (0.01, 0.11)	0.021

For all variables $n \geq 635$ except current maternal depression ($n=530$) and current parental depression ($n=267$). B=unstandardized B coefficient; CI=confidence interval; HADS=hospital anxiety and depression scale; OR=odds ratio. Child anxiety disorder includes generalised anxiety disorder and separation anxiety disorder; depressive disorder includes major depressive disorder and persistent depressive disorder.

The overall pattern of results for the regression analyses remained similar when adjusting for age, low income and impairment, and when excluding those in the sample with an IQ <70. The only differences observed were that irritability (irritable score and DMDD) was no longer significantly associated with weighted family history of depression when adjusting for child age, family income and child impairment, and that DMDD was no longer significantly associated with current maternal depression when participants with low IQ were excluded (tables 3.6, 3.7, 3.8 and 3.9).

Table 3.6: Association between DMDD and depression related measures adjusting for age, income and impairment

	Unadjusted		Adjusting for age, income and impairment	
	Test statistic (95% CI)	p value	Test statistic (95% CI)	p value
Child anxiety or depression				
Anxiety symptoms	B=0.494 (0.15, 0.84)	0.006	B=0.544 (0.14, 0.95)	0.008
Anxiety disorder	OR=2.59 (1.36, 4.93)	0.040	OR=2.52 (1.21, 5.26)	0.014
Depression symptoms	B=0.38 (0.15, 0.60)	0.001	B=0.425 (0.17, 0.68)	0.001
Depression diagnosis	OR=0.97 (0.41, 2.26)	0.940	OR=0.97 (0.35, 2.66)	0.950
Family history of depression				
Current maternal depression (% ≥11 on HADS)	OR=1.7 (1.11, 2.65)	0.016	OR=1.69 (1.04, 2.75)	0.034
Current paternal depression (% ≥11 on HADS)	OR=0.99 (0.41, 2.41)	0.983	OR=0.65 (0.22, 1.93)	0.442
Weighted family history of depression	B=0.11 (0.01, 0.22)	0.040	B=0.11 (-0.02, 0.23)	0.098

B=unstandardized B coefficient; CI=confidence interval; DMDD=disruptive mood dysregulation disorder; HADS=Hospital anxiety and depression scale; OR=odds ratio. Child anxiety disorder includes generalised anxiety disorder and separation anxiety disorder; depressive disorder includes major depressive disorder and persistent depressive disorder.

Table 3.7: Association between irritable score and depression related measures adjusting for age, income and impairment

	Unadjusted		Adjusting for age, income and impairment	
	Test statistic (95% CI)	p value	Test statistic (95% CI)	p value
Child anxiety or depression				
Anxiety symptoms	B=0.29 (0.13, 0.44)	<0.001	B=0.25 (0.07, 0.43)	0.006
Anxiety disorder	OR=1.88 (1.2, 2.96)	0.006	OR=1.78 (1.08, 2.93)	0.025
Depression symptoms	B=0.296 (0.20, 0.40)	<0.001	B=0.311 (0.20, 0.43)	<0.001
Depression diagnosis	OR=2.8 (1.36, 5.73)	0.005	OR=2.38 (1.17, 4.90)	0.017
Family history of depression				
Current maternal depression (% ≥11 on HADS)	OR=1.12 (0.9, 1.4)	0.307	OR=1.12 (0.88, 1.42)	0.376
Current paternal depression (% ≥11 on HADS)	OR=1.17 (0.79, 1.73)	0.444	OR=0.998 (0.64, 1.56)	0.995
Weighted family history of depression	B=0.058 (0.01, 0.11)	0.021	B=0.046 (-0.01, 0.10)	0.116

B=unstandardized B coefficient; CI=confidence interval; HADS=hospital anxiety and depression scale; OR=odds ratio. Child anxiety disorder includes generalised anxiety disorder and separation anxiety disorder; depressive disorder includes major depressive disorder and persistent depressive disorder.

Table 3.8: Association between DMDD and depression related measures in full sample compared to sample excluding those with low IQ

	Full sample		Excluding all cases with IQ<70	
	Test statistic (95% CI)	p value	Test statistic (95% CI)	p value
Child anxiety or depression				
Anxiety symptoms	B=0.494 (0.15, 0.84)	0.006	B=0.368 (-0.012, 0.75)	0.006
Anxiety disorder	OR=2.59 (1.36, 4.93)	0.040	OR=2.24 (1.08, 4.65)	0.031
Depression symptoms	B=0.38 (0.15, 0.60)	0.001	B=0.405 (0.16, 0.65)	0.001
Depression diagnosis	OR=0.97 (0.41, 2.26)	0.940	OR=1.22 (0.44, 3.36)	0.699
Family history of depression				
Current maternal depression (% ≥11 on HADS)	OR=1.7 (1.11, 2.65)	0.016	OR=1.33 (0.8, 2.2)	0.276
Current paternal depression (% ≥11 on HADS)	OR=0.99 (0.41, 2.41)	0.983	OR=1.3 (0.49, 3.48)	0.595
Weighted family history of depression	B=0.111 (0.01, 0.22)	0.040	B=0.158 (0.04, 0.28)	0.009

B=unstandardized B coefficient; CI=confidence interval; DMDD=disruptive mood dysregulation disorder; HADS=hospital anxiety and depression scale; OR=odds ratio. Child anxiety disorder includes generalised anxiety disorder and separation anxiety disorder; depressive disorder includes major depressive disorder and persistent depressive disorder.

Table 3.9: Association between irritable score and depression related measures in full sample compared to sample excluding those with low IQ

	Full sample		Excluding all cases with IQ<70	
	Test statistic (95% CI)	p value	Test statistic (95% CI)	p value
Child anxiety or depression				
Anxiety symptoms	B=0.29 (0.13, 0.44)	<0.001	B=0.201 (0.33, 0.37)	<0.033
Anxiety disorder	OR=1.88 (1.2, 2.96)	0.006	OR=1.58 (1.01, 2.49)	0.046
Depression symptoms	B=0.296 (0.196, 0.395)	<0.001	B=0.292 (0.19, 0.40)	<0.001
Depression diagnosis	OR=2.8 (1.36, 5.73)	0.005	OR=3.47 (1.24, 9.73)	0.018
Family history of depression				
Current maternal depression (% ≥11 on HADS)	OR=1.12 (0.9, 1.4)	0.307	OR=0.99 (0.78, 1.26)	0.946
Current paternal depression (% ≥11 on HADS)	OR=1.17 (0.79, 1.73)	0.444	OR=1.08 (0.71, 1.65)	0.719
Weighted family history of depression	B=0.058 (0.01, 0.11)	0.021	B=0.070 (0.02, 0.12)	0.010

B=unstandardized B coefficient; CI=confidence interval; HADS=hospital anxiety and depression scale; OR=odds ratio. Child anxiety disorder includes generalised anxiety disorder and separation anxiety disorder; depressive disorder includes major depressive disorder and persistent depressive disorder.

When the headstrong/hurtful dimension of ODD was examined as a predictor variable instead of irritability, different results were found. The headstrong/hurtful dimension was not significantly associated with child anxiety symptoms or disorder, child depression diagnosis, or family history of depression. However, it was associated with child depression symptoms (unstandardized B=0.166, 95% CI=0.087, 0.245, p=<0.001), current maternal depression (OR=1.2, 95% CI=1.02, 1.41, p=0.027) and current paternal depression (OR=1.35, 95% CI=1.01, 1.79, p=0.042).

3.4 Discussion

The results suggest that symptoms of irritability and DMDD are common in children with ADHD, and that increased levels of irritability are associated with markers of depression liability.

Almost all children in the sample had at least one symptom of irritability, and the 3-month prevalence of DMDD diagnosis was 31%. This is considerably higher than in the general population (Copeland et al., 2013), and is also high when compared to the 4.3-23.5% prevalence in those with ADHD from community samples (Copeland et al., 2013; Mulraney et al., 2016).

On examining the association between irritability and markers of depression liability, there were a number of important findings. Associations were observed between irritability (both as a symptom score and DMDD diagnosis) and child depression symptoms, anxiety symptoms and anxiety disorder, as well as between irritable symptom score and depression diagnosis. These results support the hypothesis that irritability may be an early marker of mood problems in children with ADHD.

Depression and anxiety symptoms in children have consistently been shown to be precursors for later depression (Batterham, Christensen, & Calear, 2013; Fergusson et al., 2005).

Even though no association was found between DMDD and child depression diagnosis, this is not surprising given that depression is relatively rare in childhood. Risk for depression increases in adolescence (Thapar et al., 2012), but the mean age of this sample was 10.9 years. Therefore, this sample may have been too young to observe the association. These findings are consistent with those of Mulraney et al. (2016) who found that, in a community sample of children with ADHD aged 6-8 years, there was no association between DMDD and depression, but there was a significant association with

anxiety (Mulraney et al., 2016). Despite this, an association between irritable score and depression diagnosis was observed in this study. However, this seemed to be driven by the association with persistent depressive disorder (dysthymia) rather than major depressive disorder (MDD). It is possible that as children get older and pass through the age of risk for depression, the power to detect an association between irritability and MDD will increase. Results showing associations between irritability and elevated risk of depression in the general population have mainly been based on longitudinal studies (Vidal-Ribas et al., 2016). Longitudinal studies following children with ADHD into adolescence and young adulthood are also needed if the relationship between irritability and depression in ADHD is to be examined.

Irritable score and DMDD diagnosis were also associated with other markers of depression liability. DMDD diagnosis was associated with family history of depression, and with current maternal depression. Irritable score was associated with family history of depression. These findings provide further support for the hypothesis that irritability is related to mood disorders, specifically depression, in children with ADHD. However, irritability was not associated with all the family history variables measured. Irritable score in the child was not associated with current maternal depression, and neither irritable score nor DMDD diagnosis were associated with current paternal depression. Also, when the analyses were rerun adjusting for age, family income and child impairment the association with family history was no longer present. Previous studies in the general population also show mixed findings when looking at these associations. Some studies support the finding that child irritability is associated with maternal depression. For example, an irritable dimension of ODD was found to be associated with the presence of maternal depression in a community sample (Krieger et al., 2013). Also, children with more severe irritability trajectories have been shown to be more

likely to have mothers with recurrent depression in a population-based cohort (Wiggins et al., 2014). However, other studies that examined the association between DMDD and parental psychopathology both in the general population and in clinical samples have not found any association (Axelson et al., 2012; Dougherty et al., 2014).

As DMDD in the context of ADHD has not been widely studied, a number of demographic and clinical characteristics in those with comorbid DMDD were examined in this sample. The results found that children with ADHD who also met diagnostic criteria for DMDD were significantly younger and were more likely to come from low income families. Results from previous studies have been mixed when looking at age and DMDD. In community samples some find higher rates in younger children (Copeland et al., 2013) while others find no difference (Mulraney et al., 2016). Lower rates of DMDD may be expected with increasing age, as prevalence of irritability decreases with age (Copeland et al., 2015). In terms of family income, the results are consistent with previous population studies which suggest that poverty is associated with DMDD (Copeland et al., 2013).

On examining clinical factors associated with DMDD, the findings suggest that children with both ADHD and DMDD have higher rates of additional comorbid disorders than those with just ADHD. These findings are in line with previous literature from community samples that suggest comorbidity is common in those with DMDD (Copeland et al., 2013; Dougherty et al., 2014). ODD was particularly common in this sample, with 89% of those meeting criteria for DMDD also meeting criteria for ODD. This compares to 90% in a community ADHD sample (Mulraney et al., 2016), and 96% in a clinical sample with elevated symptoms of mania (Axelson et al., 2012). High rates of comorbidity may be important to consider when examining the association between irritability and depression. This is because commonly comorbid conditions (e.g. ODD or

anxiety disorders) are also known to be associated with depression (Copeland, Shanahan, Costello, & Angold, 2009). They could, therefore, have an impact on associations seen between irritability and depression. The effect of comorbidity was not examined in the current study, but irritability in the context of a depressive episode has been shown to predict a more severe, chronic and complex depressive illness which was not explained by comorbidity (Judd, Schettler, & Coryell, 2013). Comorbidity will be an important factor to consider in future studies.

This study also found that young people with ADHD who have DMDD are more impaired than those without DMDD. The mean impairment score was high across the whole sample, but higher in those with DMDD. Previous findings from a community ADHD sample have also found DMDD to be associated with high levels of impairment, particularly in social functioning (Mulraney et al., 2016). High levels of impairment have consistently been shown to be associated with irritability (Brotman et al., 2007; Shaw et al., 2014). Therefore, it is not surprising that DMDD is also associated with high levels of impairment in this sample. However, it is worth noting that, in an already impaired group of children with ADHD, having DMDD adds to the level of impairment they experience.

3.4.1 Limitations

There are a number of limitations to this study that should be noted. Firstly, this study used a large clinical sample of children with ADHD in order to address its aims.

Although a clinical sample allowed a better understanding of DMDD and irritability within a group who have access to treatment, there are biases within clinical samples, and these findings are not generalisable beyond this group. The study was also limited by the fact that the diagnosis of DMDD relied on a diagnostic interview that predated the introduction of DSM-5 and thus was not designed to make DMDD diagnosis.

However, this study used the same method as used for previous studies (Copeland et al., 2013), and the information available does allow the diagnostic criteria to be followed. It should also be noted that the “depressed mood” and “irritable” symptoms that were used to make DMDD diagnosis came from the depression section of the diagnostic interview. This could potentially increase the likelihood of association between DMDD and child depression symptoms or diagnosis. However, depression symptoms were relatively rare in this sample and only two participants relied on the presence of either the “depressed mood” or “irritable” symptoms to meet diagnostic criteria for DMDD. When these symptoms were excluded from the DMDD diagnosis algorithm, there was no difference in any of the results. Another point to note when using DMDD diagnosis is that there has been some debate about its utility as a diagnostic category. It has been suggested that due to its overlap with other disorders, particularly ODD, and its lack of stability over time, more research is needed to establish whether it is a valid diagnostic category (Ambrosini et al., 2013; Axelson et al., 2012). It has a complex set of diagnostic exclusion criteria and it is not clear yet how helpful it will be in clinical practice. However, the aim of this study was not to evaluate the validity of DMDD as a diagnostic category, but to use it to understand more about a group of impaired children with ADHD and chronic irritability.

Another factor that is potentially important to take into account when examining the association between irritability and depression related factors in those with ADHD, is medication use. ADHD medication may have an effect on both symptoms of irritability and depression. For example, depression and emotional disturbance have been reported as possible adverse drug reactions in those taking ADHD medication (Aagaard & Hansen, 2011), whereas other studies have shown that irritability and depression symptoms improve in children with ADHD who take stimulant medication (Chang et

al., 2016; Fernández de la Cruz et al., 2015). As the vast majority of participants in this sample were taking regular stimulant medication the effect of medication could not be considered, but this is relevant for future work.

Another limitation is the fact that all the results reported in this study were based on parent only report. It is possible that if the parent reporting on their child's symptoms is depressed, it could bias findings. For example, a depressed mother may be more likely to report their child as irritable. Children's reports as well as parental reports of symptoms may have provided more information and reduced the risk of this bias.

However the sample is relatively young and self-reports in those aged 11 and under can also be unreliable (Schwab-Stone, Fallon, Briggs, & Crowther, 1994). Finally, the study was also limited by the fact that parent psychopathology was assessed using questionnaire measures.

3.4.2 Conclusions

Overall, findings suggest that DMDD and irritability are common in children with ADHD, linked with substantial functional impairment affecting many aspects of children's lives, and may foreshadow future risk for depression as evidenced by associations with multiple known child and familial markers of depression liability (childhood depression and anxiety symptoms, maternal depression and family history of depression).

These findings have implications when seeing children with ADHD in clinical practice. They suggest that routine assessment of irritability in ADHD may be helpful for distinguishing those at highest risk for current impairment and future depression risk. Identifying these children may also be relevant when considering treatment. Although research is still limited, emerging evidence suggests that children with ADHD and irritable symptoms show improvement in their irritability when treated with stimulant

medication (Fernández de la Cruz et al., 2015). Preliminary work in children with chronic irritability and ADHD also suggests that a group therapy, incorporating components of cognitive-behavioural therapy with a parent-training intervention may be of benefit in terms of improvement in depressive symptoms, mood lability and functioning (Waxmonsky et al., 2013). Finally, the findings highlight the importance of longer-term monitoring of risk of developing depression as these children get older.

Chapter 4: Irritability in ADHD: association with later depression symptoms

The work presented in this chapter has been revised and resubmitted for publication in *European Child and Adolescent Psychiatry* (Eyre, Riglin, Leibenluft, Stringaris, Collishaw, Thapar. Irritability in ADHD: association with later depression symptoms). The submitted paper has been edited for this chapter to reduce repetition and to include supplementary results. However, relevant information included in previous chapters is also included here.

Chapter description

This chapter follows on from Chapter 3, further addressing the first aim of the thesis- to utilise a clinical ADHD sample to test whether irritability is associated with depression symptoms. Following on from the cross-sectional analysis in Chapter 3, this chapter examines the longitudinal association between irritability and later depression symptoms. The importance of persistent irritability over time in this association is also examined. The same clinical ADHD sample is utilised as for Chapter 3, but for this analysis both the “baseline sample” and the “follow-up sample” which have been described in Chapter 2 are included.

My contribution

The “baseline sample” data was collected between 2007 and 2011 prior to the start of this thesis. The “follow-up sample” data was collected as part of this thesis. I was involved in setting up this “follow-up” study, gaining ethical approval, sending out questionnaires and undertaking interviews with the families. Once data collection was complete, I cleaned the data, derived variables and undertook all analyses included in this chapter.

4.1 Introduction

Attention/deficit-hyperactivity disorder (ADHD) is a common, impairing neurodevelopmental disorder characterised by inattention, hyperactivity and impulsivity. Comorbidity is common, with more than 50% experiencing at least one other psychiatric disorder (Jensen & Steinhausen, 2015; Spencer et al., 1999). Major depressive disorder (MDD) has been observed to occur more frequently in young people with ADHD than in those without (Biederman et al., 2008; Chronis-Tuscano et al., 2010; Daviss, 2008), and levels of depression symptoms are higher across young adulthood in those with a history of childhood ADHD than in those without the disorder (Meinzer et al., 2016). A meta-analysis found rates of MDD to be on average more than 5 times higher in those with ADHD than in those without (Angold et al., 1999).

This is important, as when depression co-occurs with ADHD, outcomes are worse than for either disorder alone. There is increased psychosocial impairment (Blackman et al., 2005), and elevated risk for psychiatric hospital admission and suicidality (Biederman et al., 2008). In addition, as ADHD precedes the onset of depression (Kessler et al., 2005), identifying those at risk provides an opportunity for early intervention and prevention.

Children with ADHD who are also irritable may be an important at-risk group for future depression. That is because population-based studies have consistently found irritability to be associated longitudinally with depression (Vidal-Ribas et al., 2016). Irritability is a propensity to react with anger, grouchiness, or tantrums disproportionate to the situation (Stringaris et al., 2009). When severe, irritability is impairing and is a common reason for referral to child psychiatry services (Mikita & Stringaris, 2013). It is particularly common in those with ADHD (Shaw et al., 2014) and thus a possible mechanism that explains the high rates of depression in this group.

There has been little research into the longitudinal association between irritability and depression in those with ADHD. Although findings from the general population suggest an association, these cannot automatically be extrapolated to young people with ADHD. Firstly, it is not clear whether the irritability observed frequently in ADHD is the same as the irritability measured in the general population. Irritability occurs more commonly in ADHD, and it is not known whether irritability seen in the presence of ADHD is comparable to irritability seen in those without ADHD. Secondly, it is possible that gender may impact on the association between childhood irritability and later depression, in particular because depression is more common in girls (Thapar et al., 2012). Children with ADHD are predominantly male, which is not reflective of general population samples.

To date, two cross-sectional clinical ADHD samples have examined the association between irritability and depression, finding that irritability symptoms and the DSM-5 diagnosis of disruptive mood dysregulation disorder (DMDD), characterised by severe temper outbursts and persistent irritability, were associated with depression symptoms (Ambrosini, Bennett, & Elia, 2013; Eyre et al., 2017 (Chapter 3)). Longitudinally, Seymour et al (2014) utilised a population sample, finding evidence that emotion regulation (a broader construct than irritability) mediates the relationship between ADHD symptoms and later depression symptoms. However, longitudinal investigation of the association between irritability and depression in a clinical ADHD sample is yet to be examined.

It is also relevant to consider whether irritability persistence is important in the relationship between irritability and depression. Understanding whether it is persistent rather than remitting irritability that confers the greatest risk of depression would allow more precise targeting of preventive interventions. Pagliaccio et al., (2018) found that,

in a sample enriched for preschool depression, those with consistently elevated irritability trajectories across childhood were more likely to develop depression than those whose levels of irritability started high but decreased over time. Wiggins et al. (2014), also derived irritability trajectories across childhood (age 3-9 years) finding that internalising symptoms generally mirrored the patterns of the irritability trajectories (children in a high, steady irritability trajectory or high, increasing irritability trajectory had higher internalising symptoms by age 9 than those with initially high but decreasing irritability) (Wiggins et al., 2014). However, the impact of persistent irritability on risk for depression in children with ADHD has not been examined.

This study aimed to utilise an ADHD patient sample that was longitudinally assessed to: (1) examine the association between childhood irritability and adolescent depression symptoms and (2) examine whether irritability persistence (vs. remittance) is important in this association.

4.2 Methods

4.2.1 Sample

The sample utilised was the Study of ADHD, Genes and Environment (SAGE) described in Chapter 2. Both the “baseline sample” and “follow-up sample” were used for analysis. As described in Chapter 2, the baseline sample was made up of 696 children (mean age=10.9 years, SD=2.99) with a clinical and research diagnosis of ADHD. The follow-up sample included a subsample of these participants who were aged ≤ 12 years at the time of initial data collection (mean age=9.2 years, SD=1.95), and whose family had consented to be contacted for future research. A total of 249 families took part in this follow-up.

4.2.2 Measures

4.2.2.1 Baseline assessment (Time 1)

Child Psychopathology

The parent-completed Child and Adolescent Psychiatric Assessment (CAPA) was used to measure baseline psychopathology in the child. It was used to ascertain presence of DSM-5 psychiatric disorders including major depressive disorder and common childhood anxiety disorders (generalized anxiety disorder and separation anxiety disorder). Symptom counts for each disorder were also derived based on the information provided in the CAPA.

Irritability: The CAPA was also used to assess baseline irritability. Irritability was defined both as a continuous score and a categorical diagnosis. The irritable score was calculated using 3 items from the oppositional defiant disorder (ODD) section of the CAPA, previously defined as making up an irritable dimension of ODD (Stringaris & Goodman, 2009a). The items were “temper tantrums”, “touchy/easily annoyed” and “angry or resentful”. A total score of 0-3 was generated based on the presence or absence of these items. A categorical DSM-5 diagnosis of disruptive mood dysregulation disorder (DMDD) was derived using items from the depression and ODD sections of the CAPA (table 2.1, Chapter 2).

Other measures

Demographic information and child ADHD medication status were recorded on parent completed questionnaires. All children completed the WISC-IV (Wechsler, 2003), providing a full scale IQ.

4.2.2.2 Follow-up assessment (Time 2)

Child Psychopathology: questionnaire data

Depression symptoms: The parent-completed Mood and Feelings Questionnaire (MFQ) (Angold et al., 1995) was used to measure depression symptoms at follow-up. Although child self-rated MFQ data were available in this sample, previous findings suggested that young people from the SAGE study may under-report their own depression symptoms (Fraser et al., 2018), so parent-reported depression symptoms were used as the outcome here.

Child Psychopathology: interview data

The parent-completed Development and Well Being Assessment (DAWBA) was used to measure child psychopathology at follow-up. Computerised DAWBA algorithms were used to generate probability bands (Goodman et al., 2011). The 2 highest probability bands (i.e. >50% probability of disorder) were used to establish the presence of DSM-5 ADHD, MDD and anxiety disorders (generalised anxiety disorder and separation anxiety disorder) at follow-up. ADHD persistence was defined as presence of ADHD diagnosis at follow-up.

Irritability: Irritability at follow-up also was assessed using the DAWBA. A continuous score was generated using the same 3 items from the ODD section that were used to make the irritable score from the CAPA at baseline. They included “temper outbursts”, “easily annoyed” and “angry and resentful”. If the item was rated as being present “rarely or never” or “at least once per week” then a score of 0 was assigned for that item. If it was rated as being present “most days” or “every day” then a score of 1 was assigned, providing a possible total score of 0-3. Irritability persistence was defined as an irritable score of ≥ 1 on the CAPA at baseline and ≥ 1 at follow-up on the DAWBA. A categorical diagnosis of DMDD was derived based on the symptoms reported in the DMDD section of the DAWBA (table 2.1, Chapter 2).

4.2.3 Analyses

Analyses were carried out using Stata version 14.

Association between irritability at baseline and depression symptoms at follow-up

Linear regression was carried out to examine the association between childhood irritability (baseline irritable score and DMDD diagnosis) and adolescent depression symptoms (follow-up parent-rated MFQ total). Due to the small numbers of participants who met diagnostic criteria for MDD on the DAWBA at follow-up (n=6), it was not possible to examine the association between irritability and MDD diagnosis. Instead a binary MFQ measure, based on being above or below the clinical cut point of ≥ 21 on the parent-rated MFQ, was used as an outcome in the longitudinal regression analyses. Regression analyses were run unadjusted, then controlling for child age, gender and baseline depression symptoms. Literature suggests that these variables may be associated with both childhood irritability (Brotman et al., 2006) and adolescent depression (Thapar et al., 2012). Further covariates were assessed as sensitivity analyses (see later).

Persistent vs. remitted irritability

The percentage of the sample with persistent irritability was established. Linear or logistic regression was used to examine whether persistent vs remitted irritability was associated with total parent-rated MFQ score at follow-up, as well as examining the association between persistent vs remitted irritability and the binary MFQ outcome. Analyses were run first unadjusted, then controlling for child age, gender and baseline depression symptoms. Further covariates were again assessed as sensitivity analyses (see below).

Sensitivity analyses

Sensitivity analyses were conducted by (i) controlling for any DSM-5 diagnosis of anxiety disorder (as anxiety commonly co-occurs with irritability and is associated with depression (Vidal-Ribas et al., 2016)) and medication status at baseline (in addition to age, gender and baseline depression symptoms), (ii) removing the irritable item (he/she felt grumpy and irritable with his/her parents) from the parent-rated MFQ at follow-up, and (iii) examining whether any association between persistent irritability and depressive symptoms was explained by persistent ADHD.

4.3 Results

4.3.1 Descriptives

Irritability was a common symptom: as described in Chapter 3, at baseline (n=696), the mean CAPA irritability symptom score was 2.19 (range=0-3, SD=1.0), with 91% of the sample reporting at least one irritable symptom. A total of 31% of the sample met diagnostic criteria for DMDD. At follow-up (n=124), the mean DAWBA irritability symptom score was 1.46 (range=0-3, SD=1.3), with 64% of the sample reporting at least one irritable symptom, and 23% meeting diagnostic criteria for DMDD.

Depression symptoms at follow-up (n=249) were also common: the mean total parent-rated MFQ score was 24.4 (range=0-68, SD=15.4), with 54.3% of the ADHD sample scoring above the clinical cut point of ≥ 21 .

4.3.2 Irritability at baseline and depression symptoms at follow-up

Baseline irritable scores and DMDD diagnosis at baseline were both associated with total parent-rated child MFQ score at follow-up, controlling for child age, gender and baseline depression symptoms (irritable score: unstandardised B=2.31, 95% CI=0.25, 4.36, standardised Beta=0.14, p=0.028; DMDD: unstandardised B=4.26, 95% CI=0.24, 8.28, standardised Beta=0.14, p=0.038) (table 4.1: model 2, and table 4.2: model 2).

Table 4.1: Association between irritable score at baseline and parent-rated total MFQ score in ADHD sample at follow-up

	Outcome: MFQ total (T2)		
	B (95% CI)	Beta (standardised)	p value
Model 1: Irritable score (T1): unadjusted	3.42 (1.38, 5.46)	0.21	0.001
Model 2: Irritable score (T1): controlling baseline age, gender, depression symptoms	2.31 (0.25, 4.36)	0.14	0.028
Model 3: Irritable score (T1): controlling for baseline age, gender, depression symptoms, ADHD medication	2.32 (0.24, 4.39)	0.14	0.029
Model 4: Irritable score (T1): controlling for baseline age, gender, depression symptoms, ADHD medication and anxiety	1.95 (-0.14, 4.03)	0.12	0.067

N for analysis=234. ADHD=attention/deficit-hyperactivity disorder; MFQ=Mood and Feelings Questionnaire; T1=Time 1; T2=Time 2. B=unstandardised B coefficient (B is the increase in MFQ score for every unit increase in irritable score); Beta=standardised Beta coefficient (Beta is the increase in standard deviations of MFQ score for every standard deviation increase in irritable score).

Table 4.2: Association between DMDD at baseline and parent-rated total MFQ score in ADHD sample at follow-up

	Outcome: MFQ total (T2)		
	B (95% CI)	Beta (standardised)	p value
Model 1: DMDD (T1): unadjusted	6.32 (2.28, 10.38)	0.20	0.002
Model 2: DMDD (T1): controlling for baseline age, gender, depression symptoms	4.26 (0.24, 8.28)	0.14	0.038
Model 3: DMDD (T1): controlling for baseline age, gender, depression symptoms, ADHD medication	4.25 (0.22, 8.29)	0.14	0.039
Model 4: DMDD (T1): controlling for baseline age, gender, depression symptoms, ADHD medication and anxiety	3.70 (-0.33, 7.72)	0.12	0.072

N for analysis=226. ADHD=attention/deficit-hyperactivity disorder; DMDD=disruptive mood dysregulation disorder; MFQ=mood and feelings questionnaire; T1=Time 1; T2=Time 2. B=unstandardised B coefficient (B is the difference in MFQ score at follow-up in those with DMDD compared to those without DMDD); Beta=standardised Beta coefficient (Beta is the standard deviation unit difference in MFQ score between those with DMDD and those without DMDD).

Using the MFQ binary measure as an outcome, associations were present for unadjusted models only (tables 4.3 and 4.4).

Table 4.3: Association between baseline irritable score and depression symptoms in ADHD sample at follow-up, using parent-rated MFQ score of ≥ 21 as a binary outcome

	Outcome: MFQ binary measure (T2)	
	OR (95% CI)	p value
Model 1: Irritable score (T1): unadjusted	1.42 (1.06, 1.87)	0.015
Model 2: Irritable score (T1): controlling for baseline age, gender, depression symptoms	1.25 (0.93, 1.68)	0.144
Model 3: Irritable score (T1): controlling for baseline age, gender, depression symptoms, ADHD medication	1.26 (0.93, 1.70)	0.131
Model 4: Irritable score (T1): controlling for baseline age, gender, depression symptoms, ADHD medication and anxiety	1.20 (0.89, 1.63)	0.234

N for analysis=234. ADHD=attention/deficit-hyperactivity disorder; MFQ=mood and feelings questionnaire.

Table 4.4: Association between baseline DMDD and depression symptoms in ADHD sample at follow-up, using parent-rated MFQ score of ≥ 21 as a binary outcome

	Outcome: MFQ binary measure (T2)	
	OR (95% CI)	p value
Model 1: DMDD (T1): unadjusted	2.23 (1.28, 3.87)	0.005
Model 2: DMDD (T1): controlling for baseline age, gender, depression symptoms	1.74 (0.96, 3.14)	0.068
Model 3: DMDD (T1): controlling for baseline age, gender, depression symptoms, ADHD medication	1.74 (0.96, 3.14)	0.068
Model 4: DMDD (T1): controlling for baseline age, gender, depression symptoms, ADHD medication and anxiety	1.66 (0.92, 3.02)	0.095

N for analysis=226. ADHD=attention/deficit-hyperactivity disorder; DMDD=disruptive mood dysregulation disorder; MFQ=mood and feelings questionnaire.

4.3.3 Persistent irritability and depression symptoms at follow-up

A total of 63% of those with an irritable score of ≥ 1 at baseline, continued to have an irritable score of ≥ 1 at follow-up. Thirty seven percent of those who had DMDD at baseline continued to have DMDD at follow-up. Those with persistent irritability (score of ≥ 1 at baseline and follow-up) had higher mean parent-rated MFQ total scores at follow-up compared to those with remitted irritability (27.8 vs 17.1, $t=-3.8$, $p<0.001$). Persistent irritability (vs remitted irritability) was associated with total parent-rated MFQ score at follow-up, controlling for age, gender and baseline depression symptoms (unstandardised $B=11.79$, 95% $CI=6.28, 17.30$, standardised $Beta=0.38$, $p<0.001$) (table 4.5: model 2). Using the MFQ binary measure as an outcome, associations were consistent ($OR=6.27$, 95% $CI=2.34, 16.80$, $p<0.001$) (table 4.6).

Table 4.5: Association between persistent irritability and parent-rated total MFQ score in ADHD sample at follow-up

	Outcome: MFQ total (T2)		
	B (95% CI)	Beta (standardized)	p value
Model 1: persistent irritability: unadjusted	10.49 (4.86, 16.12)	0.34	<0.001
Model 2: persistent irritability: controlling baseline age, gender, depression symptoms	11.79 (6.28, 17.30)	0.38	<0.001
Model 3: persistent irritability: controlling for baseline age, gender, depression symptoms, ADHD medication	12.06 (6.54, 17.59)	0.39	<0.001
Model 4: persistent irritability: controlling for baseline age, gender, depression symptoms, ADHD medication and anxiety	11.49 (6.01, 16.96)	0.37	<0.001

N for analysis=107. ADHD=attention/deficit-hyperactivity disorder; MFQ=Mood and Feelings Questionnaire; T1=Time 1; T2=Time 2. B=unstandardised B coefficient (B is the difference in MFQ score at follow-up in those with persistent irritability compared to those without persistent irritability). Beta=standardised Beta coefficient (Beta is the standard deviation unit difference in MFQ score between those with persistent irritability and those without persistent irritability).

Table 4.6: Association between persistent irritability and depression symptoms in ADHD sample at follow-up, using parent-rated MFQ score of ≥ 21 as a binary outcome

	Outcome: MFQ binary measure (T2)	
	OR (95% CI)	p value
Model 1: persistent irritability: unadjusted	4.70 (2.01, 10.99)	<0.001
Model 2: persistent irritability: controlling for baseline age, gender, depression symptoms	6.35 (2.41, 16.73)	<0.001
Model 3: persistent irritability: controlling for baseline age, gender, depression symptoms, ADHD medication	6.62 (2.49, 17.58)	<0.001
Model 4: persistent irritability: controlling for baseline age, gender, depression symptoms, ADHD medication and anxiety	6.27 (2.34, 16.80)	<0.001

N for analysis=107. ADHD=attention/deficit-hyperactivity disorder; MFQ=mood and feelings questionnaire.

4.3.4 Sensitivity analyses

Controlling for additional covariates: Sensitivity analyses found that associations for baseline irritability symptoms and later depression symptoms (table 4.1: model 4), as well as baseline DMDD and later depression symptoms (table 4.2: model 4) attenuated when including additional covariates (no longer reaching statistical significance when including anxiety disorder). However, the association was robust for persistent irritability (table 4.5: model 4).

Removing overlapping item: After removing the irritability item from the MFQ at follow-up, the association between irritable score at baseline and parent-rated MFQ total, controlling for age, gender and baseline depression symptoms was slightly weaker (unstandardised B=2.0, 95% CI=-0.02, 4.01, standardised Beta=0.13, p=0.052). The association between DMDD at baseline and parent-rated MFQ total at follow-up remained similar (unstandardised B=4.28, 95% CI= 0.35, 8.21, standardised Beta=0.14,

$p=0.033$), as did the association between persistent irritability and depression symptoms (unstandardised $B=11.44$, 95% CI= 6.06, 16.81, unstandardised Beta=0.38, $p<0.001$).

Persistent ADHD: Irritability was found to persist alongside ADHD. Of those who had persistent irritability ($n=71$), 75% also had persistent ADHD ($n=53$) (OR=2.3, 95% CI=1.02, 5.21, $p=0.045$). Persistent irritability continued to be associated with depression symptoms at follow-up after controlling for persistent ADHD (unstandardised $B=10.85$, 95% CI=5.41, 16.29, standardised Beta=0.35, $p<0.001$).

4.4 Discussion

The main aims of this study were to use a longitudinal, clinical ADHD sample to examine whether childhood irritability is associated with later depression symptoms and establish whether persistent irritability accounts for this association.

The results suggest that childhood irritability at baseline (whether defined as a continuous measure or categorical diagnosis of DMDD) is associated with adolescent depression symptoms at follow-up. These results support previous cross-sectional findings that have suggested irritability is associated with depression symptoms in those with ADHD (Ambrosini et al., 2013; Eyre et al., 2017 (Chapter 3)). These results are also consistent with findings from a longitudinal population-based sample that found emotion regulation mediated the association between ADHD symptoms and depression symptoms (Seymour et al., 2014). However, in the current study, the association no longer reached statistical significance when baseline anxiety was included as a covariate. One possible explanation for this is that the current study used the MFQ as a measure of depression symptoms at follow-up, rather than depression diagnosis.

Although the MFQ is a widely used depression screening instrument (Wood et al., 1995), items do overlap with symptoms of anxiety (e.g. restlessness, finding it hard to

think properly or concentrate, worries about aches and pains, not sleeping as well as usual) which may explain why anxiety is an important predictor of MFQ total score. It is also possible that the association between baseline irritability and later depression symptoms is explained by co-occurring anxiety disorder. Irritability is associated with anxiety (Vidal-Ribas et al., 2016), and anxiety (particularly generalised anxiety disorder) is closely linked to depression (Clark & Watson, 2006). Therefore, anxiety would be a feasible explanation for any association between irritability and depression. However, both irritability and anxiety have been observed to be important independent antecedents for adolescent depression in other populations, including those at high-familial risk for depression (Rice et al., 2017).

These results also clearly suggest that children with ADHD and persistent irritability have significantly higher depression symptoms in adolescence, with the association remaining after accounting for all covariates, including anxiety. This finding is consistent whether total parent-rated MFQ score or an MFQ clinical cut off of ≥ 21 was used as an outcome measure. The association also remained when the irritability item was removed from the MFQ at follow-up, suggesting that the high MFQ score in those with persistent irritability was not as a result of the irritable item on the MFQ. Finally, the association between persistent irritability and depression symptoms remained when controlling for persistent ADHD. This suggests that it is the persistence of irritability rather than ADHD symptoms per se that might be important in mediating risk for depression here. The association between persistent irritability and depression is supported by the evidence from studies examining irritability trajectories. These also show that those with persistently high irritability seem to have more depression and internalising symptoms than those who have high initial irritability that decreases over time (Pagliaccio et al., 2018; Wiggins et al., 2014). However, what was not clear from

this study is whether persistent irritability or adolescent-onset irritability (i.e. present only at follow-up) conferred greatest risk for depression. Due to the majority of this sample having irritability at baseline, it was not possible to test this here.

Overall, these findings suggest irritability is important in the link between ADHD and depression symptoms, although it may be specifically persistent irritability that is important. These findings are relevant for clinicians. They suggest that, in those with a diagnosis of ADHD, irritability is important and should be identified and monitored. Those who continue to have irritability over time may be at particular risk for depression, and may be the ones who should be considered as a target for early intervention/prevention of depression.

4.4.1 Limitations

It is important to consider a number of limitations in this study. Firstly, the size of the follow-up sample was relatively small, with only a subset of parents completing follow-up interviews. As a result of this there were too few meeting the threshold for a diagnosis of MDD at follow-up to use this as an outcome measure (although all 6 with MDD at follow-up met criteria for DMDD at baseline). The young age of the follow-up sample (mean=14.4 years), may also have contributed to this, with many of the sample not yet reaching the age of risk for depression. Follow-up into early adulthood would be helpful in future studies.

Another limitation was that the interview measure used to assess irritability and ADHD at follow-up (DAWBA) differed from that used at baseline (CAPA). The DAWBA was used at follow-up as it is a briefer measure than the CAPA, and more feasible to complete with the families involved. However, this change in measure across the 2 time points meant that it was not possible to directly compare prevalence of disorders across time in this sample. Despite this, it is worth noting that when comparisons of DAWBA

and CAPA have been made (Angold et al., 2012), no significant differences in rates of ADHD have been found, and the majority of those with DAWBA diagnosis also receive CAPA diagnosis.

Finally, these results are relevant to a clinical ADHD sample, and may not be generalizable outside this group. Even so, it could be argued that early intervention and prevention of depression may be most feasible for those who are already known to clinical services.

4.4.2 Conclusions

This study found that persistent irritability in those with ADHD is associated with depression symptoms in adolescence. This suggests that chronically irritable children with ADHD may be a target group for early intervention and prevention of depression, and that those who remain irritable over time should be monitored most carefully.

Chapter 5: Investigating the genetic underpinnings of early-life irritability

The results reported in this chapter have been published in *Translational Psychiatry*:

Riglin*, Eyre*, Cooper, Collishaw, Martin, Langley, Leibenluft, Stringaris, Thapar AK, Maughan, O'Donovan, Thapar A. (2017). Investigating the genetic underpinnings of early-life irritability. *Translational Psychiatry* 7, e1241. *Joint first authors.

In the original publication three datasets were used to examine the genetic underpinnings of irritability, in collaboration with Dr Lucy Riglin (joint first author). For the purpose of this thesis, only the findings using the Study of ADHD, Genes and Environment (SAGE) are included. The full paper is included in appendix 1.

Chapter description

This chapter will address the second aim of the thesis- to test whether irritability is associated with an increased polygenic risk score for depression in a clinical sample of children with ADHD. Findings from Chapter 3 suggest that irritability is associated with family history of depression in children with ADHD. The current chapter aims to utilise the same ADHD sample to examine further whether irritability is a marker of genetic liability for depression, using polygenic risk scores. As irritability occurs frequently in ADHD, and genetic links between ADHD and irritability have also been demonstrated, the association between irritability and ADHD polygenic risk scores was also examined. Genetic and phenotypic data collected as part of the “baseline sample” described in Chapter 2 were used to address these aims.

My contribution

The “baseline sample” data were collected between 2007-2011 prior to the start of this thesis. Quality control of the genetic data collected at baseline was undertaken by Dr Evie Stergiakouli and Dr Joanna Martin. Preparation of the genetic data prior to

polygenic risk score generation was carried out by Dr Joanna Martin. Polygenic risk scores were derived by Dr Lucy Riglin. I observed the generation of polygenic risk scores, derived the phenotypic variables necessary for analysis, and conducted all statistical analyses included in this chapter.

5.1 Introduction

Irritability is commonly defined as a propensity to react with anger, grouchiness, or tantrums disproportionate to the situation (Stringaris et al., 2009). Within DSM-5, it is included as a feature of a number of different diagnostic categories. However, longitudinal studies have consistently shown that childhood irritability is associated with future unipolar depression (Vidal-Ribas et al., 2016). As a result of these findings, severe chronic childhood irritability, recently categorized by DSM-5 as disruptive mood dysregulation disorder (DMDD), has been classed as a mood disorder. Genetic associations between irritability and depression have also been examined, with one twin study finding that irritability shares genetic liability with depression (Stringaris et al., 2012). Family studies have also shown higher rates of maternal depression in those with irritable symptoms (Krieger et al., 2013). Findings from Chapters 3 and 4 of this thesis suggest that irritability in children with ADHD is associated with depression symptoms cross-sectionally and longitudinally, as well as being associated with family history of depression. Therefore, it could be hypothesised that children with ADHD who are irritable also have a higher genetic loading for depression.

However, as well as having strong associations with depression, severe irritability has also long been recognized as a common accompanying difficulty to neurodevelopmental disorders. It is particularly common in attention-deficit/hyperactivity disorder (ADHD) (Eyre et al., 2017; Leibenluft, 2017; Shaw et al., 2014) with recent estimates suggesting it is present in around 25-45% of children with ADHD, when defined broadly as emotion dysregulation (a construct closely related to irritability) (Shaw et al., 2014). Childhood irritability also behaves similarly to ADHD (and other neurodevelopmental disorders) in that its onset is early in development and symptom levels tend to decline from childhood to adolescence (Copeland et al., 2015; Wiggins et al., 2014). This raises

the possibility that earlier-onset irritability behaves like a neurodevelopmental difficulty such as ADHD. Evidence from a twin study supports this possibility, finding a significant genetic overlap between emotion dysregulation and ADHD symptoms (Merwood et al., 2014). Family studies have also found elevated levels of emotional lability (another construct related to irritability) in family members of individuals with ADHD (Epstein et al., 2000; Surman et al., 2011). Therefore, it could also be hypothesized that children who are irritable may have a higher genetic loading for ADHD.

Overall there is a limited understanding of the genetic architecture of irritability. Twin studies suggest that irritability has a heritability of 30% to 40% (Vidal-Ribas et al., 2016), and as discussed, there is some evidence of genetic overlap both between irritability and depression, and between irritability and ADHD. However, investigations at a molecular level are lacking. Large genome-wide association studies of patients with a particular disorder of interest and healthy controls can be used (as discovery samples) to derive individual composite genetic risk scores (PRS - polygenic risk scores) that serve as an index of genetic liability for the disorder of interest in an independent (target) sample (Wray et al., 2014).

This study aimed to use this method to derive both major depressive disorder (MDD) and ADHD polygenic risk scores in a clinical sample with ADHD, in order to examine the association between (1) irritability and polygenic risk scores for MDD and (2) irritability and polygenic risk scores for ADHD.

5.2 Methods

5.2.1 Sample

The sample utilised was the Study of ADHD, Genes and Environment (SAGE) “baseline sample” described in Chapter 2. This sample consisted of 696 participants (84% male), aged 6-18 years (mean=10.9, SD=2.99) with a clinical and research diagnosis of ADHD. Genotype data were available for 569 individuals following quality control (described in Chapter 2).

5.2.2 Polygenic risk scores

PRS were generated as the weighted mean number of disorder risk alleles in approximate linkage equilibrium using standard procedures (Cross-disorder group of the Psychiatric Genomics Consortium, 2013a). Only autosomal variants with minor allele frequency (MAF) >0.01, call rate >0.99, and those that did not deviate from Hardy-Weinberg equilibrium at $p < 1 \times 10^{-5}$ were included.

ADHD and MDD risk alleles were identified from publicly available Psychiatric Genomics Consortium (PGC) case-control GWAS (Genome-Wide Association Studies). As the ADHD discovery GWAS (Cross-disorder group of the Psychiatric Genomics Consortium, 2013b; Neale et al., 2010; Yang et al., 2013) included data from SAGE cases, meta-analyses excluding these samples were performed to identify ADHD risk alleles for the purpose of generating PRS. This independent ADHD discovery dataset thus included 4 980 cases and 11 837 controls. The MDD discovery dataset included 9 240 cases and 9 519 controls (Ripke et al., 2013). Please note that these analyses were conducted prior to the availability of the most recent ADHD GWAS (Demontis et al., 2018) and the most recent MDD GWAS (Wray et al., 2018). Risk alleles were defined as those associated at p-threshold <0.5 (previously reported to

maximally capture phenotypic variance for ADHD and MDD), although analyses across a range of p-thresholds were undertaken for the purpose of sensitivity testing.

5.2.3 Child psychopathology

The parent-completed Child and Adolescent Psychiatric Assessment (CAPA) was used to measure psychopathology in the child. Individuals were categorised as irritable if they were rated as having at least one of three irritable symptoms (“temper tantrums”, “touchy or easily annoyed” or “angry and resentful”) from the oppositional defiant disorder (ODD) section of the CAPA. This binary irritability variable was used as it was most consistent with the irritability measures available in the other 2 samples included in the published paper (Avon Longitudinal Study of Parents and Children (ALSPAC) and National Child Development Study (NCDS)-see appendix 1). However, a continuous irritable score (possible range 0-3) was also generated, consistent with the continuous measure of irritability used in this thesis. ADHD symptoms were measured using the ADHD section of the parent-reported CAPA (possible range 0-18), and conduct disorder (CD) symptoms from the CD section of the parent-reported CAPA (possible range 0-9).

5.2.4 Analyses

First, irritability was examined: specifically, how common it was, whether it varied with age (splitting the sample into <12 years (n=408) and ≥12 years (n=288)), and whether it was associated with gender and total ADHD symptom scores.

Then associations between MDD PRS and irritability, and ADHD PRS and irritability were examined, using logistic regressions in SPSS. Gender (due to its known association with depression), ten principal components (to account for population stratification) and genotyping batch (to account for the 2 different arrays used- see Chapter 2) were included as covariates in all PRS analyses. The effects of age were

investigated by testing for a PRS-by-age interaction and the effects of gender by testing for a PRS-by-gender interaction.

5.3 Results

A total of 91% of the sample met criteria for irritability (at least one irritable symptom). Irritability was more common in the ‘younger’ (<12 years) than ‘older’ (≥12 years) group (93.5% and 87.0% respectively, $\chi^2(1)=8.36$, $p=0.004$), but the prevalence of irritability did not differ by gender. Irritability was associated with ADHD total symptom score (table 5.1).

Table 5.1: Irritability frequency, and associations with age, gender and ADHD symptoms

Frequency of irritability, % (n)	90.9% (616)
Frequency of irritability by age:	
< 12 years, % (n)	93.5% (375)
≥ 12 years, % (n)	87.0% (241)
Frequency of irritability by gender:	
Males, % (n)	91.2% (569)
Females, % (n)	89.0% (97)
Gender difference (χ^2)	0.54, $p=0.461$
ADHD symptoms (OR (95% CI))	1.25 (1.16-1.35), $p<0.001$

5.3.1 Association between irritability and MDD PRS

MDD PRS were not associated with irritability. This was the case both for the binary measure of irritability (table 5.2) as well as the continuous irritable score (table 5.3).

Figure 5.1 shows results were consistent across a range of p-thresholds. There were no clear age effects (younger subsample OR=0.84 (0.54-1.32), $p=0.448$; older subsample

OR=1.19 (0.77-1.81), $p=0.435$), and there was no evidence for an interaction between MDD PRS and gender ($p=0.985$).

5.3.2 Association between irritability and ADHD PRS

ADHD PRS were associated with irritability (table 5.2). When the continuous measure of irritability was used, the pattern of association was similar but non-significant (standardised Beta=0.077, $p=0.073$) (table 5.3). Figure 5.1 shows results across a range of p-thresholds (ORs for the association between ADHD PRS and irritability increased as the p-threshold became more lenient and as more SNPs were included in the PRS). There were no clear age effects (younger subsample: OR=1.48 (0.92-2.39), $p=0.110$; older subsample: OR=1.53 (0.99-2.36), $p=0.053$) and there was no evidence of any interaction between ADHD PRS and gender ($p=0.986$).

After identifying the association between ADHD PRS and irritability, sensitivity analyses were undertaken adjusting for ADHD symptom severity and conduct disorder symptom severity (ADHD PRS have previously been found to be associated with conduct disorder in this ADHD sample (Hamshere et al., 2013)). The association between ADHD PRS and irritability remained after adjusting for ADHD symptom severity (OR=1.48 (1.08-2.04), $p=0.016$), with the pattern of results remaining similar after adjusting for conduct disorder symptom severity (OR=1.32 (0.98-1.80), $p=0.072$), although not meeting the threshold for statistical significance.

Table 5.2: Associations between MDD and ADHD polygenic risk scores and binary measure of irritability

	OR	(95% CI)	p value
MDD PRS	1.05	(0.78-1.41)	0.763
ADHD PRS	1.37	(1.02-1.86)	0.039

Polygenic risk scores using p-threshold <0.5. Analyses controlling for gender, 10 principal components and batch.

Table 5.3: Associations between MDD and ADHD polygenic risk scores and continuous measure of irritability

	Beta (standardised)	(95% CI)	p value
MDD PRS	-0.039	(-0.124, 0.046)	0.354
ADHD PRS	0.077	(-0.006, 0.162)	0.073

Polygenic risk scores using p-threshold <0.5. Analyses controlling for gender, 10 principal components and batch.

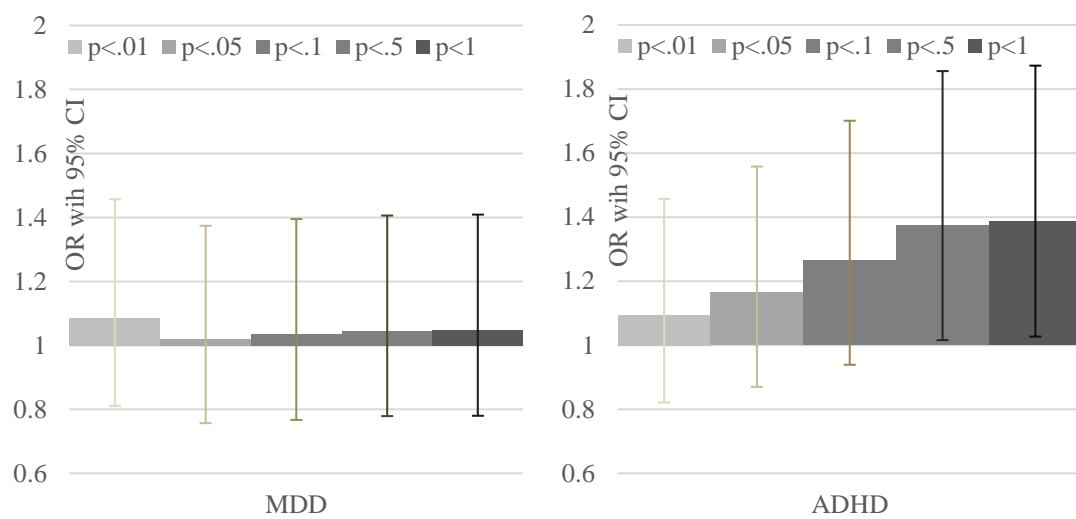


Figure 5.1: Associations between MDD and ADHD polygenic risk scores and irritability, using a range of p-value thresholds from the discovery sample

5.4 Discussion

This study aimed to investigate the genetic underpinnings of early irritability in a clinical ADHD sample, by firstly, investigating the association between irritability and MDD PRS and secondly, investigating the association between irritability and ADHD PRS. The results of the study did not find any association between irritability and MDD PRS, but did find associations between ADHD PRS and irritability.

The finding of an association between irritability and ADHD PRS is in keeping with findings from a previous twin study, and suggests modest genetic overlap between

ADHD and irritability at a molecular (common genetic variant) level. There are several reasons why ADHD PRS might be associated with irritability. One possibility is that irritability is a core feature of ADHD. Irritability has historically been included as an associated feature of ADHD in diagnostic classification systems and it is a commonly co-occurring symptom (American Psychiatric Association, 2013; Shaw et al., 2014). It also appears to show similar epidemiological patterns to ADHD and many other DSM-5 neurodevelopmental disorders: symptom levels have been reported to be highest in childhood and to reduce with age (Copeland et al., 2015), with some studies reporting a male preponderance for irritability, although gender differences in irritability have not been consistent (Ambrosini et al., 2013; Axelson et al., 2012; Copeland et al., 2013, 2015; Dougherty et al., 2014; Roberson-Nay et al., 2015). There is also some evidence that effective ADHD treatment with stimulant medication improves irritability in children with ADHD (Fernández de la Cruz et al., 2015). However, symptoms of irritability are not prominent in all children with ADHD (Shaw et al., 2014) (although they are very common in this ADHD sample), suggesting that irritability might provide additional information regarding severity of disorder and genetic loading in those with ADHD. Notably, associations between ADHD PRS and irritability were similar after taking into account ADHD (and conduct disorder) symptom levels.

Another possibility is that ADHD common genetic risk variants have pleiotropic effects on ADHD and early irritability. Studies have already shown that ADHD PRS are associated with other features that commonly accompany ADHD, such as lower IQ, impairment in working memory and conduct disorder (Hamshere et al., 2013; Martin et al., 2015). This is the first study that has shown an association with irritability, thereby addressing a gap in knowledge of the genetic architecture of early irritability. Twin studies highlight that psychopathology co-occurs, in part, as a result of shared genetic

risks (Lahey, Van Hulle, Singh, Waldman, & Rathouz, 2011) and molecular genetic studies concur in showing that ADHD genetic risk variants impact upon a wide range of early neurodevelopmental and behavioral traits. It is possible that ADHD PRS could have non-specific effects on multiple psychiatric traits in early life, although findings do suggest there could also be some specificity in the pattern of effects (Martin et al., 2015).

The lack of association between irritability and MDD PRS is less consistent with what might be expected based on previous study findings. Previous longitudinal studies have found associations between early irritability and later depression in general population samples (Copeland et al., 2015; Epstein et al., 2000), and these links appear to be partially genetically mediated (Savage et al., 2015; Stringaris et al., 2012). Such findings have suggested that childhood irritability is an early manifestation of mood problems. Indeed, severe childhood-onset irritability (disruptive mood dysregulation disorder (DMDD)) is classified as a mood disorder in the DSM-5. The DSM-5 classification of childhood-onset irritability as a mood disorder would predict an association between early irritability and MDD PRS, but this was not found in this study.

However, these findings should be interpreted cautiously. Despite similar GWAS discovery sample sizes, MDD PRS will be underpowered compared to ADHD PRS for several reasons, including that MDD is more common and less heritable than ADHD (Power et al., 2017). Another difference worth noting is that while the ADHD PRS were generated based on a GWAS of children with ADHD, the MDD PRS were generated based on a GWAS of adults with MDD. Indeed, there is emerging evidence that the genetic architecture of MDD may differ by age-at-onset (Power et al., 2017; Riglin et al., 2018) and MDD PRS derived from a GWAS of younger patients with MDD may

have resulted in stronger associations with childhood irritability. Nevertheless, if childhood irritability is an early manifestation of later, adult mood problems, an association between childhood irritability and adult MDD PRS would be predicted. Thus, while it may be possible to exclude large effect sizes of MDD PRS on early irritability, an association with genetic liability for depression cannot be ruled out, especially given findings from twin studies (Savage et al., 2015; Stringaris et al., 2012). Large scale international molecular genetic studies show genetic overlap between ADHD and depression (Anttila et al., 2018; Bulik-Sullivan et al., 2015; Cross-disorder group of the Psychiatric Genomics Consortium, 2013) and these disorders co-occur more often than would be expected by chance (Spencer et al., 1999). It is possible that irritability is a common factor between the two.

Another explanation is that early irritability is neurodevelopmental in nature (i.e. given that it manifests early and is more common in males) but its links with later depression are mediated via gene-environment correlation (for example via eliciting adverse social stressors such as peer rejection). Such mechanisms would be incorporated into estimates of shared genetic effects in twin studies.

Finally, another possibility is that irritability might represent different underlying problems depending on age and gender; that is, it could be more like ADHD in childhood and more like mood disorder later in development. This could help explain why in a childhood sample with ADHD, irritability was associated with ADHD PRS rather than MDD PRS. Although our results did not show any evidence of interaction between MDD or ADHD PRS and age or gender, there may have been limited power to detect this, and future work investigating irritability across different developmental stages, across gender and within different disorders will be important.

In conclusion, this study suggests that irritability, when manifest during childhood in patients with ADHD, is associated with ADHD genetic liability as indexed by PRS. This finding, coupled with observations that irritability tends to decline from childhood to adolescence, suggests that early irritability is similar to ADHD and, when early in onset, may be better conceptualised as a neurodevelopmental difficulty rather than a mood disorder-related problem. Further work is needed to better understand the developmental nature of irritability and its links with psychiatric disorders.

Chapter 6: Childhood neurodevelopmental difficulties and risk for adolescent depression: the role of irritability

The work presented in this chapter has been submitted for publication in the *Journal of Child Psychology and Psychiatry* (Eyre, Hughes, Thapar AK, Leibenluft, Stringaris, Davey Smith, Stergiakouli, Collishaw, Thapar A. Childhood neurodevelopmental difficulties and risk for adolescent depression: the role of irritability). The submitted paper has been edited for this chapter to avoid repetition and to incorporate supplementary materials.

Chapter description

This chapter follows on from work in Chapters 3 and 4, where an association between irritability and depression symptoms was found in a clinical ADHD sample. This chapter utilises a longitudinal population sample to examine whether irritability is also important in terms of future depression in those with a broader group of neurodevelopmental difficulties. It addresses the final aim of the thesis, testing whether irritability contributes to the longitudinal association between childhood neurodevelopmental difficulties and later adolescent depression. The Avon Longitudinal Study of Parents and Children (ALSPAC) was utilised for this analysis, which has been described in Chapter 2.

My contribution

For this chapter, I utilised existing ALSPAC data. However, I was involved in defining exposure and outcome variables (in particular, deciding how best to define neurodevelopmental difficulties and depression diagnosis), deriving these variables and undertaking all analyses included in this chapter. I also undertook multiple imputation as a method of dealing with missing data, with advice from a statistician (Dr Rachael Hughes) at Bristol MRC Integrative Epidemiology Unit (IEU).

6.1 Introduction

Neurodevelopmental disorders are common (Boyle et al., 2011), typically starting in early life, and resulting in impaired functioning across the lifespan (Howlin, Goode, Hutton, & Rutter, 2004; Klein et al., 2012). According to the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5), this group include intellectual disability (ID), communication disorders, autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), specific learning disorders and motor disorders. There is a scientific rationale for this grouping. First, clinical overlap between these disorders is high (Fombonne, 2003; Ghirardi et al., 2018; Jensen & Steinhausen, 2015; Kadesjö & Gillberg, 2001). These disorders also behave as highly correlated traits. Thus, research that focuses on a single diagnosis (e.g. autism) does not allow for testing the contribution of accompanying neurodevelopmental difficulties. Neurodevelopmental disorders also share common features; they onset early in development, tend to show a steady course, and affect males more commonly than females (Bishop & Rutter, 2008; Thapar et al., 2017). There is also strong genetic overlap across different neurodevelopmental problems (Ghirardi et al., 2018; van Hulzen et al., 2017; Willcutt, Pennington, & DeFries, 2000). Thus, considering neurodevelopmental disorders together may be useful clinically and for research purposes (Thapar et al., 2017).

Children with neurodevelopmental disorders are at increased risk of later depression (Daviss, 2008; Ghaziuddin et al., 2002). High rates of major depressive disorder (MDD) as well as elevated levels of depressive symptoms are seen across the different categories of neurodevelopmental disorders (Biederman et al., 2008; Gadow et al., 2012; Kim et al., 2000; Mammarella et al., 2016; Meinzer et al., 2016). This pattern extends to those with sub-threshold neurodevelopmental problems. For example, those with high autistic traits reported more depressive symptoms than those with minimal

autistic traits (Kanne et al., 2009), and children with subthreshold ADHD had higher rates of depression diagnosis than those without (Roy et al., 2014).

Depression in young people with neurodevelopmental disorders is clinically important. For example, in those with ADHD, it is associated with greater impairment in social and academic functioning (Blackman et al., 2005), as well as increased rates for psychiatric hospital admission, suicidality (Biederman et al., 2008) and completed suicide (James et al., 2004). Depression in ASD has been found to have a negative impact on the family (Gold, 1993) and been associated with low levels of functioning (Mattila et al., 2010). Identifying mechanisms that contribute to risk of depression in individuals with neurodevelopmental disorders could inform prevention and treatment strategies; furthermore, recognising children with neurodevelopmental disorders at highest risk of developing depression could allow early identification and intervention.

One potential mechanism that has attracted growing interest is childhood irritability; this is described as a propensity to react with anger, grouchiness, or tantrums disproportionate to the situation (Stringaris et al., 2009). Irritability is a well-established feature of oppositional defiant disorder (ODD). Recent studies highlight an irritable dimension of ODD (Burke et al., 2014; Krieger et al., 2013; Rowe et al., 2010; Stringaris & Goodman, 2009a; Whelan et al., 2013). The symptoms that best define this dimension include “often loses temper”, “often touchy or easily annoyed” and “often angry and resentful” (Evans et al., 2017). Irritability, when operationalised in the context of the irritable dimension of ODD or as a separate trait, has been found to predict future emotional disorders and depression (Krieger et al., 2013; Rowe et al., 2010; Stringaris & Goodman, 2009a; Vidal-Ribas et al., 2016; Whelan et al., 2013). Severe irritability is particularly common in children with neurodevelopmental disorders (Shaw et al., 2014; Simonoff et al., 2012) and may contribute to later

depression in this group. However, research into the association between irritability and depression in those with neurodevelopmental disorders is limited.

Cross-sectional studies have examined the association between irritability and depression in children with ADHD (Ambrosini et al., 2013; Eyre et al., 2017; Seymour et al., 2012). Further, in a clinical ASD sample, an irritable dimension of ODD was associated with emotional problems (Mandy et al., 2014). However, these studies examined the association between irritability and depression prior to the typical age of onset of depressive disorder in adolescence. Their cross-sectional design precludes any temporal relationship between irritability and depression being established.

Longitudinal studies of the links between neurodevelopmental disorders, irritability and depression are lacking.

This study utilised a case-comparison design with groups selected from a large UK population-based cohort. Aims were to (1) test for an association between childhood neurodevelopmental difficulties and adolescent MDD; and (2) test the hypothesis that childhood irritability contributes to the association between concurrent neurodevelopmental difficulties and later MDD. Finally, as the grouping of neurodevelopmental difficulties includes problems from multiple DSM-5 diagnostic categories, the study assessed whether any particular category was driving the results.

6.2 Methods

6.2.1 Sample

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a longitudinal population-based cohort that recruited 14,541 pregnant women resident in Avon, UK with expected delivery dates between 1st April 1991 and 31st December 1992 (Boyd et al., 2013; Fraser et al., 2013). They were followed up at multiple time points using a

range of clinic and questionnaire based measures. The ALSPAC study is described in detail in Chapter 2. A total of 1697 with neurodevelopmental difficulties at age 7-9 years, and a comparison group of 3177 with no evidence of any neurodevelopmental difficulties were included in this study. Ethical approval for the ALSPAC study was obtained from the ALSPAC Ethics and Law Committee and Local Research Ethics Committees. All participants provided written informed consent.

6.2.2 Measures

6.2.2.1 Childhood neurodevelopmental difficulties

Children with neurodevelopmental difficulties were identified at ages 7-9 years using seven scales from six validated parent-reported measures, which cover each of the DSM-5 neurodevelopmental disorder categories (details included in table 2.7, Chapter 2). If participants scored in the bottom 5% on at least one measure they were classified as having neurodevelopmental difficulties, even if data from other measures were missing. A comparison group with no evidence of neurodevelopmental difficulties on any of the seven scales was also identified. Therefore, those in the comparison group were required to have data available on all neurodevelopmental measures. The flow chart in figure 2.3 (Chapter 2) details the numbers in the neurodevelopmental difficulties and comparison groups.

6.2.2.2 Childhood irritability

Irritability was assessed using three symptoms from the ODD section of the age 7 years 7 months parent-reported Development and Well Being Assessment (DAWBA) (Goodman et al., 2000): “temper outbursts”, “touchy or easily annoyed” and “angry and resentful”. These symptoms make up an irritable dimension of ODD (Stringaris & Goodman, 2009a), as previously operationalised in this sample (Burke et al., 2014). Symptoms occurring over the last 6 months were rated “no more than others” (score 0),

“a little more than others” (score 1) and “a lot more than others” (score 2). Total scores ranged from 0-6.

6.2.2.3 Adolescent MDD

The depression section of the DAWBA was completed by parents at ages 10 years 8 months and 13 years 10 months, and by adolescents at age 15 years 7 months. DAWBA algorithms were used to generate diagnoses of DSM-IV MDD in the previous 4 weeks (Goodman, Heiervang, Collishaw, & Goodman, 2011) (DSM-IV was the most recent edition available at the time of data collection). Information was combined to provide the outcome measure: any diagnosis of MDD between ages 10-15 years.

6.2.2.4 Other study measures

The parent-reported DAWBA at age 7 years 7 months provided information about depression and anxiety diagnosis. Demographic measures included social class based on mother’s occupation, maternal and paternal age at birth of child, and maternal and paternal education (A-levels or higher vs those without i.e. comparing those with or without education up to at least age 18 years).

6.2.3 Analyses

Data were analysed using Stata version 14. Group comparisons used chi square analysis for categorical variables and t-tests for continuously distributed measures.

Figure 6.1 shows the proposed path model. Neurodevelopmental difficulties precede the onset of depression and are associated with later depression (Daviss, 2008) (path a, figure 6.1). Irritability precedes the onset of depression and is associated with later depression (Stringaris et al., 2009) (path c, figure 6.1). As neurodevelopmental difficulties and irritability often co-occur (Shaw et al., 2014; Simonoff et al., 2012), the direction of this association is less clear (i.e., path b or path d, figure 6.1). However, as

neurodevelopmental difficulties start very early in life, and I was interested in the contribution of irritability to the association between neurodevelopmental difficulties and depression, I tested neurodevelopmental difficulties → depression (path a) and neurodevelopmental difficulties → irritability → depression (paths b and c). As there is no evidence to suggest that irritability is temporally preceded by neurodevelopmental difficulties, it was not possible to use a standard mediation model that would hypothesise a path from neurodevelopmental difficulties to later irritability (the mediator).

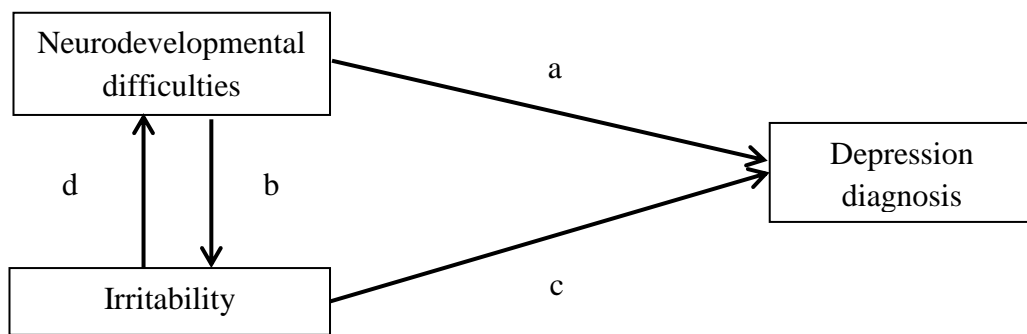


Figure 6.1. Possible paths between neurodevelopmental difficulties and irritability to depression.

1. Neurodevelopmental difficulties → depression (path a)
2. Irritability → depression (path c)
3. Neurodevelopmental difficulties → irritability → depression (path b and c)
4. Irritability → Neurodevelopmental difficulties → depression (path d and a)

Prior to all analyses, those with MDD at age 7 years were removed from the sample.

Therefore, all individuals where the outcome (depression) temporally preceded assessment of the predictor variables were excluded.

Logistic regression analysis was used to first examine the association between neurodevelopmental difficulties (ages 7-9) and MDD (ages 10-15) controlling for

gender. Gender was included as a covariate as gender is associated with both neurodevelopmental difficulties and depression (Thapar et al., 2012, 2017). Logistic regression analysis then examined the association between irritability (age 7) and MDD (ages 10-15), again controlling for gender. The association between neurodevelopmental difficulties and irritability at age 7-9 was examined by calculating a polychoric correlation coefficient.

To assess the contribution of irritability to the association between childhood neurodevelopmental difficulties and adolescent depression, the “khh” command in Stata (Kohler, Karlson, & Holm, 2011) was used to decompose the path from neurodevelopmental difficulties to depression into direct (path a) and indirect (via irritability- paths b and c) effects, while controlling for gender. This is a general decomposition method that can be used to examine the degree to which a particular variable explains the relationship between an exposure and an outcome, providing information on total, direct and indirect effects. It allows the comparison of coefficients between two nested non-linear probability models (Kohler et al., 2011), which was necessary due to the categorical nature of the variables in this study.

Regression analyses were conducted on both complete cases and imputed datasets (see section 6.2.4). As it was not possible for the khb command to be used on multiple imputed datasets in Stata, path analysis was conducted on complete cases only.

Finally, as the neurodevelopmental difficulties group was made up of multiple diagnostic categories, analyses were undertaken to examine whether any particular category was driving the results. Analyses were repeated for each neurodevelopmental problem category (ID, communication disorders, ASD, ADHD, specific learning disorders, motor disorders).

6.2.3.1 Supplementary analyses

Three sensitivity analyses were undertaken. First, to assess the impact of missing data on the definition of the study groups, regression and path analyses were repeated on (i) a sample with complete neurodevelopmental data on all seven indicators (n=3824), and (ii) a sample with neurodevelopmental data on at least one indicator (n=9977).

Second, anxiety disorder at age 7 was added as a covariate, to establish whether any association observed between neurodevelopmental difficulties and depression was explained by irritability rather than co-occurring anxiety. Third, analyses were repeated using a binary measure of irritability (individuals with no irritability (score=0) vs those with any irritability (score ≥ 1)).

6.2.4 Missing data

The total sample size for this study was 4874. Of these individuals, 4512 (93%) had data available for the irritable score variable at age 7 years, 2668 (55%) had data available for the outcome variable (MDD age 10-15) and 2546 (52%) individuals had data on all variables included in the model. To minimise the bias from missing data as well as to improve precision, multiple imputation by chained equations was used to impute the missing outcome (White, Royston, & Wood, 2011).

The imputation model included all variables in the analysis model (neurodevelopmental difficulties age 7-9, irritability age 7, depression age 10-15 and gender), variables that predicted missingness in the outcome (social class, maternal age, maternal education, maternal history of severe depression, paternal age, paternal education), and variables associated with the outcome (parent rated depression symptoms using the Mood and Feelings Questionnaire (MFQ) at 9, 11, 13 and 16 years, self-rated depression symptoms using the MFQ at 12, 13 and 17 years, self-rated depression diagnosis at age 18 years using the Clinical Interview Schedule- Revised (CIS-R), self-rated self-harm at

age 18 years using the CIS-R, parent-rated diagnosis of anxiety disorder, ODD and CD at age 7 years using the Developmental and Well Being Assessment (DAWBA), and parent rated Strength and Difficulties Questionnaire (SDQ) subscale symptom scores at age 7, 9 and 11 years). Where continuous variables were not normally distributed, predictive mean matching was applied. Fifty imputed datasets were created using 10 cycles of regression switching. Analyses were run on imputed datasets by combining estimates using Rubin's rules (White et al., 2011).

6.3 Results

6.3.1 Sample description

Children with neurodevelopmental difficulties at age 7-9 were more likely to be male, come from lower social class families, have higher rates of psychopathology, have a higher mean irritable score at age 7, and were more likely to be classified as having special education needs by their school than those in the comparison group (table 6.1).

Table 6.1: Characteristics of those with neurodevelopmental (ND) difficulties compared to those without

	ND difficulties (n≤1697)	No ND difficulties (n≤3177)	Test statistic
Gender^a, % male (n)	63.1% (1071)	47.3% (1503)	$\chi^2=110.8, p<0.001$
Social class based on mother's occupation^b, % I/II (n)	29.2% (407)	40.2% (1153)	$\chi^2=49.4, p<0.001$
Oppositional defiant disorder at age 7 years^c, % (n)	16.4% (228)	0.6% (20)	$\chi^2=468.8, p<0.001$
Any anxiety disorder at age 7 years^d, % (n)	4.8% (68)	1.1% (36)	$\chi^2=60.3, p<0.001$
Major depressive disorder at age 7 years^e, % (n)	2.2% (30)	0.4% (11)	$\chi^2=35.7, p<0.001$
Irritable score at age 7 years^f, mean (range, SD)	1.25 (0-6, SD=1.73)	0.33 (0-6, SD=0.80)	$t(4510)=-24.5, p<0.001$
Special Educational Needs^g, % (n)	29.9% (403)	3.2% (101)	$\chi^2=672.5, p<0.001$

Numbers for analysis: ^a n=4874, ^b n=4261, ^c n=4566, ^d n=4582, ^e n=4506, ^f n=4512, ^g n=4488.

Social class based on occupation split into I/II or III/IV/V. DSM-IV diagnoses of oppositional defiant disorder, any anxiety disorder and major depressive disorder derived using parent-rated Development and Well Being Assessment (DAWBA) at age 7. Irritable score calculated using 3 items from parent-rated DAWBA at age 7 (temper outbursts, touchy/easily annoyed, angry/resentful)-possible score=0-6.

6.3.2 Childhood neurodevelopmental difficulties and adolescent depression

Children with neurodevelopmental difficulties had higher rates of depression at ages 10-15 than the comparison group (4.5% vs 2.0%; $\chi^2=11.48, p=0.001$).

The association between child neurodevelopmental difficulties and later MDD remained significant after removing those with MDD at age 7 and controlling for gender, both using complete cases (OR=2.11, 95% CI=1.24, 3.60, $p=0.006$) and imputed datasets (OR=2.25, 95% CI=1.54, 3.29, $p<0.001$).

6.3.3 Contribution of childhood irritability to the association between neurodevelopmental difficulties and depression

There was a significant association between irritability and neurodevelopmental difficulties ($r=0.50, p<0.001$). Irritability at age 7 was associated with MDD age 10-15 after controlling for gender and removing those with age 7 MDD, both using complete

cases (OR=1.48, 95% CI=1.29, 1.72, $p<0.001$) and imputed datasets (OR=1.41, 95% CI=1.28, 1.56, $p<0.001$).

The hypothesised path diagram included direct and indirect (via irritability) paths from neurodevelopmental difficulties to depression (figure 6.2). Using complete cases for analysis, adding irritability reduced the coefficient (log odds) between neurodevelopmental difficulties and depression from 0.62 (95% CI=0.06, 1.17, $p=0.029$) to 0.36 (95% CI=0.23, 0.95, $p=0.234$), with an indirect effect of 0.26 (95% CI=0.14, 0.38, $p<0.001$). Forty two percent of the total effect was explained by irritability.

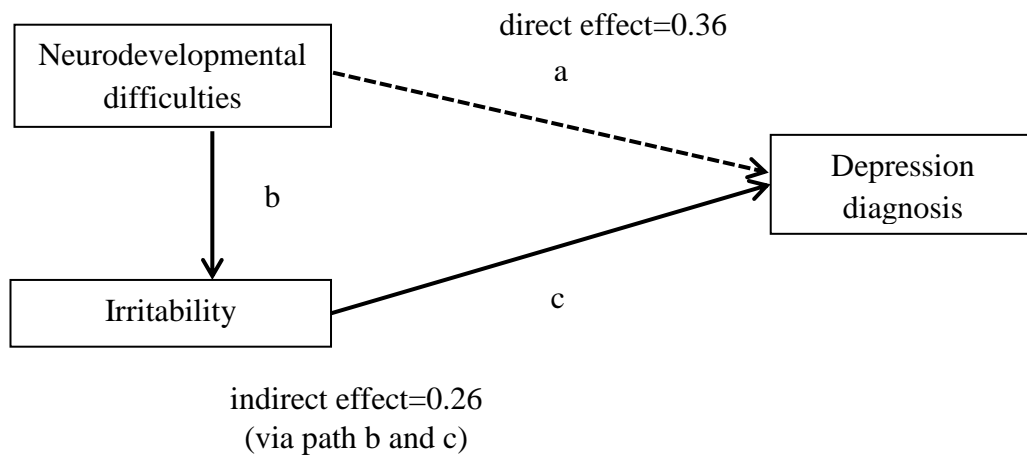


Figure 6.2. Indirect effect of irritability on the association between neurodevelopmental difficulties and depression.

Interrupted line shows a path for which the magnitude of the path coefficient does not reach conventional levels of statistical significance.

6.3.4 Testing individual neurodevelopmental disorders

Analyses of each of the neurodevelopmental categories and depression separately suggested that difficulties in pragmatic language (CCC), social communication (SCDC) and ADHD (DAWBA symptoms) were associated with later depression (table 6.2).

Other neurodevelopmental indicators were not associated with later depression. For the measures of ASD and ADHD, irritability explained a large proportion of the association. Irritability explained 29% of the association between pragmatic language difficulties and depression (indirect effect: log odds=0.39, 95% CI=0.20,0.59, $p<0.001$), 51% of the association between social communication difficulties and depression (indirect effect: log odds=0.73, 95% CI=0.31,1.14, $p=0.001$), and 42% of the association between ADHD problems and depression (indirect effect: log odds=0.55, 95% CI=0.27,0.83, $p<0.001$).

Table 6.2: Examining association between each neurodevelopmental category and depression age 10-15

Neurodevelopmental category	Depression age 10-15	
	OR (95% CI)	P value
WISC III- Full scale IQ ^a	0.85 (0.20, 3.5)	0.824
CCC-Speech and syntax subscale ^b	0.98 (0.35, 2.72)	0.967
CCC- Pragmatic composite subscale ^c	5.12 (2.64, 9.92)	<0.001
SCDC ^d	4.63 (2.34, 9.16)	<0.001
DAWBA ADHD symptoms ^e	4.27 (2.10, 8.69)	<0.001
WORD- basic reading subtest ^f	1.83 (0.65, 5.16)	0.256
MABC ^g	1.25 (0.45, 3.50)	0.671

Numbers for analysis: ^an=2604, ^bn=2634, ^cn= 2581, ^d=2600, ^e n=2616^fn=2599, ^gn=2538. WISC-III (Wechsler Intelligence Scale for Children); CCC (Children’s Communication Checklist); SCDC (Social Communication Disorders Checklist); DAWBA (Development and Well Being Assessment); ADHD (attention-deficit/hyperactivity disorder); WORD (Wechsler Objective Reading Dimension); MABC (Movement Assessment Battery for Children). The association between the bottom 5th percentile on each measure of neurodevelopmental difficulties and later depression was examined. Results are for complete cases. Analyses controlled for gender and those with baseline depression diagnosis were removed from analysis.

6.3.5 Supplementary sensitivity analyses

Alternative ways of defining the study groups using either complete or any available neurodevelopmental data respectively, yielded very similar findings to the study full sample. When including those with complete data on neurodevelopmental measures, the sample size was reduced to 3824 (number with neurodevelopmental difficulties=647, number without neurodevelopmental difficulties=3177 (i.e. 17% of the sample with

complete data had neurodevelopmental difficulties)). Using this sample, childhood neurodevelopmental difficulties continued to be associated with depression diagnosis age 10-15, when controlling for gender and after removing those with baseline depression diagnosis: OR=2.61, 95% CI= 1.46, 4.69; p=0.001. The results from the path model found that adding irritability to the model reduced the coefficient between neurodevelopmental difficulties and depression from 0.86 (95% CI=0.26, 1.47; p=0.005) to 0.61 (95% CI =-0.04, 1.26; p=0.064), with an indirect effect of 0.25 (95% CI= 0.11, 0.39; p<0.001). A total of 29% of the total effect was explained by irritability.

When including those with data on at least one measure of neurodevelopmental difficulties for either the neurodevelopmental difficulties group or the comparison group, the sample size was increased to 9977 (number with neurodevelopmental difficulties=1697, number without evidence of neurodevelopmental difficulties=8280 (i.e. 17% of the sample with at least one neurodevelopmental measure available had neurodevelopmental difficulties)). Using this sample, childhood neurodevelopmental difficulties continued to be associated with depression diagnosis age 10-15 when controlling for gender and after removing those with baseline depression diagnosis: OR=2.32, 95% CI=1.47, 3.66; p<0.001. The results from the path model found that adding irritability reduced the coefficient between ND difficulties and depression from 0.65 (95% CI=0.14, 1.16; p=0.013) to 0.43 (95% CI= -0.11, 0.97; p=0.120), with an indirect effect of 0.22 (95% CI=0.11, 0.33; p<0.001). A total of 34 % of the total effect was explained by irritability.

Controlling for anxiety disorder did not affect the results. Childhood neurodevelopmental difficulties continued to be associated with depression diagnosis age 10-15, after controlling for baseline anxiety disorder (in addition to gender and

removing those with baseline depression diagnosis), using complete cases (OR=1.97, 95% CI=1.15, 3.38; p=0.013) and imputed datasets (OR=2.15, 95% CI=1.46, 3.15; p<0.001). Using the path model in complete cases, irritability continued to explain 42% of the association between neurodevelopmental difficulties and depression after controlling for baseline anxiety disorder. Table 6.3 shows the association between childhood neurodevelopmental difficulties and depression decomposed into total, direct and indirect effect (through irritability), after controlling for anxiety disorder.

Table 6.3: Path analysis examining the association between neurodevelopmental difficulties and depression, after controlling for anxiety disorder at age 7

Path	Coefficient (log odds)	95% CI	P value
Total effect	0.58	0.015, 1.14	0.044
Direct effect	0.33	-0.26, 0.93	0.270
Indirect effect	0.24	0.08, 0.40	0.004

Finally, when a binary measure of irritability was used in the path analysis, instead of the continuous measure, irritability explained 40% of the association between neurodevelopmental difficulties and later depression (controlling for gender and after removing those with baseline depression diagnosis). Table 6.4 shows the association between childhood neurodevelopmental difficulties and depression decomposed into total, direct and indirect effect, through the binary measure of irritability.

Table 6.4: Path analysis examining the association between neurodevelopmental difficulties and depression, through a binary measure of irritability

Path	Coefficient (log odds)	95% CI	P value
Total effect	0.71	0.17, 1.25	0.009
Direct effect	0.43	-0.13, 0.99	0.131
Indirect effect	0.28	0.14, 0.43	<0.001

6.4 Discussion

Using a longitudinal design, this study found that neurodevelopmental difficulties in childhood are associated with later adolescent depression, and that a significant proportion of this association is explained by childhood irritability. In fact, when irritability is taken into account, operationalised using the irritable dimension of ODD, the magnitude of association between neurodevelopmental difficulties and depression drops below the threshold for statistical significance. This suggests that irritability is a major contributor in explaining the link between neurodevelopmental problems and later depression.

Previous studies have found that individuals with neurodevelopmental disorders are at elevated risk for depression. Most of this research examined associations between ADHD or ASD and depression (Daviss, 2008; Ghaziuddin et al., 2002; Kim et al., 2000; Meinzer et al., 2016). However, associations between other neurodevelopmental disorders and depression have also been found (e.g. reading and tic disorders) (Gadow et al., 2012; Mammarella et al., 2016). The results from this study are partially consistent with this literature, suggesting that whilst children with neurodevelopmental difficulties are at increased risk for later depression, findings may vary for specific problem types. This is clinically relevant, in terms of understanding which children with neurodevelopmental difficulties are at high risk for depression; regardless of the primary presenting problem; elevated levels of ASD/social communication and ADHD symptoms appear to be associated with greatest risk.

The second aim involved examining the contribution of irritability to the association between neurodevelopmental difficulties and depression. The results suggest that irritability, when measured as an irritable dimension of ODD, plays an important role. Previous studies have shown that irritability is an important predictor of future

depression in the general population (Althoff, Kuny-Slock, Verhulst, Hudziak, & Van Der Ende, 2014; Brotman et al., 2006; Copeland, Shanahan, Egger, Angold, & Costello, 2014; Stringaris et al., 2009). The results suggest it is also important for those with neurodevelopmental difficulties. Even when controlling for baseline depression and anxiety, the contribution of irritability was important, with 42% of the association between neurodevelopmental difficulties and depression explained by irritability.

These findings are clinically relevant. Identifying irritability in children with neurodevelopmental difficulties (particularly ADHD and ASD), may help to identify those at risk for later depression. This may help with early identification and treatment of depression in a group where depression is common and impairing (Daviss, 2008; Ghaziuddin et al., 2002). It may also provide an opportunity to prevent the onset of depression, e.g. by treating irritability early.

Understanding the mechanisms underlying irritability and its association with depression will inform development of effective treatments. Literature suggests that genetic factors may be important. Family history of depression has been associated with irritability in a general population sample (Krieger et al., 2013) and a clinical ADHD sample (Eyre et al., 2017 (Chapter 3)). Twin studies suggest irritability and depression have common genetic underpinnings (Savage et al., 2015; Stringaris et al., 2012).

However, it should also be noted that findings from Chapter 5 of this thesis do not suggest an association between molecular genetic risk for depression (MDD polygenic risk score) and childhood irritability.

Environmental factors may also be of relevance in the association between irritability and depression. For example, studies of adolescent depression have found stressful life events, particularly stressors affecting relationships, to be important risk factors (Thapar et al., 2012). Irritability is associated with significant impairment in multiple areas of

functioning including family relationships (Copeland et al., 2013). Therefore, irritability (including the irritable dimension of ODD) could predispose to family relationship problems, which may predispose to depression. If this was the case, interventions such as parent training may be of benefit. Indeed, the effectiveness of parenting interventions has been well established in ODD (Scott & Gardner, 2015). However, more research is needed to test whether such interventions prevent depression onset in those with neurodevelopmental difficulties. Further research is also needed to examine whether mechanisms responsible for irritability and their possible links with depression differ in young people with neurodevelopmental difficulties compared to those without.

6.4.1 Limitations

Although the use of a large longitudinally assessed sample was a strength of the study, several limitations should be mentioned. Firstly, as for any large longitudinal cohort study, there was a significant proportion of missing outcome data (MDD age 10-15). However, the pattern of results remained the same for complete case analyses and imputed data. Also, the way in which the neurodevelopmental difficulties categorical variable was derived meant that, in order to be categorised as having any neurodevelopmental difficulty, data on a minimum of one measure of neurodevelopmental difficulties were needed. However, to be categorised as having no neurodevelopmental difficulty, data on all neurodevelopmental measures were necessary. Despite this, the pattern of results remained the same when sensitivity analyses were undertaken firstly, including only those with complete data and secondly, allowing missing data in both neurodevelopmental and comparison groups. Secondly, there are limitations in the measures used. The neurodevelopmental grouping variable aimed to cover a broad range of difficulties based on the DSM-5 neurodevelopmental disorder categories. Symptoms in most but not all of the categories

listed in DSM-5 were included due to the available measures in the ALSPAC sample (e.g. tic disorders, or specific learning disorders with impairment in written expression or mathematics were not included). Also, for the outcome, even though the measurement of depression across three time points was a strength of the study, the rater changed from parent-report to self-report at age 15. However, this reflects clinical practice, where there is greater reliance on parental-reports in younger children and self-reports in adolescents. Finally, these findings cannot automatically be generalised to clinical samples; further longitudinal research in clinical samples is needed.

6.4.2 Conclusions

This longitudinal study suggests that children with neurodevelopmental difficulties, specifically ASD and ADHD problems, are at increased risk of developing later adolescent depression. We found that irritability was an important contributor to this association. This suggests that the high rates of irritability known to be present in those with neurodevelopmental problems might explain the high rates of depression in this group. The next step is to identify the mechanisms involved in this association, which could facilitate the search for effective interventions.

Chapter 7: Discussion

7.1 Summary of findings

The overall aim of this thesis was to examine the association between irritability and depression in young people with ADHD and a broader group of neurodevelopmental difficulties. This involved firstly, examining the association between irritability and depression symptoms, both concurrently and longitudinally, in a clinical sample with ADHD (Chapters 3 and 4); secondly, testing whether, in the same clinical ADHD sample, those with irritability showed increased genetic liability for depression, as indexed by major depressive disorder (MDD) polygenic risk scores (Chapter 5), and finally, in a longitudinal population sample, examining the role of irritability in the association between a broad group of neurodevelopmental difficulties and later depression diagnosis (Chapter 6).

The results suggest that, in a British, clinical ADHD sample, irritability is common. At baseline assessment, 91% of the sample had at least one symptom of irritability and 31% met diagnostic criteria for disruptive mood dysregulation disorder (DMDD). Those with more symptoms of irritability or who met diagnostic criteria for DMDD had higher concurrent depression symptom scores than those without irritability (Chapter 3).

Irritability was also associated with other measures of depression liability, including anxiety disorder and family history of depression. No association was found between childhood irritability symptoms and a concurrent depression diagnosis, but very few in the sample met full diagnostic criteria for major depressive disorder at this age (mean 10.9 years).

This cross-sectional investigation was extended using longitudinal data, collected in a subset of the same clinical ADHD sample, to examine the association between childhood irritability and later depression symptoms (Chapter 4). At follow-up,

depression symptoms were common, with more than half of the sample scoring above the clinical cut-off on the depression questionnaire measure used. Results showed that irritability in childhood, both measured as irritability symptom score and as DMDD diagnosis, was associated with later depression symptoms. This association was present when controlling for age, gender and baseline depression symptoms, but no longer met the threshold for statistical significance once baseline childhood anxiety disorder was also accounted for. However, for those who had persistent symptoms of irritability across childhood and adolescence, the association with depression symptoms remained after taking into account all covariates, including childhood anxiety disorder and ADHD persistence. This suggests that persistent irritability in children with ADHD may be an important marker of increased risk for depression.

When the same clinical ADHD sample was used to examine whether childhood irritability indexed higher genetic loading for depression (measured using MDD polygenic risk scores) (Chapter 5), no association between irritability and depression polygenic risk scores was found. Therefore, explanations other than overlapping genetic risks may be relevant in the association between childhood irritability and depression in children with ADHD. Further analyses did show an association between irritability and ADHD polygenic risk scores, suggesting that childhood irritability may be more closely genetically linked to ADHD than depression.

Finally, in a population-based cohort, irritability was found to play an important role in the association between more broadly defined neurodevelopmental difficulties and later depression, explaining over a third of this association (Chapter 6). In fact, once irritability was included in the model, the association between neurodevelopmental difficulties and later depression diagnosis no longer reached the threshold for statistical significance. Within the neurodevelopmental difficulties group, it was those with

ADHD or autism spectrum disorder (ASD) problems who had a particularly high risk for later depression, with irritability also explaining a large proportion of each of these associations.

7.2 Interpretation of findings

Overall, this thesis provides evidence that childhood irritability is associated with increased depression risk in those with ADHD and other neurodevelopmental difficulties. As has been discussed in the individual results chapters, these findings are consistent with and extend results from previous general population studies (Brotman et al., 2006; Copeland et al., 2014; Stringaris et al., 2009).

When interpreting the thesis findings, there are a number of important issues to consider. Firstly, it is important to consider how irritability and depression are defined. The way in which these variables were defined and measured may impact on the interpretation of the findings. Secondly, the possible reasons for the association between irritability and depression in those with neurodevelopmental difficulties are important. There are a number of possible explanations for the observed associations, some of which are considered in the thesis (e.g. the possible role of anxiety disorder and genetic factors), and these need to be better understood if prevention of depression is to be successful in these children. Also, the finding that irritability seems to be particularly important in the link between ADHD and ASD difficulties and later depression, more so than for other neurodevelopmental problems, is important. Understanding which neurodevelopmental difficulties confer particular risk for depression through irritability is of clinical relevance. Finally, it is important to consider the overall clinical implications of the thesis findings. Each of these issues will be discussed in turn below.

7.2.1 Measurement of irritability

The observed association between irritability and depression consistently found across the chapters of this thesis was based on irritability being defined in two ways. First, it was defined as a continuous irritable dimension of oppositional defiant disorder (ODD) (Chapters 3, 4, 5 and 6), and second, as a categorical diagnosis of disruptive mood dysregulation disorder (DMDD) (Chapters 3 and 4). However, measuring irritability is not straight forward, as it is not clear how best to define it. This is illustrated by the different approaches taken by DSM-5 and the new ICD-11. DSM-5 includes both the irritable dimension of ODD (included in the “disruptive, impulse-control, and conduct disorders” section of the manual), as well as DMDD diagnosis (included in the “depressive disorders” section). ICD-11 includes an irritable dimension of ODD (ODD with chronic irritability/anger), but no DMDD diagnosis. There are reasons why DSM-5 and ICD-11 have taken these different approaches, and there has been some debate over the validity of the diagnostic category of DMDD. However, despite these differences in classification, the findings from this thesis suggest that associations with depression are consistent whether irritability is defined as the irritable dimension of ODD, or as DMDD diagnosis. The definition used in this thesis did not impact on the results. Therefore, it is possible that the irritable dimension of ODD and the diagnostic category of DMDD describe similar clinical phenomena (as also suggested by Evans et al., 2017), with similar clinical outcomes.

Another important point to consider when defining irritability is the timing of its presentation, for example, whether it presents in childhood or later in adolescence or adulthood. There is emerging evidence to suggest that childhood irritability differs from adolescent onset irritability. Irritability trajectory classes derived across childhood and adolescence suggest that irritability starting early in childhood and persisting across

time is associated with childhood ADHD and a higher genetic loading for ADHD (ADHD polygenic risk scores), whereas irritability starting in adolescence and increasing over time is more strongly associated with major depressive disorder (MDD) and higher genetic loading for depression (MDD polygenic risk scores) (Riglin et al., 2018). This suggests that irritability in childhood may be more closely linked to ADHD and other neurodevelopmental difficulties, whereas later onset irritability may be more strongly linked to depression. This is supported by the genetic findings in Chapter 5 of this thesis, where an association between childhood irritability and ADHD polygenic risk scores was observed, but no association with MDD polygenic risk scores was found. Interestingly, a study of older adults in the UK Biobank found mood instability was associated with MDD polygenic risk score (Ward et al., 2017). Due to these possible differences between childhood and later onset irritability, and the fact that only childhood irritability was examined in this thesis, the results reported in this thesis should be interpreted in relation to childhood irritability. However, it should be noted that this thesis also found persistent irritability across childhood and into adolescence to be particularly strongly associated with depression symptoms in the clinical ADHD sample. Studies from the general population support this finding, with evidence for an association between adolescent irritability and depression in adulthood (Stringaris et al., 2009). Therefore, it seems that childhood irritability may differ from later onset irritability, and that early onset persistent irritability may be a particularly important marker of risk for depression in children with neurodevelopmental disorders such as ADHD.

Finally, the context in which irritability is measured (i.e. whether it is in the presence of other disorders or not) is also important to consider. Irritability occurs across a number of psychiatric diagnoses, including ADHD, ODD, depression, anxiety and bipolar

disorder, and it is not yet clear whether the irritability seen across these different disorders is the same. Therefore, the results reported in this thesis should be seen in the context of children with ADHD and other neurodevelopmental difficulties. They are not automatically generalisable to other groups.

7.2.2 Measurement of depression

Considering the way in which depression is defined and measured is also important when interpreting the thesis findings. In this thesis, depression symptoms and diagnosis have been measured from late childhood to mid-adolescence. In the clinical ADHD sample, depression symptoms were measured at a mean age of 14.4 years (Chapter 4), and in the population sample depression diagnosis was measured at age 10, 13 and 15 years (Chapter 6). Therefore, the results suggest that childhood irritability is important in increasing the risk of depression presenting in late childhood and early adolescence. These findings may not be generalisable to later onset depression. There are a number of reasons for this. Childhood depression is known to differ from adolescent and adult onset depression (Maughan et al., 2013). It is rarer, has a more even gender split, and is more strongly associated with multiple comorbidities (Egger & Angold, 2006; Maughan et al., 2013; Thapar et al., 2012). In addition to this, earlier onset depression may be associated with different genetic risks when compared to later onset depression. A study by Rice et al (2018) examined the association between psychiatric polygenic risk scores and developmental depression trajectories across childhood and adolescence (Rice et al., 2018). They found that early adolescent onset depression (with clinically significant symptoms at age 12) was associated with polygenic risk scores for schizophrenia and ADHD (as well as MDD), whereas late adolescent onset depression was associated with MDD polygenic risk scores only. Power et al (2017) has also previously reported that earlier onset MDD is genetically more similar to schizophrenia and bipolar disorder

than adult onset MDD (Power et al., 2017). Finally, there is also evidence to suggest that the association between ADHD and depression may be stronger for earlier onset depression (Bird et al., 1993) than later onset depression. As childhood irritability often co-occurs with ADHD, and may have a neurodevelopmental component, it is possible that this stronger association with earlier onset depression may also be observed for childhood irritability.

7.2.3 Explaining the association between childhood irritability and depression

As has been discussed, this thesis consistently shows that childhood irritability is associated with depression symptoms in individuals with ADHD. However, it is important to consider why this association may occur. Understanding the mechanisms responsible for this association may be important for identifying interventions to prevent the onset of depression. There are a number of explanations that should be considered.

One possible explanation for the association between childhood irritability and depression is that irritability is part of depression. Indeed, DSM-5 includes irritability as a symptom of depression in adolescence (American Psychiatric Association, 2013). If irritability is a marker of depression, it would not be surprising that irritability is associated with depression. However, based on the results from this thesis, this explanation seems unlikely. All the analyses presented in this thesis controlled for depression diagnosis or depression symptoms in childhood and this did not impact on the association between irritability and later depression. In addition to this, when the irritability item was removed from the depression symptom score at follow-up, the association also remained (Chapter 4).

Another possible explanation is that irritability and depression share causal risk factors. The association between them could be observed due to common genetic or environmental risk factors. In terms of genetic risk factors, Stringaris et al., (2012) used a twin study design to show that irritability shares genetic liability with depression (Stringaris et al., 2012). Savage et al (2015) also found shared genetic factors to play a role in the link between irritability and anxiety/depression (Savage et al., 2015).

Chapter 3 examined whether those with ADHD and irritability had an increased family history of depression, and Chapter 5 investigated whether those with ADHD and irritability had higher polygenic risk scores for depression. Irritability was found to be associated with increased family history of depression, but not with MDD polygenic risk scores. As discussed in Chapter 5, there are possible reasons why an association between irritability and MDD polygenic risk scores cannot be ruled out in this sample (e.g. lack of power to detect the association), but overall, these results do not seem to strongly support a genetic explanation for the association. Also, it should be considered that even though an association between child irritability and family history of depression was observed in Chapter 3, not all of this association may be due to genetic factors. History of maternal depression contributed significantly to the measure of depression family history in this study, and the presence of maternal depression in this sample could have been influenced by the child's irritability. There is literature to suggest that child psychopathology may impact on maternal depression symptoms (Sellers et al., 2016). Therefore, it is possible that at least some of the association between child irritability and family history of depression seen in Chapter 3 could be explained by the impact the child's irritability has on the mother's depression. However, it is also worth noting that although MDD PRS was not associated with irritability in Chapter 5, ADHD PRS was. ADHD PRS has also been found to be associated with

depression (Du Rietz et al., 2018). Therefore, it is possible that ADHD PRS is associated with both irritability and depression and could play a role in explaining the association observed between irritability and depression.

It is also possible that there are environmental factors associated with both irritability and depression which contribute to their co-occurrence. Unmeasured environmental confounders could be responsible for explaining the observed association. For example, socioeconomic status has been found to be associated with both irritability (Copeland et al., 2013) and depression (Freeman et al., 2016) and could be a confounder explaining the association between the two. Although the results from this thesis suggest that the association between irritability and depression remain after controlling for family income (Chapter 3), there are many other possible environmental factors that may play a part in explaining the association which were not examined. For example, a number of environmental risk factors known to be associated with depression such as stressful life events, adverse family environments, negative parental and peer relationships, and family conflict (Arseneault, 2017; Birmaher et al., 1996; Daviss, 2008; Maughan, Collishaw, & Stringaris, 2013; Thapar et al., 2012), could also be associated with irritability. Although further work is needed to examine the association between irritability and many of these environmental factors, DMDD has been shown to be associated with single parent families (Copeland et al., 2014) and impairment in parental, sibling and teacher relationships (Copeland et al., 2013). Therefore, factors such as these may be relevant when considering possible explanations for the association between irritability and depression.

Another possible explanation for the observed association is that irritability may be associated with later depression due to the presence of a co-occurring disorder. The results from Chapter 4 suggest that this could be a possibility. In the longitudinal

analysis undertaken in the clinical ADHD sample, the association between irritability at baseline and depression symptoms at follow-up no longer met the threshold for conventional levels of statistical significance when baseline anxiety disorder was added as a covariate. As irritability is associated with anxiety (Vidal-Ribas et al., 2016), and anxiety is closely linked to depression (Clark & Watson, 2006), the presence of anxiety could explain the association observed between irritability and depression. However, again, this explanation does not seem to fully account for the thesis findings.

Controlling for anxiety disorder did not affect the cross-sectional association between irritability and depression symptoms in the clinical ADHD sample (Chapter 3), it did not affect the association between irritability and depression diagnosis observed in the population based sample (Chapter 6), and it did not affect the results in the longitudinal ADHD sample when the association between persistent irritability and depression symptoms was examined (Chapter 4). Therefore, co-occurring anxiety does not seem to fully explain the association between irritability and depression symptoms in the samples examined here. Both irritability and anxiety have been shown to be important antecedents for adolescent depression (Rice et al., 2017) and it is more likely that both are important risk factors.

Finally, it is possible that childhood irritability itself may increase the risk for later depression i.e. it could be that irritability causes depression. Savage et al (2015) provided evidence consistent with a causal association between irritability and later anxiety/depression, finding that irritability more strongly predicted anxious/depressive symptoms than vice versa. A causal association has not been tested in this thesis, but there are plausible mechanisms through which this could occur. For example, irritability is impairing and impacts on family relationships (Copeland et al., 2013). Studies of adolescent depression suggest that stressors affecting relationships may be important

risk factors for depression (Thapar et al., 2012). Therefore, it is possible that the impact of irritability on peer and family relationships may lead to depression in those with irritability (i.e. irritability may evoke an environmental response that predisposes to depression (Stringaris et al., 2018)). Further research is needed firstly to determine whether the association between irritability and depression is causal, and if so, what mechanisms may be responsible for this.

7.2.4 Comparing ADHD and ASD to other neurodevelopmental difficulties

The findings from the population sample (Chapter 6) suggested an association between a broad group of childhood neurodevelopmental difficulties and later depression, with a large proportion of the association explained by irritability. However, when each neurodevelopmental difficulty was examined separately, it was the ADHD and ASD symptoms that were most strongly associated with later depression, and it was for these difficulties that irritability was important in this association. The importance of irritability in the link between ADHD difficulties and depression in the general population supports the results from the clinical ADHD sample (Chapter 4), and suggests that irritability is important in increasing risk for depression not only in those with an ADHD diagnosis but also in those with a broader ADHD phenotype. The role of irritability in the association between ASD difficulties and depression also supports the limited existing literature which suggests that irritability in children and adolescents with autism is associated with emotional problems cross-sectionally (Mandy et al., 2014). The lack of association between other neurodevelopmental difficulties (e.g. cognitive impairment, specific learning difficulties and co-ordination difficulties) and depression is more surprising. Due to the high clinical overlap across neurodevelopmental difficulties, and evidence from other studies suggesting that neurodevelopmental difficulties other than ADHD and ASD are also associated with

depression (Mammarella et al., 2016; Maughan et al., 2003; Simonoff, 2015; Yew & O’Kearney, 2013), it was expected that the results would be consistent across the various neurodevelopmental difficulties. However, the link between irritability and depression in neurodevelopmental disorders other than ADHD and ASD had not previously been examined.

It is possible that the expected associations were not seen in this thesis, as a population-based cohort was utilised, measuring symptoms of neurodevelopmental difficulties rather than clinical diagnoses of neurodevelopmental disorders. However, neurodevelopmental disorders behave as continuously distributed traits so this approach should not have been a problem. It is also possible that when splitting the sample for these additional analyses there was not enough power to detect associations with depression for each neurodevelopmental difficulty separately. However, the association was still present for those with ADHD and ASD difficulties, suggesting that if a clear association was present for the other neurodevelopmental difficulties, it would have been observed. It may be that grouping together such a broad heterogeneous group of neurodevelopmental difficulties, despite their clinical and genetic overlap, may not have been the optimal approach in these analyses. Given the novelty of this study, further research is needed before conclusions can be drawn about possible differences in association with depression and the role of irritability in different categories of neurodevelopmental difficulties.

7.2.5 Clinical implications of findings

The observation that childhood irritability was associated with depression symptoms both cross-sectionally and longitudinally in a clinical sample with ADHD has important potential clinical implications. As has been discussed, children with ADHD are at increased risk for depression (Angold et al., 1999; Meinzer et al., 2014), and when

ADHD and depression co-occur, the outcomes are worse than for either condition alone (Biederman et al., 2008; Blackman et al., 2005; James et al., 2004). Therefore, identifying those at highest risk of depression provides potential for early identification and treatment of depression, or even prevention. The results suggesting that irritability (particularly persistent irritability) is a risk factor for depression in those with ADHD are, therefore, of clinical importance. Routine assessment for irritability in patients with ADHD, could allow clinicians to identify those at particular risk for depression, facilitating early identification and treatment of depression, with the potential to improve outcomes. A similar argument could be made for those with ASD, although more research is needed to establish whether the results examining ASD problems in a population sample generalise to a clinical sample with ASD diagnoses.

In addition to using irritability as a way of identifying those at risk of depression in order to intervene early, if irritability is a mechanism through which children with ADHD and ASD go on to develop depression, it may be that treating irritability could prevent the onset of depression. However, in order for this to be possible, there would need to be effective treatments for irritability.

With the increasing interest in childhood irritability, there has been recent research into its treatment. However, most recommended treatments are still focused on treating existing comorbid conditions. Stringaris et al (2018) provided an algorithm for the treatment of irritability in young people, suggesting that if comorbidity is present then it should be treated first (Stringaris et al., 2018). For example, if a diagnosis of ADHD is present alongside irritability, then a parenting intervention and stimulant medication are recommended. In individuals with ADHD, treatment with methylphenidate has been shown to improve irritability symptoms alongside ADHD symptoms (Fernández de la Cruz et al., 2015; Waxmonsky et al., 2008). It has also been suggested that for those

who have ODD or ASD, as well as irritability, parenting interventions should be offered as part of their treatment. Parenting interventions have been shown to be effective in improving symptoms of ODD (Scott & Gardner, 2015), some of which overlap with irritability.

There has also been some research looking at specifically treating irritability, but it is limited. In a small sample, group therapy incorporating components of cognitive behavioral therapy (CBT) with parent training, led to improvements in irritability among children with severe mood dysregulation (SMD) and ADHD (Waxmonsky et al., 2013). Preliminary results from a randomised clinical trial also suggested that parent training may improve irritability (Waxmonsky et al., 2016). With regards to pharmacological treatments, a randomised control trial of lithium for severe irritability found no benefit over placebo (Dickstein et al., 2009). Another study found that low dose risperidone reduced irritable scores in children and adolescents with SMD (Krieger et al., 2011). However, prescribing antipsychotic medication in children is not generally recommended unless severe irritability is unresponsive to a series of other treatments (Stringaris et al., 2018). Research into antidepressant medication (SSRIs) for the treatment of irritability is ongoing (Stringaris et al., 2018).

Newer treatment approaches for irritability are also under investigation. The neurocognitive mechanisms hypothesised to be involved in irritability have provided a basis for the development of new interventions. For example, young people with high levels of irritability have been shown to be more likely to interpret ambiguous faces as angry (Stoddard et al., 2016). Computer-based interpretation bias training (IBT), encouraging young people to perceive ambiguous faces as less threatening, has been shown to result in a shift towards happy (rather than angry) interpretations, and to reduce irritability in those with severe chronic irritability (Stoddard et al., 2016).

Therefore, treatments for irritability are actively being investigated. Once irritability can be treated successfully, it will be important to establish whether treating it can prevent depression onset. It will also be important to establish whether treatment of irritability in those with ADHD or ASD should be the same as for those without these neurodevelopmental difficulties.

7.3 Strengths and limitations

7.3.1 Strengths

The main strength of this thesis was the use of two different, but complementary, samples to examine the association between irritability and depression in those with ADHD and a broader group of neurodevelopmental problems. The first sample, recruited through child psychiatry and paediatric clinics, consisted of a clinical group of children with ADHD. Examining the association between irritability and depression in this group provided results that could be generalised to other children with clinical ADHD diagnoses. These children are often already in contact with health services, making it possible for clinicians to act on the findings. For example, monitoring children with ADHD and irritability for symptoms of depression is easier to do if they are already attending clinic.

However, as is well known, clinical samples are often subject to several biases.

Children attending clinics often have more severe disorder and have a greater level of comorbidity (Berkson's bias). Also, many children with ADHD are not identified or referred. In addition to this, ADHD and other neurodevelopmental difficulties are well known to behave as continuous traits, with many individuals who do not meet diagnostic criteria for a disorder still experiencing adverse outcomes (Rodriguez et al., 2007; Roy et al., 2014; Thapar et al., 2017). Therefore, clinic-referred samples do not always provide a full picture. As such, utilising a large longitudinal population-based

cohort to address the research aims, in addition to the clinical sample, was a particular strength of this thesis. The population sample used, the Avon Longitudinal Study of Parents and Children (ALSPAC), is particularly well-suited to addressing the aims of this thesis, as it is a large cohort that has been followed up across childhood and into early adulthood, with multiple measures of child psychopathology collected at multiple time points. The findings from the population sample were largely consistent with those from the clinical ADHD sample in terms of showing that irritability is important in identifying those at particular risk of developing depression. Having consistency in results across these different study designs, which use different measures, allows greater confidence in the results and strengthens the findings.

7.3.2 Limitations

7.3.2.1 Sample size and attrition

Despite the strengths of the samples used in this thesis, there were also limitations that should be noted. Firstly, although the clinical ADHD sample was large at baseline (n=696), only a proportion were followed up into adolescence (n=249), with a smaller subset completing interviews at follow-up (n=124). This meant that too few of the sample met the threshold for a diagnosis of major depressive disorder at follow-up for it to be used as an outcome measure. Instead, it was necessary to rely on depression symptoms. This is still a valid outcome measure, as symptoms of depression are impairing and are associated with later depression diagnosis (Fergusson et al., 2005). However, having a sufficiently powered study to examine diagnosis would have added to the clinical relevance.

With regards to the longitudinal population-based sample, the main limitation was attrition over time. Although the initial study sample used for analysis was large (n=4874), a significant proportion of the sample had missing data on the outcome of

depression. Attrition in ALSPAC is not completely at random (Howe, Tilling, Galobardes, & Lawlor, 2013), which has the potential to bias results. To address this, multiple imputation was carried out and analyses run on complete cases and imputed data. The pattern of results was similar for complete case analyses and those using imputed data, suggesting that the missing data did not impact on the results.

7.3.2.2 Measurement issues

There were limitations in the measures used across both the clinical ADHD sample, and the population sample (ALSPAC), including in the measurement of irritability, depression and neurodevelopmental difficulties.

Measurement of irritability: In the ADHD sample, irritability at baseline was assessed using the Child and Adolescent Psychiatric Assessment (CAPA), both as an irritable dimension of oppositional defiant disorder (ODD), as well as the diagnosis of disruptive mood dysregulation disorder (DMDD). The CAPA was not specifically designed to derive DMDD diagnosis, so this was done retrospectively based on symptoms that are included in the ODD and depression sections. Although this is not ideal, the CAPA does contain all the symptoms required to establish the presence of DMDD diagnosis, and the method used in this thesis has been used previously (Copeland et al., 2013). The other limitation in the ADHD sample was that the interview used to measure irritability at follow-up (Development and Well-Being Assessment (DAWBA)), was different to the one used at baseline (CAPA). The DAWBA was used at follow-up as it is a briefer measure than the CAPA and was more feasible to complete with the participants. However, this change in measure limited the comparison of the prevalence of irritability across time in this sample.

In the population sample, due to the measures available, it was only possible to assess the irritable dimension of ODD. Therefore, the role of DMDD in the later onset of

depression in those with a broad group of neurodevelopmental difficulties was not examined.

Measurement of depression: The depression outcome measure in the population sample also had some limitations. Even though it included information on depression diagnosis across 3 time points (a strength of the study), the rater changed from parent-report to self-report at age 15. However, this reflects clinical practice, where parent-reports are often used in younger children, and self-reports in adolescents. Self-reports have been found to be unreliable in younger children, particularly when children are asked about duration and onset of symptoms (Schwab-Stone et al., 1994).

In the clinical ADHD sample, only parent-reported measures of depression symptoms were used. Although this is a different approach to that used in the population sample, there is evidence to suggest that adolescents with ADHD under-report their own depression symptoms when compared to reports from their parents (Fraser et al., 2017). Therefore, taking into account parent report of depression symptoms for those with ADHD is likely to be important.

Measurement of neurodevelopmental difficulties: In the population-based sample, the aim was to identify children with a broad group of neurodevelopmental difficulties based on the neurodevelopmental disorder categories listed in DSM-5 (American Psychiatric Association, 2013). Symptoms from all the categories were included in the neurodevelopmental difficulties group, but due to the available measures in the ALSPAC sample, not all of the specific diagnoses could be covered (e.g. tic disorders were not included). The selection of a broad and heterogeneous group of children with neurodevelopmental symptoms also potentially limited the generalisability of the findings to children with clinical diagnoses of neurodevelopmental disorders.

7.3.2.3 Analyses

The overall aim across chapters was to examine links between irritability and depression, using the appropriate analytic methods. However, it should be noted that when examining the association between irritability and depression across the different chapters there were some inconsistencies in the choice of covariates included in the analyses. One reason for this was a difference in measures available in the clinical ADHD sample and population-based sample. For example, the measures of impairment and family income that were available for the clinical ADHD sample were not available in the population-based sample. Another inconsistency was the inclusion of age as a covariate in the clinical ADHD sample but not the population-based sample. The rationale here was that in the clinical ADHD sample there was a large variation in age of participants at baseline and follow-up (e.g. participants were age 6-18 years at baseline), whereas in the population-based sample there was little variation in age between individuals at each point of data collection. However, this lack of consistency is a potential limitation of this work.

7.4 Future research

Evidence of a link between childhood irritability and depression in children with ADHD and other neurodevelopmental difficulties is clinically important, with implications discussed earlier in this chapter. The findings of this thesis also lead to further questions and suggestions for future research.

Firstly, although I observed that irritability is an important marker of depression risk in children with ADHD, the findings do not provide an explanation for why this might be. The possible reasons for the association have been discussed, but I could not test whether irritability causes depression and I did not assess additional mechanisms that

might contribute, as discussed earlier (e.g. family discord). Understanding the mechanisms responsible for this association is an important next step.

Linked to this, another important area for future research is into the treatment of irritability. As discussed, given that irritability predicts the onset of later depression, it may be that treating irritability could prevent depression onset. Although there are treatments that improve irritability in those with ADHD, further research is needed to establish evidence-based treatments for irritability and to test whether treating childhood irritability can reduce risk of later depression.

Another area that would benefit from further research is the role of irritability in the association between neurodevelopmental difficulties other than ADHD and ASD with later depression. The findings from this thesis suggested that irritability is important in the association between ADHD and ASD problems and later depression, but not other neurodevelopmental difficulties. However, as there is no other literature on this subject, it will be important to see if these results are replicated in other samples.

Finally, it is possible that irritability which presents early in children with neurodevelopmental difficulties differs from irritability that presents later in young people without these difficulties. The measurement of irritability is an important consideration for future research i.e. how it is measured, when in development it is measured (at a single time point or across time), and the context in which it is measured (e.g. whether it occurs alongside other diagnoses). Further research is needed to establish whether irritability differs across development and across different diagnostic categories.

7.5 Conclusions

Overall, my thesis findings suggest that irritability is an important predictor of depression symptoms in children with a clinical diagnosis of ADHD. These findings are

supported by results from a longitudinal population sample which found that irritability explains a large proportion of the association between neurodevelopmental difficulties (particularly ADHD and ASD problems) and later depression. Identifying irritability in these children may allow early intervention and treatment of depression, as well as possible prevention. Further research into the mechanisms by which irritability is associated with later depression could help to inform the development of treatments for irritability. Future research examining whether irritability differs across development and across different diagnostic categories will also be important if it is to be fully understood.

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Appendices

Appendix 1: Investigating the genetic underpinnings of early-life irritability.

Riglin*, Eyre*, Cooper, Collishaw, Martin, Langley, Leibenluft, Stringaris, Thapar AK, Maughan, O'Donovan, Thapar A. (2017). Investigating the genetic underpinnings of early-life irritability. *Translational Psychiatry* 7, e1241. *Joint first authors.